From: Gokhale, Runa Hatti (CDC/DDID/NCEZID/DHQP)
Sent: Wed, 28 Oct 2020 19:57:09 +0000
To: Datta, Deblina (CDC/DDPHSIS/CGH/GID); McDonald, Clifford (CDC/DDID/NCEZID/DHQP); Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Cc: Natarajan, Pavithra (CDC/DDID/NCEZID/DFWED); Nakao, Jolene H. (CDC/DDPHSIS/CGH/DGHP); Schweitzer, Beth (CDC/DDID/NCEZID/DPEI); Bamrah Morris, Sapna (CDC/DDID/NCHHSTP/DTE); CDC IMS 2019 NCOV Response HSWS TF Clin Dis and Hlth Srvs Team; Chiller, Tom (CDC/DDID/NCEZID/DFWED)
Subject: RE: CNBC- SEEKING INFORMATION
Attachments: COVID-19 IM 2020-10-26 FINAL .pdf

Thanks, Deblina.

Cliff, slides 16-20 from Monday's IM slide deck (attached) give a great overview of the studies that the Natural History Team in the Epi TF has funded to study the natural history and outcomes of COVID-19, including long-term sequelae.

As Deblina mentioned, we can follow up with information regarding current Clinical Team projects, which I believe (b)(5) (b)(5)

Runa

From: Datta, Deblina (CDC/DDPHSIS/CGH/GID) <skd2@cdc.gov>
Sent: Wednesday, October 28, 2020 3:28 PM
To: McDonald, Clifford (CDC/DDID/NCEZID/DHQP) <ljm3@cdc.gov>; Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Cc: Natarajan, Pavithra (CDC/DDID/NCEZID/DFWED) <qdb5@cdc.gov>; Nakao, Jolene H. (CDC/DDPHSIS/CGH/DGHP) <fvg8@cdc.gov>; Gokhale, Runa Hatti (CDC/DDID/NCEZID/DHQP) <yet7@cdc.gov>; Schweitzer, Beth (CDC/DDID/NCEZID/DPEI) <hzt5@cdc.gov>; Bamrah Morris, Sapna (CDC/DDID/NCHHSTP/DTE) <feu3@cdc.gov>; CDC IMS 2019 NCOV Response MCCM Clinical Team <eocevent272@cdc.gov>; Chiller, Tom (CDC/DDID/NCEZID/DFWED) <tnc3@cdc.gov>
Subject: RE: CNBC- SEEKING INFORMATION

Cliff/John,
We have received message from IM that Late Sequelae is a priority for the response and we are working to stand up website and studies. The Late Sequelae (is our term for it) webpage is going through clearance as a priority document. As of this morning it was in X-clearance but ask our Ops coordinator cc'd here to give the latest status.

In terms of studies, it turns out that CT as well as other parts of response, mostly Epi TF have projects and Beth Unger's Chronic Viral Disease Branch are also running two BAA's.

I can ask our CT folks cc'd here (Pavithra, Jolene) to help list out the projects which are underway or are under consideration.

I also ask these SME's to use some of the material from our website to answer the original question. (b)(5)

(b)(5)

This Friday, there will be cross TF meeting with Epi TF and HSWS TF where we will hear more about their studies.

+HSWS TF leadership Tom, Runa for SA
+CT leadership for SA Sapna, Beth

Thanks
Deblina

S. Deblina Datta, MD FIDSA (she/her)
CAPT, USPHS
On temporary assignment to:
Lead, Clinical Team
Health Systems and Worker Safety Task Force
COVID 19 Emergency Operations Center (EOC)
Centers for Disease Control and Prevention, Atlanta, GA

From: McDonald, Clifford (CDC/DDID/NCEZID/DHQP) <ljm3@cdc.gov>
Sent: Wednesday, October 28, 2020 3:15 PM
To: Datta, Deblina (CDC/DDPHSIS/CGH/GID) <skd2@cdc.gov>; Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Subject: FW: CNBC- SEEKING INFORMATION

Deb,

Just remind us (if you see this in short timeframe), what is status of the long term sequelae webpage? Also, what studies do we have in the works or underway?

L. Clifford McDonald, MD
Chief Medical Officer
CDC COVID-19 Response

From: Skinner, Thomas W. (CDC/DDID/NCEZID/OD) <tws3@cdc.gov>
Sent: Wednesday, October 28, 2020 3:02 PM
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>; McDonald, Clifford (CDC/DDID/NCEZID/DHQP) <ljm3@cdc.gov>; Walke, Henry (CDC/DDID/NCEZID/DPEI) <hfw3@cdc.gov>
Cc: McDonald, Jason (CDC/DDPHSIS/CPR/OD) <gnf0@cdc.gov>; Haynes, Benjamin (CDC/OD/OADC) <fxq2@cdc.gov>
Subject: FW: CNBC- SEEKING INFORMATION

Please see below. I imagine the answer is yes, CDC monitoring but we don't have a lot of details right now? Maybe a paper in the works?

Thoughts? We will clear whatever response.

Thanks,

Tom Skinner
Senior Public Affairs Officer
CDC
404-625-7579

From: Larocco, Lori Ann (NBCUniversal) <LoriAnn.Larocco@nbcuni.com>
Sent: Wednesday, October 28, 2020 2:39 PM
To: Skinner, Thomas W. (CDC/DDID/NCEZID/OD) <tws3@cdc.gov>; Roebuck, Von (CDC/DDNID/NCEH/DLS) <ver5@cdc.gov>
Subject: RE: CNBC- SEEKING INFORMATION

Yes. Here are some of them which I know you are aware of.

- Lesions were particularly evident in the lower lobes, posterior lung fields, and peripheral lung zones. Various combinations of pure GGOs, GGOs plus reticular or interlobular septal thickening, and GGOs plus consolidation were common.
- Myocarditis
- lung opacities "ground glass opacities"
- extreme fatigue and shortness of breath
- taste and smell not returning to normal.
- muscle weakness,
- tingling or numbness in the hands and feet,
- dizziness, confusion, delirium, seizures, and stroke.

Lori Ann
Lori Ann LaRocco
Sr. Editor of Guests, CNBC Business News, Breaking News/BookingCNBC
Author, "Trade War- Containers Don't Lie, Navigating the Bluster", "Opportunity Knocking", "Dynasties of the Sea" Series, "Thriving in the New Economy"
Cell: 201-618-1566

From: Skinner, Thomas W. (CDC/DDID/NCEZID/OD) <tws3@cdc.gov>
Sent: Wednesday, October 28, 2020 2:01 PM
To: Larocco, Lori Ann (NBCUniversal) <LoriAnn.Larocco@nbcuni.com>; Roebuck, Von (CDC/DDNID/NCEH/DLS) <ver5@cdc.gov>
Subject: [EXTERNAL] RE: CNBC- SEEKING INFORMATION

Hi Lori Ann – can you be more specific in regards to what you mean by long term effects?

Thanks

Tom Skinner
Senior Public Affairs Officer
CDC
404-625-7579

From: Larocco, Lori Ann (NBCUniversal) <LoriAnn.Larocco@nbcuni.com>
Sent: Wednesday, October 28, 2020 1:16 PM
To: Skinner, Thomas W. (CDC/DDID/NCEZID/OD) <tws3@cdc.gov>; Roebuck, Von (CDC/DDNID/NCEH/DLS) <ver5@cdc.gov>
Subject: CNBC- SEEKING INFORMATION

Hi,

This is Lori Ann over at CNBC. I wanted to reach out to see if the CDC is monitoring and quantifying how many Americans are suffering long-term effects of COVID-19, the "long haulers". Please let me know.

Thanks, I look forward to hearing from you.

Best,
Lori Ann
Lori Ann LaRocco
Sr. Editor of Guests, CNBC Business News, Breaking News/Booking
Author, "Trade War- Containers Don't Lie, Navigating the Bluster", "Opportunity Knocking", "Dynasties of the Sea" Series, "Thriving in the New Economy"
Phone: 201-735-3044 | Cell: 201-618-1566 | @loriannlarocco

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COVID-19 Response
Incident Manager Meeting

Monday, 26 October 2020

Day 295 of Response, Day 280 of IMS Activation

(Click Here to Bring up the Time Tracker Application)

Priorities of the Week, Oct 25th-Oct 31st

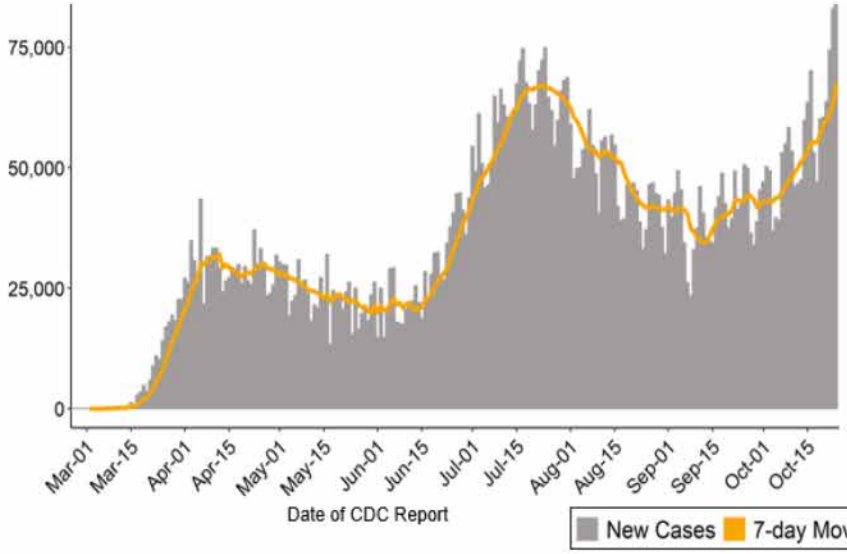
- Present refined models to ACIP to inform which initial populations to prioritize
- Launch crowd survey (parent attitudes for alternative quarantine approaches)
- Roll out post-CRAFT "CORE" process to provide TA and field engagements
- Provide TA to jurisdictions to report sewage surveillance data into DCIPHER
- Implement communication plan to promote COVID-19 mitigation strategies
- Generate data for antigen test performance in asymptomatic persons
- Post late sequelae webpages
- Participate in US Black Chamber webinar to discuss prevention activities
- Review jurisdictional & federal entity vaccination plans
- Deploy staff to support states and local jurisdictions
- Disseminate key findings through *MMWR*, CDC.gov, and partner call

Case Surveillance

Daily Change in COVID-19 Cases and Deaths

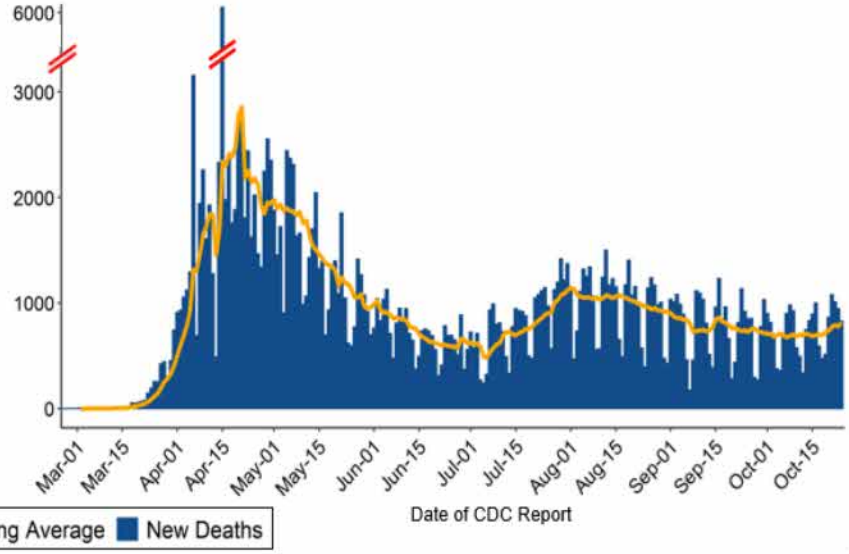
Daily change in COVID-19 case counts

As of October 24, N=8,553,827 (new: 83,851)
67,477 average over past 7 days vs. 55,232 over 7 previous days (+22%)



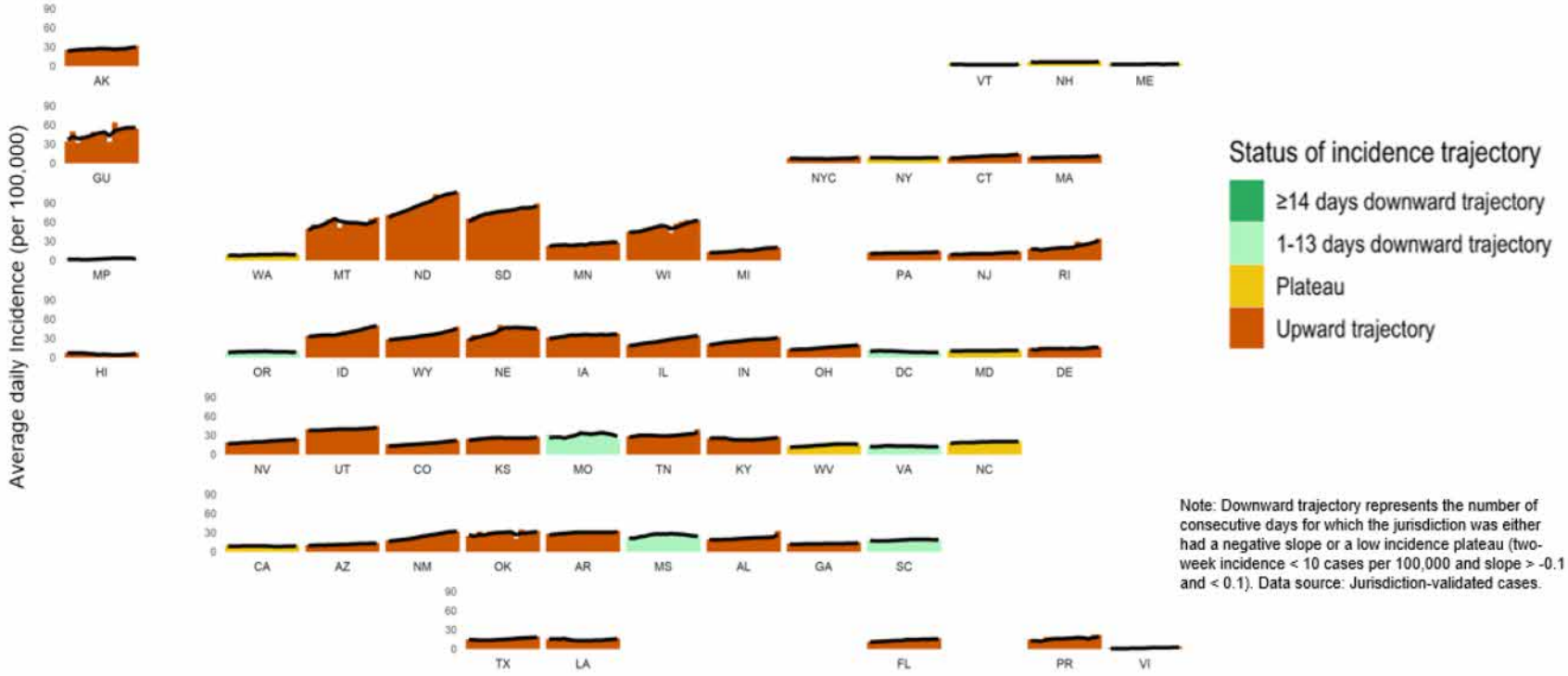
Daily change in COVID-19 death counts

As of October 24, N=224,221 (new: 828)
816 average over past 7 days vs. 700 over 7 previous days (+17%)



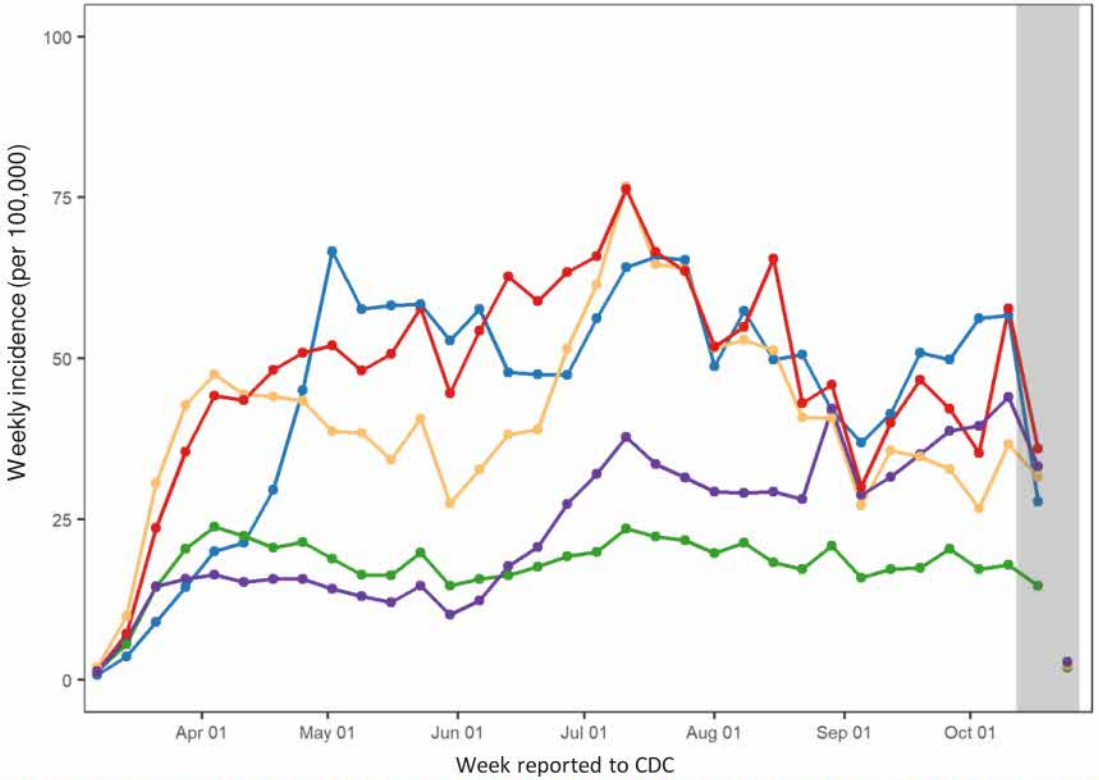
New Cases | 7-day Moving Average | New Deaths

COVID-19 Incidence, by Jurisdiction, Oct 10 – 23, 2020



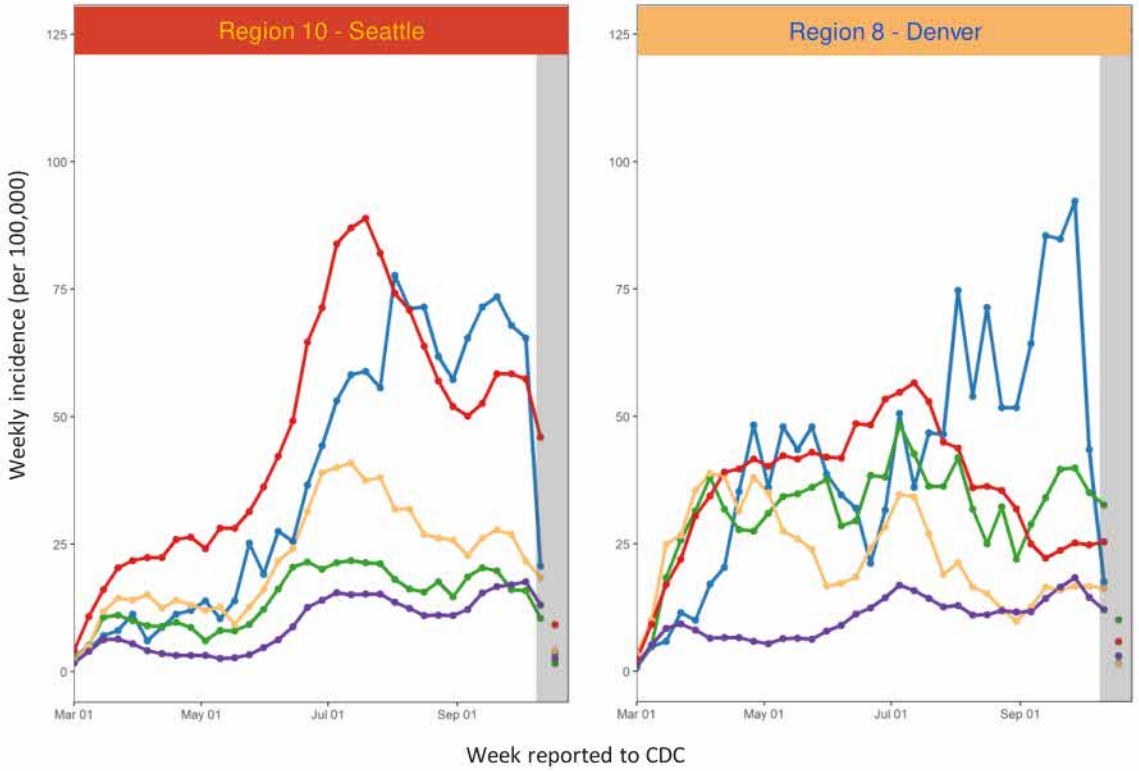
Note: Downward trajectory represents the number of consecutive days for which the jurisdiction was either had a negative slope or a low incidence plateau (two-week incidence < 10 cases per 100,000 and slope > -0.1 and < 0.1). Data source: Jurisdiction-validated cases.

COVID-19 Incidence by Race/Ethnicity — United States, March 1–October 24, 2020



Note: Data are provisional and subject to change. Reporting for some states is incomplete. Race/ethnicity data is missing for 48% of COVID-19 case reports. Data displayed in the gray shadow box are subject to change due a lag in reporting.

COVID-19 Incidence by Race/Ethnicity — HHS Regions 10 and 8, Mar 1–Oct 24

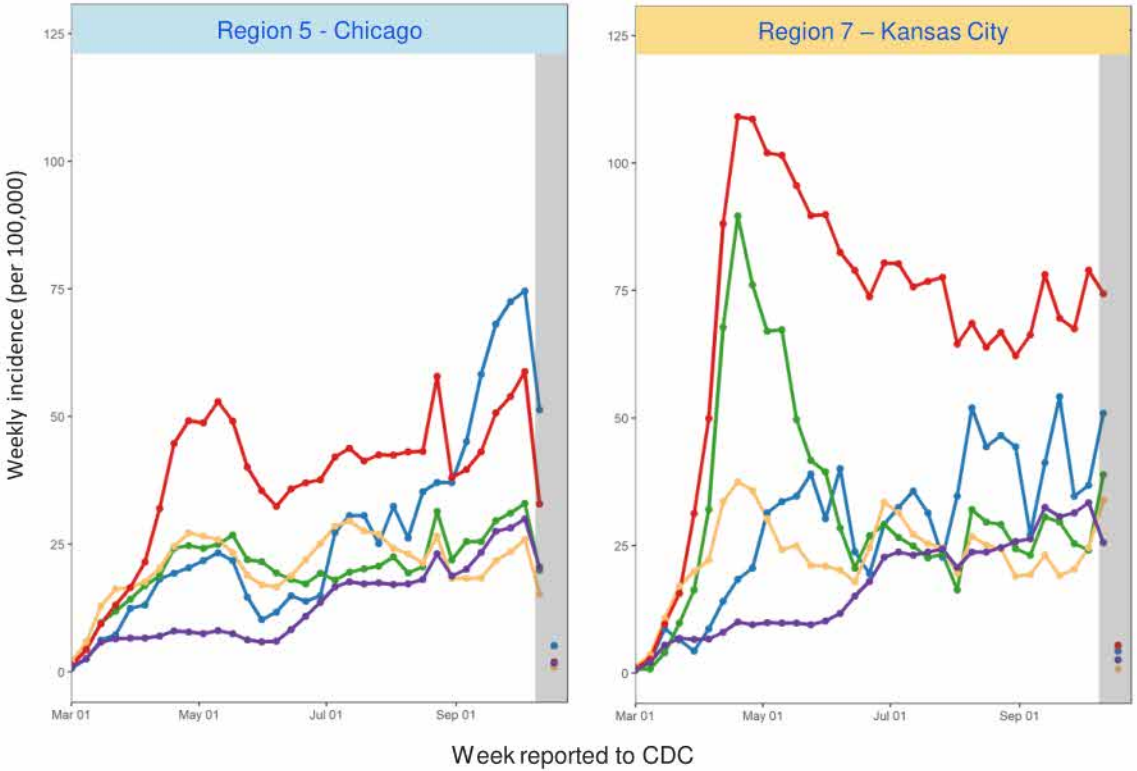


Race/Ethnicity

- AI/AN, NH
- Asian/PI, NH
- Black, NH
- Hispanic
- White, NH

Note: Data are provisional and subject to change. Reporting for some states is incomplete. Race/ethnicity data is missing for 48% of COVID-19 case reports. Data displayed in the gray shadow box are subject to change due a lag in reporting.

COVID-19 Incidence by Race/Ethnicity — HHS Regions 5 and 7, Mar 1–Oct 24



Note: Data are provisional and subject to change. Reporting for some states is incomplete. Race/ethnicity data is missing for 48% of COVID-19 case reports. Data displayed in the gray shadow box are subject to change due a lag in reporting.

Case Surveillance Summary

- **Increasing COVID-19 case incidence**
  - 40 (71%) jurisdictions in upward trajectory
  - 9 (16%) jurisdictions in plateau
  - 7 (13%) jurisdictions in downward trajectory
- **Worsening**
  - 3 (AR, GA, HI) → Plateau to upward trajectory
  - 1 (CA) → Downward trajectory to plateau
- **Improving**
  - 1 (WV) → Upward trajectory to plateau
  - 1 (SC) → Plateau to downward trajectory
  - 1 (MP) → Upward trajectory to downward trajectory
- **COVID-19 incidence remains high among Hispanics in most of the regions**

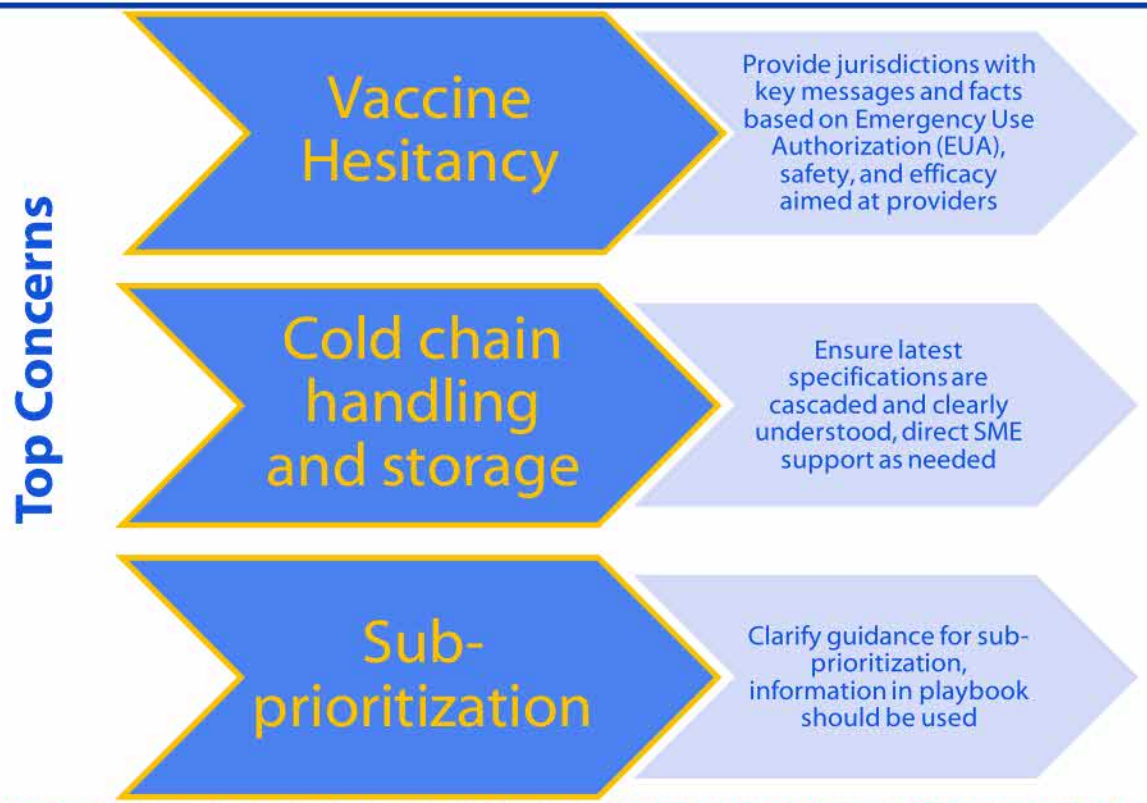
Vaccine

Input from State Health Officials

Conversations with 30 State Health Officials (SHO) over past 2 weeks in coordination with ASTHO

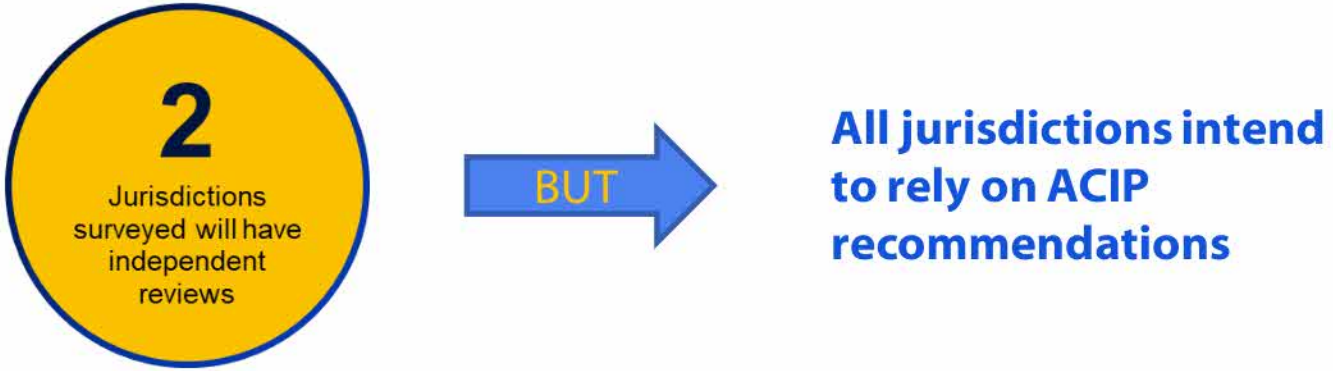
- What are you most **concerned** about regarding the COVID-19 vaccine roll out?
- What have you done already to engage the healthcare community?
- What are your biggest **obstacles** to being ready for Phase 1?
- Are you getting reports of healthcare providers who are hesitant to provide vaccine?
- Is your jurisdiction developing an independent review body of the vaccines?
- What concerns do you have about prioritizing types of Phase 1 health care providers when vaccine is in limited supply?
- Once you receive vaccine, who makes the final decision on how it's allocated?
- What types of communication materials would you be interested in having available?
- What concerns do you have about administering a vaccine authorized under an EUA?
- Have you begun developing any of your own communication materials?

Preliminary Results and Next Steps



Surveys with State Health Officials (SHO)

- Jurisdictions were asked, **"Is your jurisdiction developing an independent review body of the vaccines?"**



Y

Requested Vaccine Communication Materials

80% of jurisdictions consulted have kicked off communications development; all surveyed would like more CDC-led collateral and key messages

Healthcare providers

- Vaccine factsheets and one-pagers
- Packaged guidance, videos, and graphics
- Vaccine safety profiles from clinical trials
- Standard survey to assess provider vaccine hesitancy

General Public

- Consistent, basic CDC key messages
- Social media kits (i.e., packaged tweets, graphics, branding)
- Succinct policy statements on vaccine planning
- Communication lines on vaccine development process and clinical trials

Epidemiology

Projects Funded to Assess Natural History and Outcomes of COVID-19: Cohorts

Institution (sites)	Cohort (planned size*)	Viral shedding	Household transmission	Immune response	Clinical sequelae	Functional sequelae
University of Washington (1 health system)	**Children SARS-CoV-2+** (n~50); **Sera collected** (transplant recipients, residual sera)			✓	✓	✓
Tulane (2 hospitals)	**Inpatients SARS-CoV-2+** (n~500); **Convalescent clinic attendees** (n~200)	✓		✓	✓	✓
UCSF (local public health surveillance)	**Households with positive case** (n~75; and household contacts)	✓	✓	✓		
Rush, Yale, UW, Other (8 health systems)	**Health care users SARS-CoV-2+** (n~3,600); **SARS-CoV-2- controls** (n~1,200)				✓	✓
JHU Center for American Indian Health (local health system)	**Households with positive case** (n~40; and household contacts)	✓	✓	✓	✓	✓
Vysnova Partners (6 health systems)	**Health care users** (n~100,000 symptom log + health record data; n~30,000 serology subgroup)			✓	✓	✓

**Some analyses limited to subgroups*

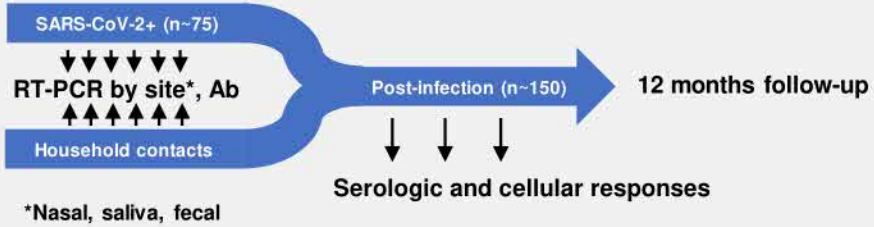
Projects Funded to Assess Natural History and Outcomes of COVID-19: Cohort timelines

Institution (sites)	**Status**	**Enrolment began (or expected to begin)**	**Proposed period of enrolment**	**Proposed duration of participant follow up**	**Participant follow up expected to end**
University of Washington	Enrolling	August 2020	Continuous	24 months	July 2022
Tulane	Enrolling	August 2020	6 months	12 months	February 2022
UCSF	Enrolling	October 2020	6 months	12 months	April 2022
Rush, Yale, UW, Other	Planning	November 2020	6 months	18 months (possible additional year)	November 2022 (or 2023)
JHU Center for American Indian Health	Planning	November 2020	6-8 months	12 months	July 2022
Vysnova Partners	Planning	January 2021	Continuous	6 months (possible additional year)	June 2021 (or 2022)

Y

Projects Funded to Assess Natural History and Outcomes of COVID-19: Household Cohorts

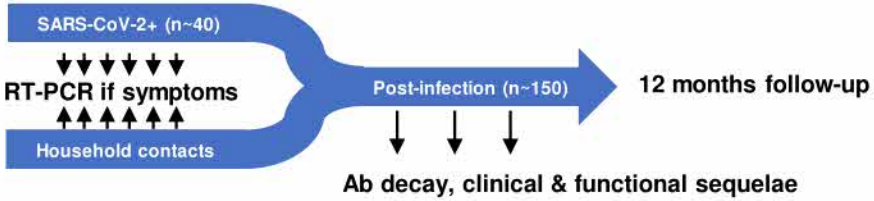
University of California, San Francisco



Planned outcomes

- Risk factors for infection and viral shedding
- Secondary transmission within households
- Timing of seroconversion and immune response

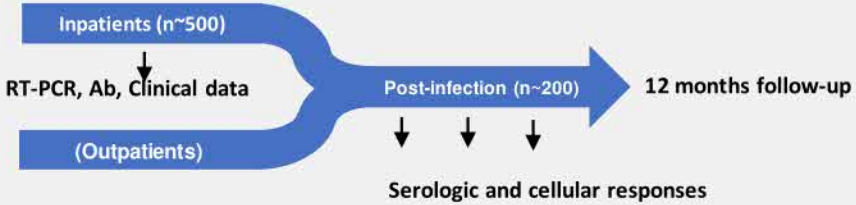
Johns Hopkins Center for American Indian Health



- Transmission dynamics within households
- Clinical complications, long-term sequelae
- Risk factors associated with sequelae
- Antibody persistence following infection

Projects Funded to Assess Natural History and Outcomes of COVID-19: Virologic and Immune Response

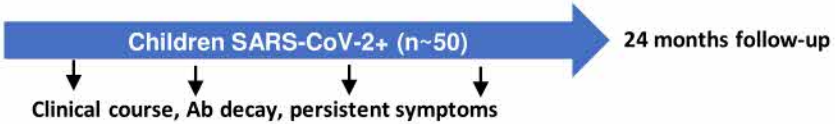
Tulane (2 hospitals)



Planned outcomes

- Risk of morbidity and mortality in Louisiana
- Temporal comparison of viral shedding (multiple sites), cytokine production, sequencing, antibody response

University of Washington (Seattle Children's Hospital)



+ serosurvey of outpatients and inpatients (n~8000); transplant recipients (n~100)

- Describe clinical course of SARS-CoV-2 infection among children
- Describe pediatric immunity overtime
- Measure seroprevalence in children

Y

Projects Funded to Assess Natural History and Outcomes of COVID-19: Health Care User Cohorts

Vysnova (6 health systems)

Daily symptom log linked to electronic health data

Health system users (n~100,000) → 6 months follow-up

↓ ↓ ↓ ↓ ↓ ↓

Serology in subgroup (n~30,000)

Planned outcomes

- Incidence and risk factors for SARS-CoV-2 infection in the population
- Characteristics, clinical sequelae and antibody persistence following seroconversion

Rush Cohort (8 health systems)

Includes patients from both outpatient and inpatient settings, diverse communities and backgrounds

Inpatients, outpatients, ED, controls (n~4,800) → 18 months follow-up

↓ ↓ ↓ ↓ ↓ ↓

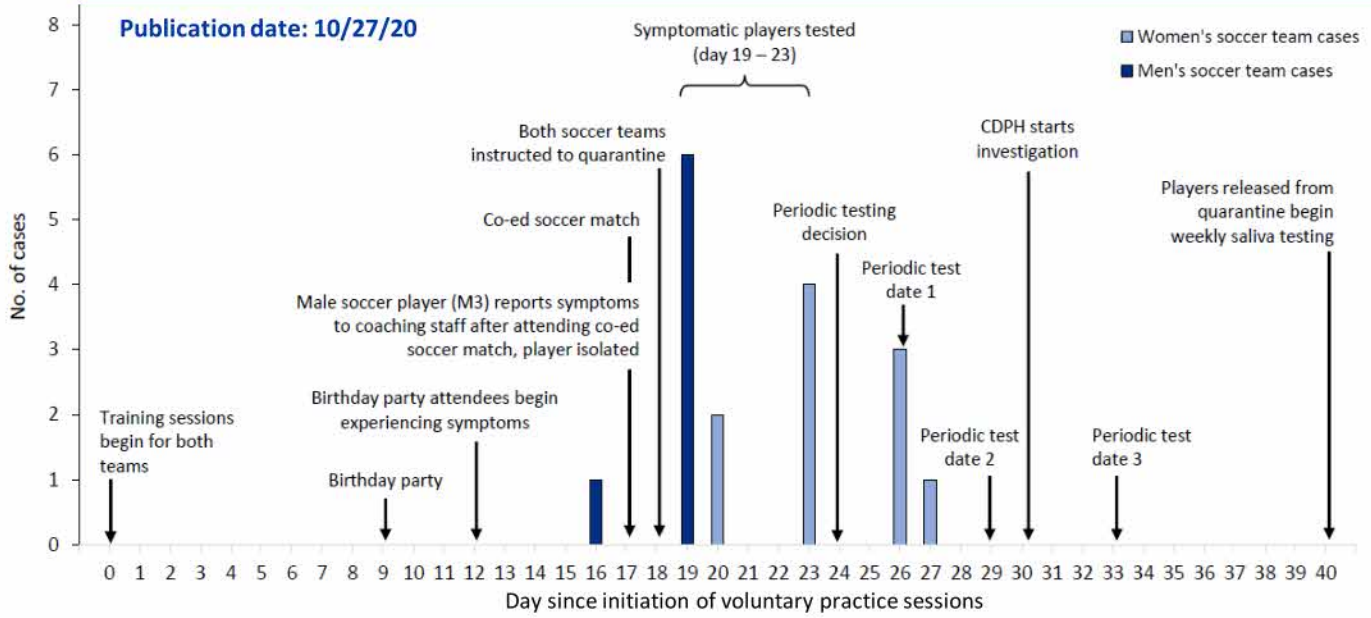
Detailed clinical data, validated surveys

- Clinical course following SARS-CoV-2 infection
- Longer term clinical sequelae and validated assessment of neurocognitive outcomes

STLT Support:
Health Department Section

R

MMWR: COVID-19 Outbreak Among a University's Men's and Women's Soccer Teams —Chicago, Illinois, July–August 2020



Case-Control investigation involved…

45 students **18** social gatherings **17** cases

There is a need for improved strategies to promote mask use and social distancing among college-age adults.

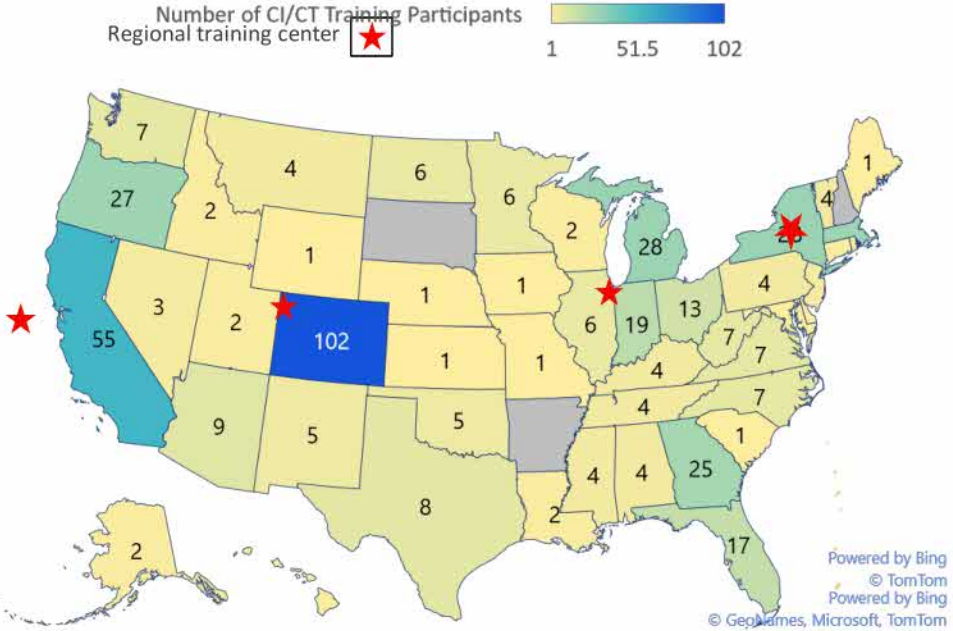
Periodic repeat testing could help identify asymptomatic infections and prevent outbreaks among groups with frequent close contact on and off campus.

STLT Support:
Contact Tracing & Innovation Section

Y

National Network of Disease Intervention Training Center (NNDITC): Case Investigator and Contact Tracing Training Update

Total Trainees by State that Participated in the NNDITC Training for Skills-based Case Investigators and Contact Tracing (CI/CT)



Knowledge-based Training

(ASTHO Prerequisite Course – launched April 2020)

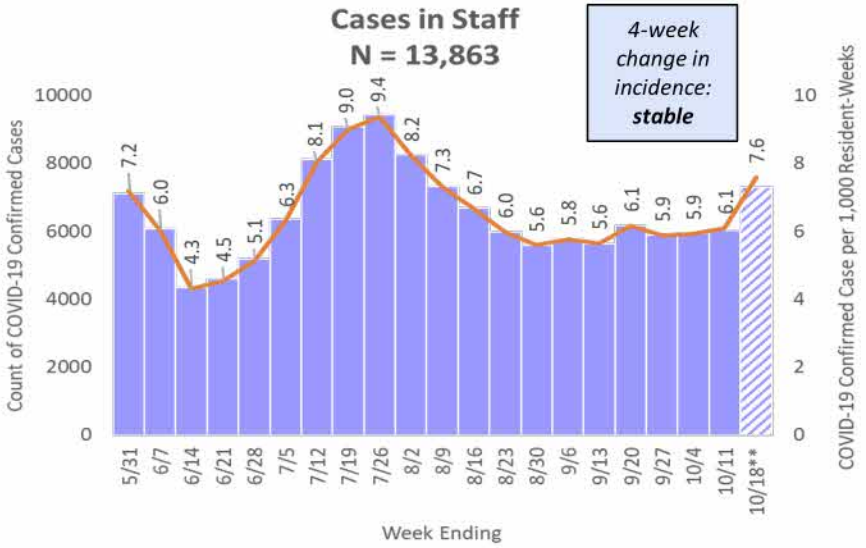
Making Contact: A Training for COVID-19 Contact Tracers– 75,000+ trained

Skills-based Training

Cumulative Number of Participants for the Skills-based CI/CT Training as of Oct. 9 2020

HSWS: IPC/SNF

COVID-19 Cases and Deaths Among Staff in Skilled Nursing Facilities, by CCN, Inferred Data



**Number of facilities reporting may vary from week to week*

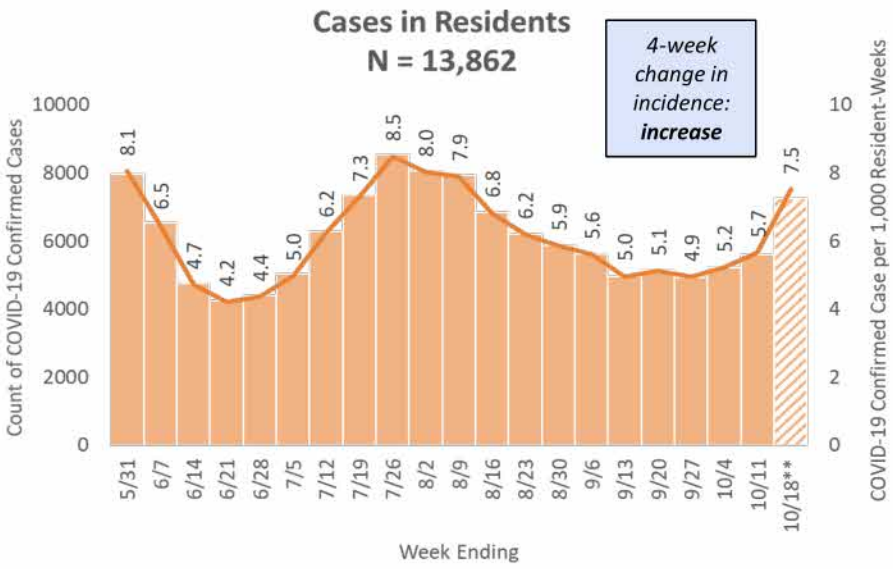
*** Pattern-fill represents potential incomplete data due to reporting lag from facilities*

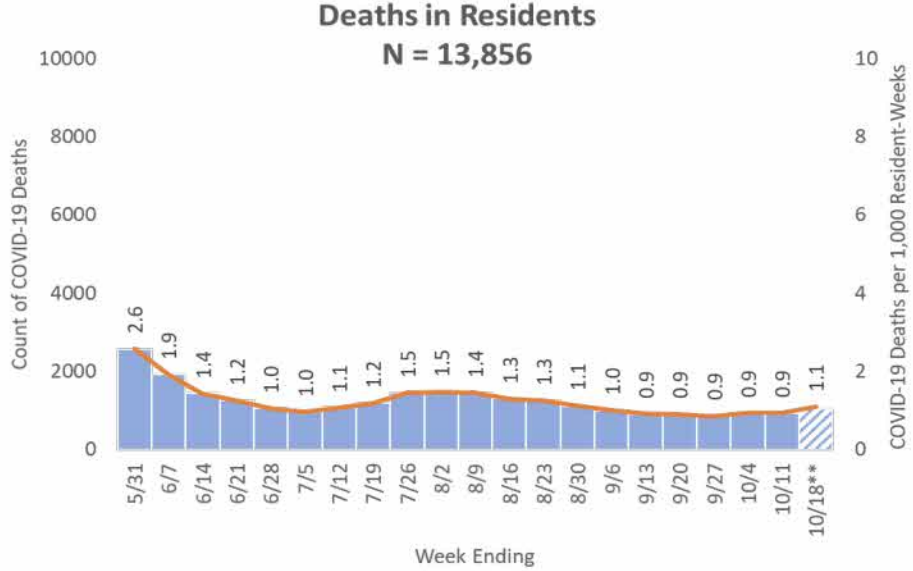
Inferred Data: For the purpose of best epidemiological understanding, data that fail quality checks or appear inconsistent with surveillance protocols are assigned a value based on their patterns of data-entry or excluded from

4-Week Change Definition (apply to last 4 weeks)
Increase: meet both: (1) rate for week 4 was greater than week 1; (2) at least two out of three paired consecutive rate comparisons showed a significant increase.
Decrease: meet both: (1) rate for week 4 was lower than week 1; (2) at least two out of three paired consecutive rates comparisons showed a significant decrease.
Note: Mid-p (1-tailed) method was used to test a statistical significance

Y

COVID-19 Cases and Deaths Among Residents in Skilled Nursing Facilities, by CCN, Inferred Data





**Number of facilities reporting may vary from week to week*

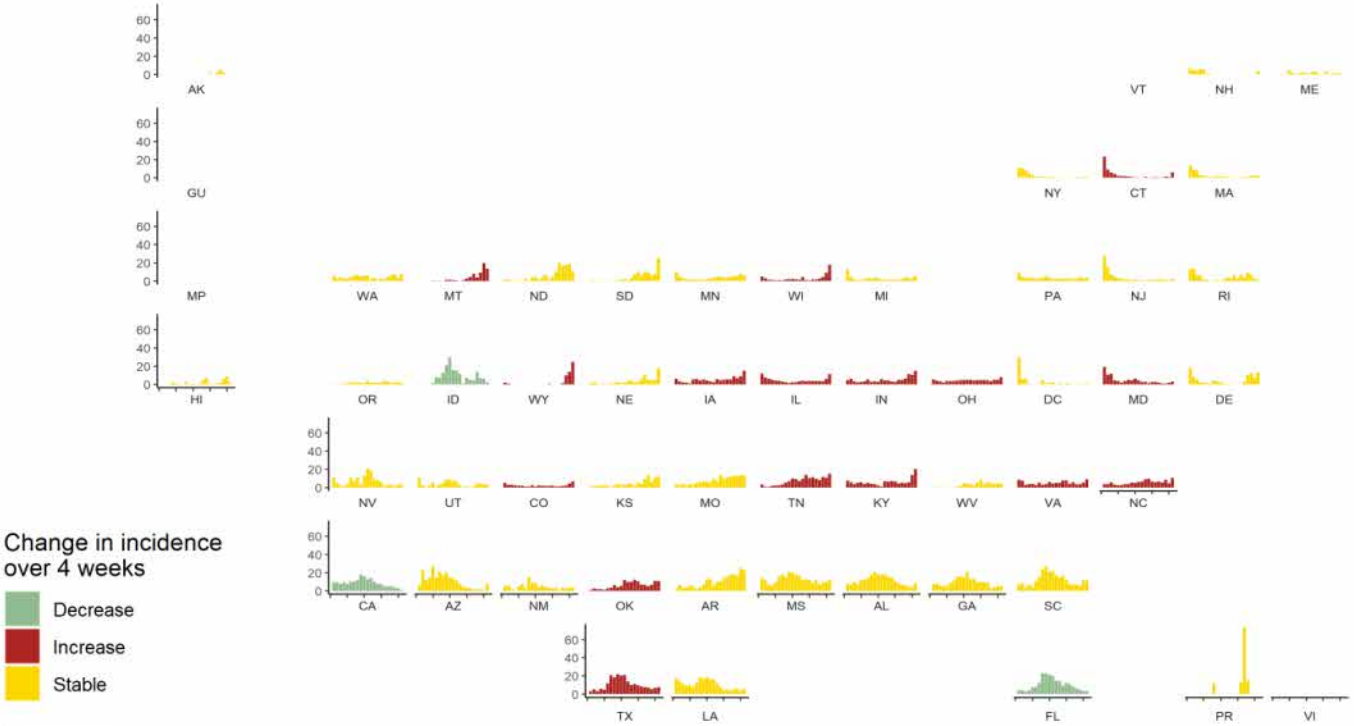
*** Pattern-fill represents potential incomplete data due to reporting lag from facilities*

Inferred Data: For the purpose of best epidemiological understanding, data that fail quality checks or appear inconsistent with surveillance protocols are assigned a value based on their patterns of data-entry or excluded from analysis

4-Week Change Definition (apply to last 4 weeks)
Increase: meet both: (1) rate for week 4 was greater than week 1; (2) at least two out of three paired consecutive rate comparisons showed a significant increase.
Decrease: meet both: (1) rate for week 4 was lower than week 1; (2) at least two out of three paired consecutive rates comparisons showed a significant decrease.
Note: Mid-p (1-tailed) method was used to test a statistical significance

NHSN NATIONAL HEALTHCARE SAFETY NETWORK

Change in Incidence Rates of Confirmed COVID-19 Cases in the Past 4 Weeks among Residents in Skilled Nursing Facilities, Inferred Data



Change in incidence over 4 weeks

- Decrease
- Increase
- Stable

Definition (apply to the last 4 weeks)

Increase: meet both: (1) rate for week 4 was greater than week 1; (2) at least two out of three paired consecutive rate comparisons showed a significant increase.

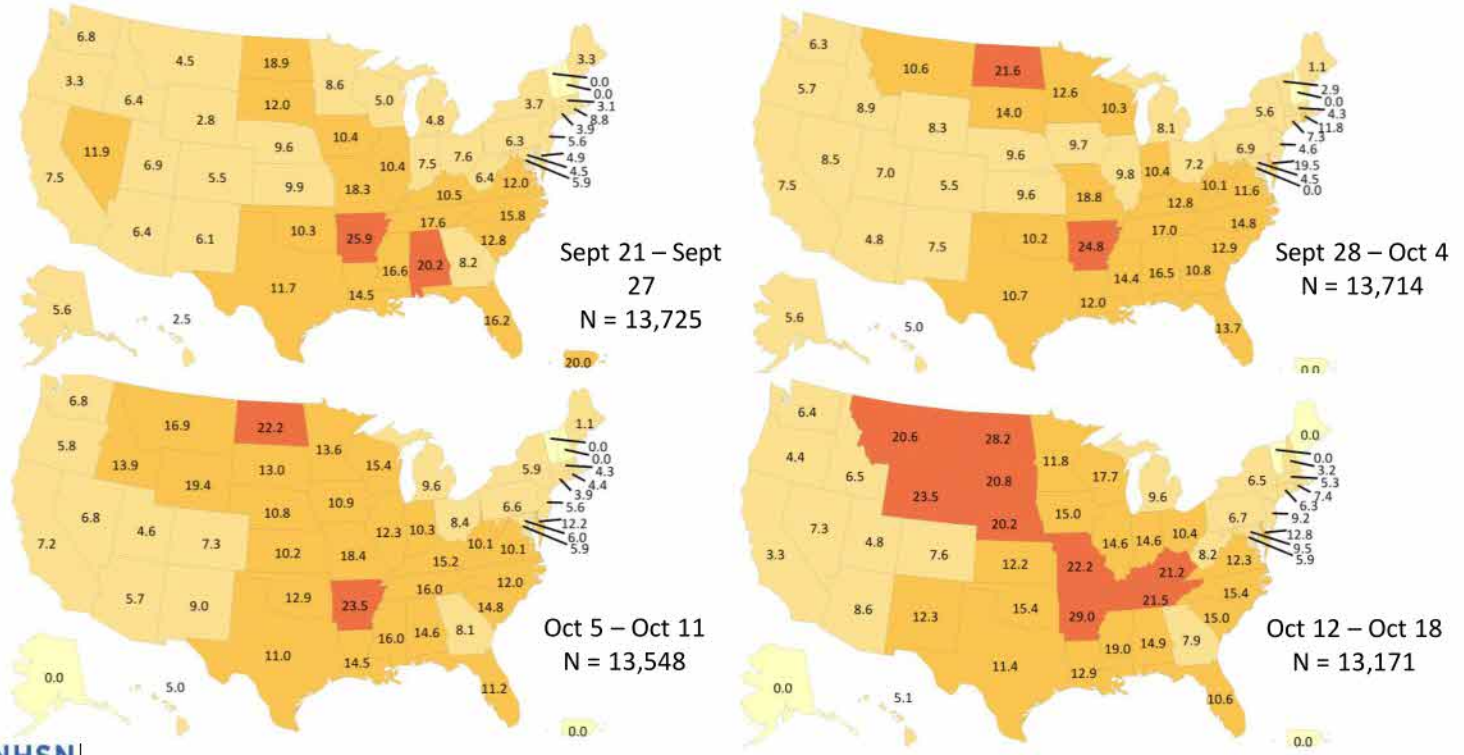
Decrease: meet both: (1) rate for week 4 was lower than week 1; (2) at least two out of three paired consecutive rates comparisons showed a significant decrease.

Note: Mid-p (1-tailed) method was used to test a statistical significance

Inferred Data: For the purpose of best epidemiological understanding, data that fail quality checks or appear inconsistent with surveillance protocols are assigned a value based on their patterns of data-entry or excluded from analysis.

NHSN

Percent of Skilled Nursing Facilities with ≥1 Confirmed COVID-19 Cases among Residents, by CCN, Inferred Data



Inferred Data: For the purpose of best epidemiological understanding, data that fail quality checks or appear inconsistent with surveillance protocols are assigned a value based on their patterns of data-entry or excluded from analysis.

NHSN NATIONAL HEALTHCARE SAFETY NETWORK

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Summary of Oct 12 – Oct 18, 2020 NHSN Nursing Home Data

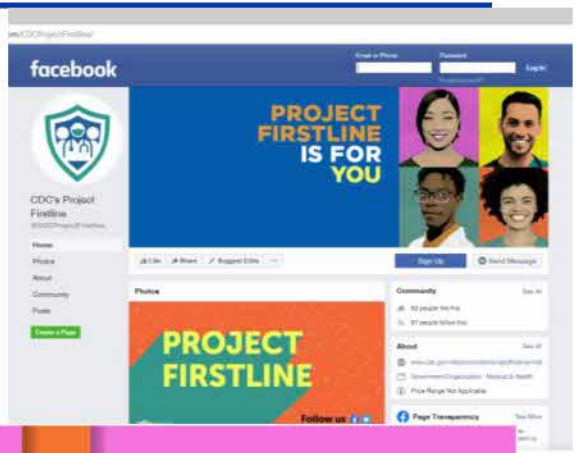
- Rates of cases in residents and in staff per 1,000 resident-weeks are increasing
- Resident cases are increasing over the past 4 weeks in 16 states
- 20-30% of SNFs in several Midwestern states reported at least 1 confirmed resident case, more than in recent weeks

HSWS: IPC

G

Project Firstline: CDC's National Training Collaborative for Healthcare Infection Control

- Infection control training targets all frontline healthcare workers
  - Strong partner engagement
  - Informed by direct healthcare personnel input
  - Curriculum addresses the reasons behind practices
- Program launch this week
  - Incl. Partner webinars, social media, press release
- First modules in November
  - Videos + supporting materials



HSWS: WSH

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Optimizing PPE Supplies

https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html

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Reports of Healthcare Personnel Use of Isolation Gowns

- Through partner calls and reports of outbreaks of multi-drug resistant organisms, CDC became aware of concerning practices regarding the use of isolation gowns
  - Use of double or triple gowns by HCP
  - Re-use of disposable gowns
  - Extended use of gowns even in situations of increasing supply

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Updates to Strategies for Optimizing the Supply of Isolation Gowns

- Added considerations for returning to conventional capacity practices
- Moved use of reusable (i.e., washable or cloth) isolation gowns to conventional capacity strategies
- Added a recommendation that isolation gowns, as part of Contact Precautions, should continue to be used for patients colonized or infected with emerging highly-resistant organisms including
  - Candida auris
  - Carbapenem-resistant Enterobacterales, Pseudomonas, and Acinetobacter
  - Pan-resistant organisms
- Added cautionary statements about the re-use of gowns on risks to HCP and patient safety

For questions, contact eocwsh@cdc.gov

Policy

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Policy

Congressional Briefings

- 10/27 – Appropriations Committee, Labor Health and Human Services Sub-Committee 4 corners briefing on vaccine manufacturing and distribution. Amanda Cohn and Anita Patel to discuss CDC distribution. Alison Kelly will address questions related to current or future budget issues.
- TBD – Representative Ed Case (D-HI) – requests briefing on options for HI to require pre-boarding COVID testing for all direct flights

Partnership

- Today: Healthy Happy Holidays: Fall Travel and Gathering Guidance

JCC Update

Chief of Staff

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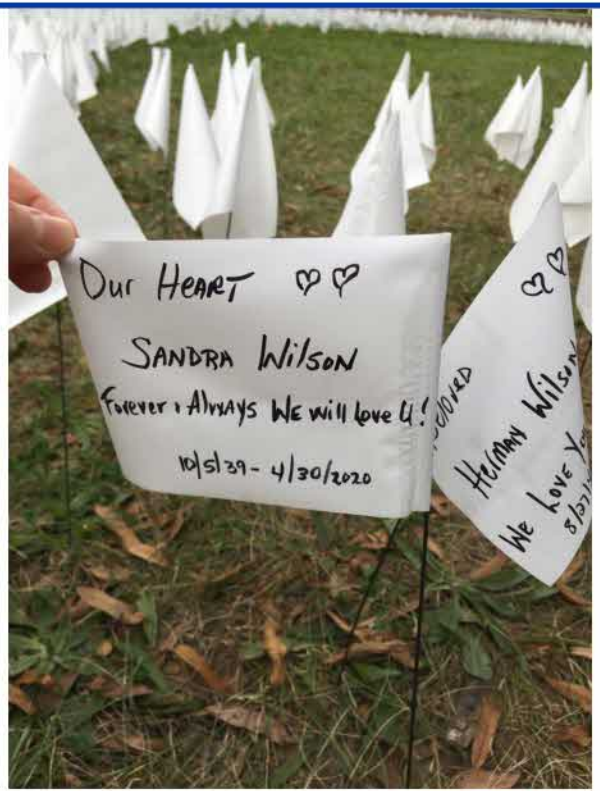
Suzanne Firstenberg Commemoration



Thanks to Athalia Christie

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G – **Green = public information/okay for wider distribution**. – e.g., All info is available on CDC website or is public

Questions/Comments

For more information, contact CDC Emergency Operations Center
770-488-7100
www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Backup Slides

Incident Manager

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Agenda

- Incident Manager
- Case Surveillance
- Analytics
- NHSN Data
- Modeling
- Epidemiology
- Laboratory
- STLT Support
- Health Systems and Worker Safety
- Food Systems
- Community Interventions and Critical Populations
- One Health
- Global/International
- Chief Health Equity Officer
- Associate Director for Science
- Chief Medical Officer
- Communication
- Policy
- Chief of Staff
- JCC

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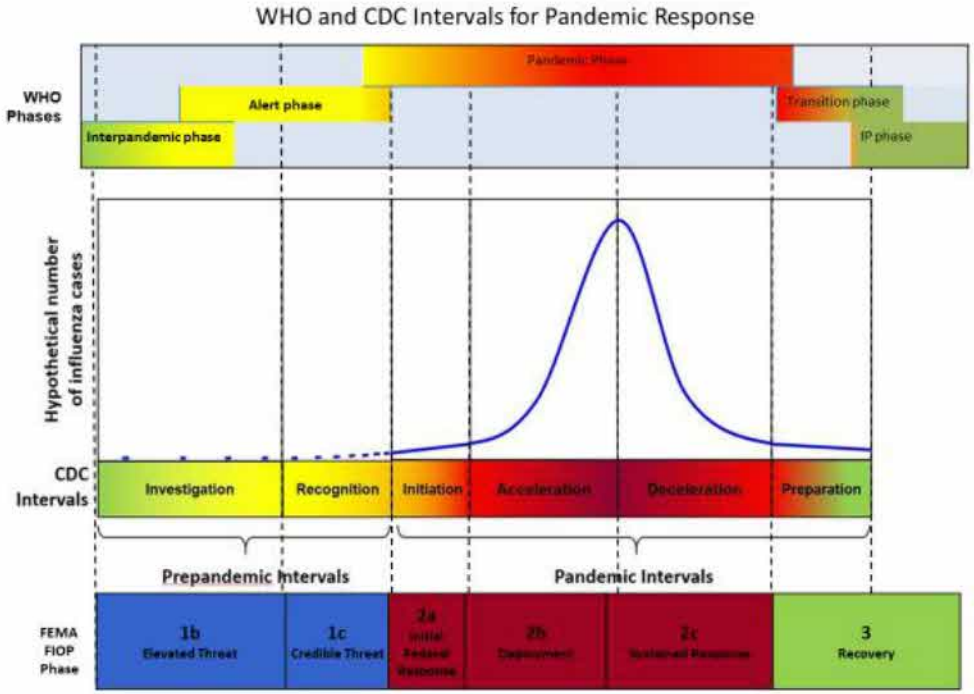
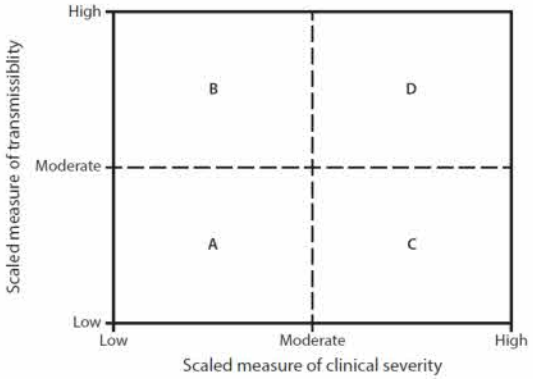
Incident Manager Priorities



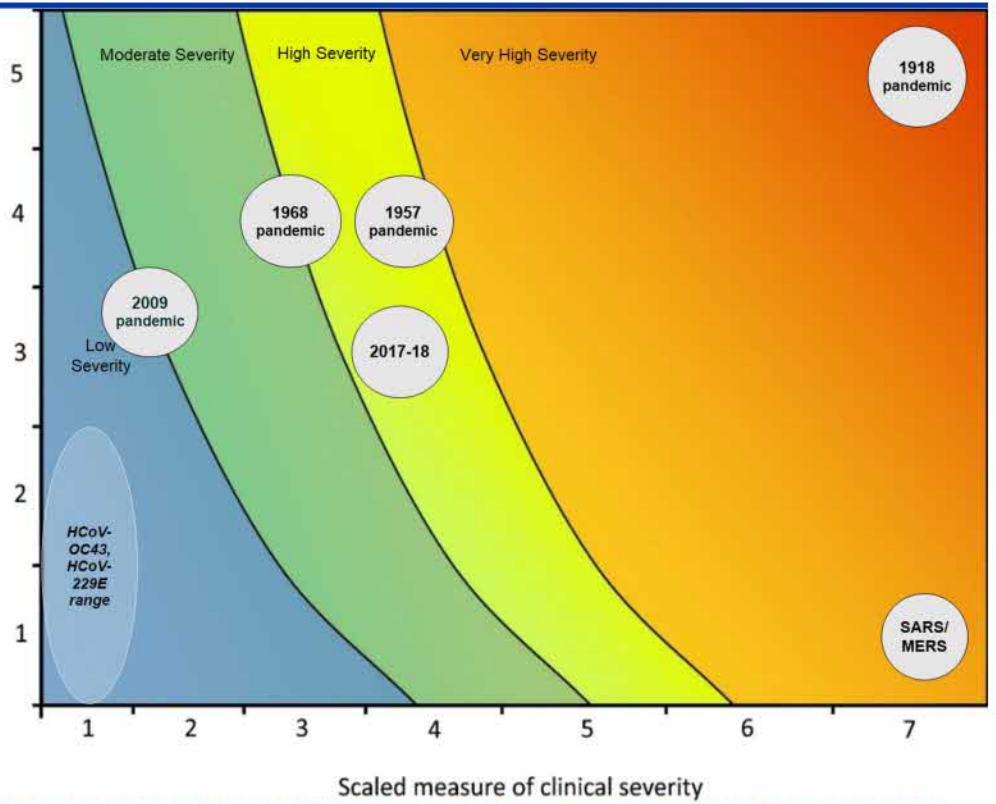
Adapted from: MMWR Recomm Rep. 2014 Sep 26;63(RR-06):1-18. **Updated preparedness and response framework for influenza pandemics.** Holloway R et al

Incident Manager Priorities

FIGURE 3. Pandemic Severity Assessment Framework for the initial assessment of the potential impact of an influenza pandemic



Source: Reed C, Biggerstaff M, Finelli L, et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 2013;19:85–91.



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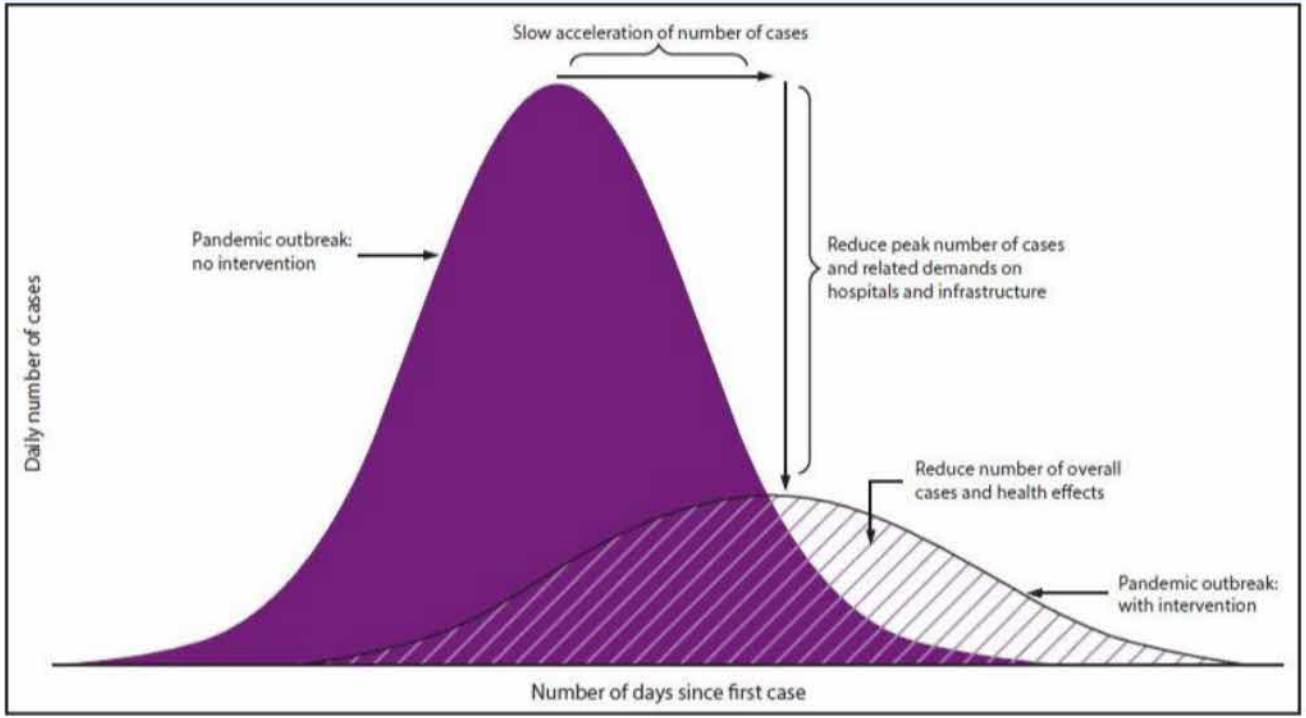
Incident Manager Priorities



Source: Adapted from: CDC. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States—early, targeted, layered use of nonpharmaceutical interventions. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. https://stacks.cdc.gov/view/cdc/11425.

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CDC Response Mission Statement

- CDC will implement strategies to slow the introduction and impact of COVID-19 in the United States. CDC will coordinate with international and domestic partners to provide clinical and infection control guidance and implement other methods to mitigate the impact of this virus.

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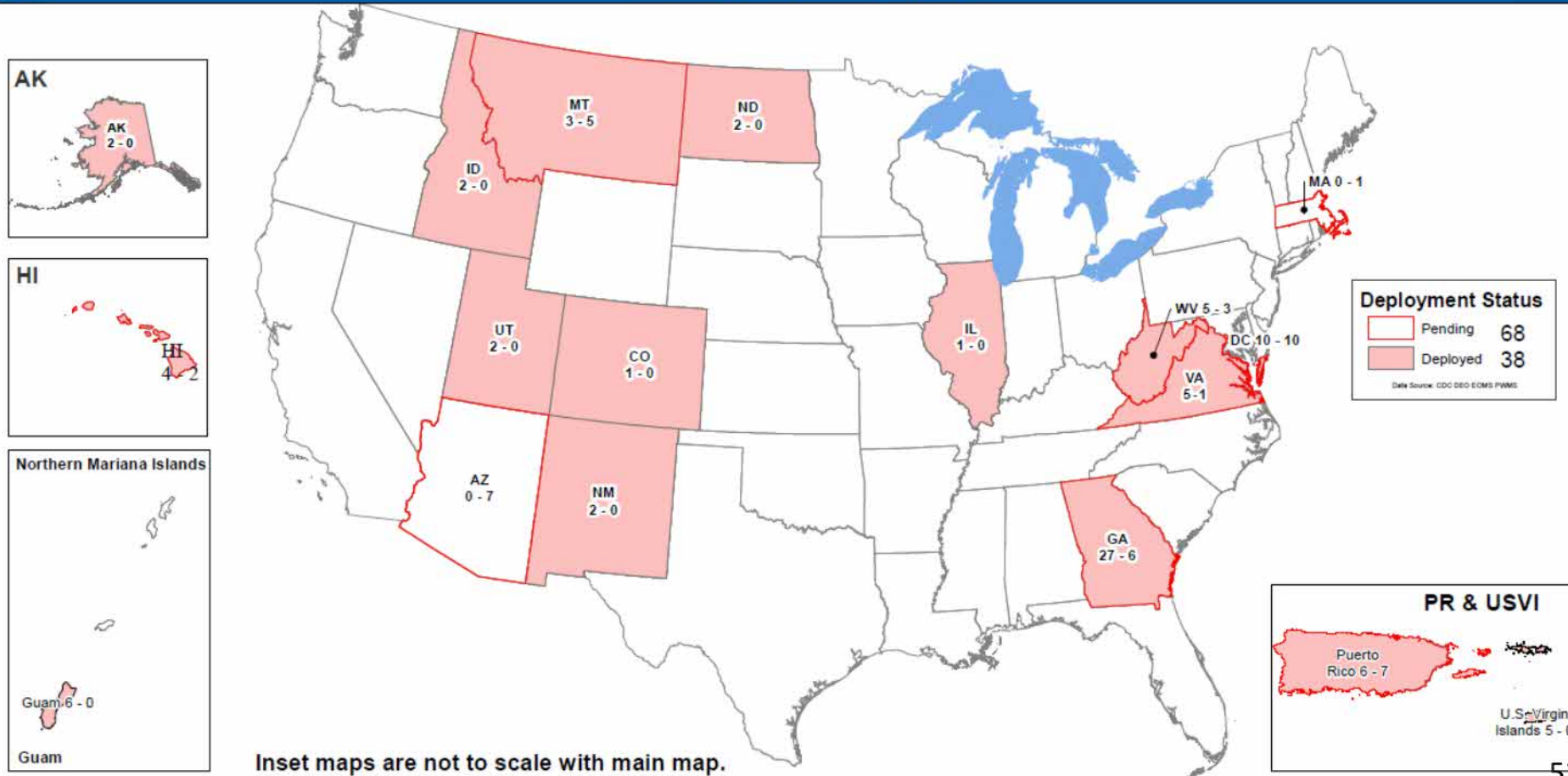
COVID-19 Response: CDC US Deployments

Monday, October 26, 2020

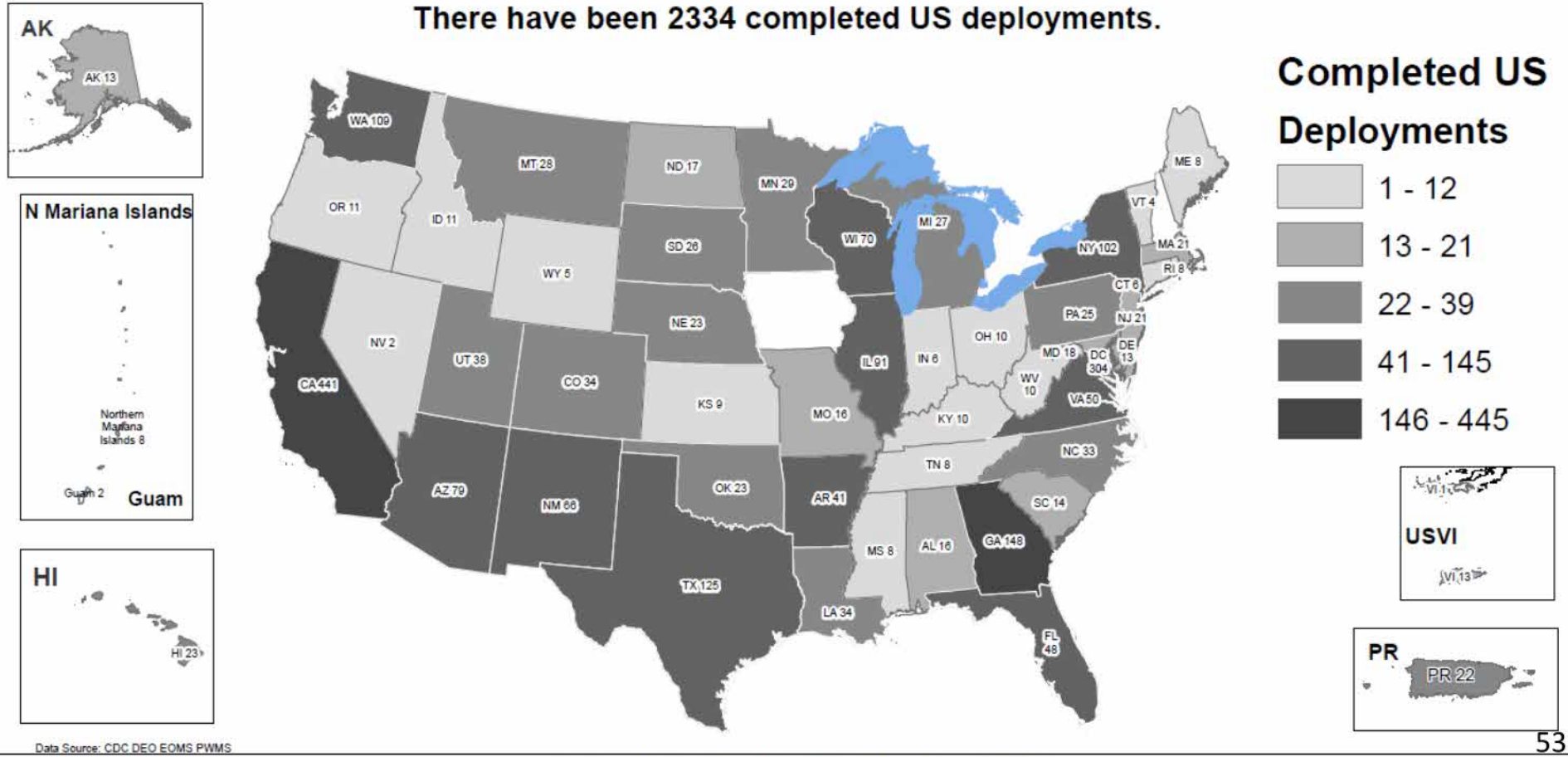


COVID-19 Response: CDC Completed US Deployments by State / Territory

Monday, October 26, 2020

SITUATIONAL AWARENESS GIS

There have been 2334 completed US deployments.



Data Source: CDC DEO EOMS PWMS

COVID-19 Response: CDC Deployments by Country

Monday, October 26, 2020

SITUATION AWARENESS GIS

There are currently 68 deployed and 38 pending.

COVID-19 Response: CDC Completed Global Deployments

Monday, October 26, 2020

SITUATION AWARENESS GIS

There have been 2368 completed global deployments.

Source: PWMS

From: Thornburg, Natalie (CDC/DDID/NCIRD/DVD)
Sent: Fri, 21 Aug 2020 12:42:17 +0000
To: Goldsmith, Cynthia (CDC/DDID/NCEZID/DHCPP)
Cc: Limbago, Brandi (CDC/DDID/NCIRD/OD); Langley, Gayle E. (CDC/DDID/NCEZID/DFWED); Campbell, Angela J. P. (CDC/DDID/NCIRD/DVD); Schuh, Amy (CDC/DDID/NCEZID/DHCPP); Hall, Aron (CDC/DDID/NCIRD/DVD); Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Subject: opinion on (b)(5)
Attachments: Lancet 20200821 MIS-C.pdf

Cynthia,
I imagine you've already seen this paper, but if not I've attached. Can you tell me your opinion (b)(5)
(b)(5)

Natalie J. Thornburg, Ph.D.
Respiratory virus immunology team lead
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases

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SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome

Marisa Dolhnikoff, Juliana Ferreira Ferranti*, Renata Aparecida de Almeida Monteiro, Amaro Nunes Duarte-Neto, Michele Soares Gomes-Gouvêa, Natália Viu Degaspare, Artur Figueiredo Delgado, Carolina Montanari Fiorita, Gabriela Nunes Leal, Regina Maria Rodrigues, Khallil Taverna Chaim, João Renato Rebello Pinho, Magda Carneiro-Sampaio, Thais Mauad, Luiz Fernando Ferraz da Silva, Werther Brunow de Carvalho, Paulo Hilario Nascimento Saldiva, Elia Garcia Caldini*

We report the case of an 11-year-old child with multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 who developed cardiac failure and died after 1 day of admission to hospital for treatment. An otherwise healthy female of African descent, the patient was admitted to the paediatric intensive care unit (ICU) with cardiovascular shock and persistent fever. Her initial symptoms were fever for 7 days, odynophagia, myalgia, and abdominal pain. On admission to the ICU, the patient presented with respiratory distress, comprising tachypnoea (respiratory rate 70 breaths per min) and hypoxia, and signs of congestive heart failure, including jugular vein distention, crackles at the base of the lungs, displaced liver, hypotension (blood pressure 80/36 mm Hg), tachycardia (134 beats per min [bpm]), and cold extremities with filiform pulses. Non-exudative conjunctivitis and cracked lips were present on physical examination. The patient was promptly intubated and antibiotic treatment was started with ceftriaxone and azithromycin. Peripheral epinephrine was initiated in the emergency room before the patient was moved to paediatric ICU.

A point-of-care echocardiogram showed diffuse left-ventricular hypokinesia with no segmental wall motion abnormalities. Left-ventricular ejection fraction was

	0 h	7 h	14 h	17 h	24 h	Normal range
Haemoglobin, g/dL	10·0	11·8	12·1	11·4	11·0	12·7–14·7
Hematocrit, %	28·8%	34·3%	36·4%	34·3%	33·0%	38·0–44·0%
Platelets, ×10³ cells per µL	167	..	191	..	145	150–450
White blood cell count, ×10³ cells per mm³	25·73	24·28	35·90	40·30	38·22	4·50–14·40
Lymphocytes, %	1·03%	0·73%	0·36%	0·40%	3·44%	38·00–42·00%
Urea, mg/dL	67	73	78	78	93	11–38
Creatinine, mg/dL	1·27	1·31	1·56	1·73	2·19	0·53–0·79
D-dimer, ng/mL	11 495	..	54 153	..	..	<500
Troponin, ng/dL	0·281	..	0·290	0·342	..	<0·014
Creatine kinase myocardial band, ng/dL	5·76	..	28·50	15·66	..	0·10–2·88
Interleukin-6, pg/mL	4105·0	..	..	..	..	0·2–7·8
Creatine kinase, U/L	96	..	..	..	..	<167
Blood pH	7·21	7·30	..	7·28	7·31	7·35–7·45
Bicarbonate, mEq/L	15·7	16·4	..	17·6	17·2	21·0–28·0
$PaCO_2$, mm Hg	41	32	..	31	..	35–45
PaO_2, mm Hg	60	270	..	133	..	80–90
$ScvO_2$, %	87·2%	97·3%	..	82·0%	82·2%	60·0–85·0%
Lactate, mg/dL	38·0	39·0	..	27·0	..	4·5–14·4
C-reactive protein, mg/dL	266·6	..	309·5	..	..	<500
Total protein, g/dL	5·0	..	..	..	..	6·0–8·0
Albumin, g/dL	2·6	..	..	..	..	3·8–5·4
Aspartate aminotransferase, U/L	61	..	67	..	..	13–35
Alanine aminotransferase, U/L	67	..	67	..	..	7–35
Oxygenation index	..	3·1	..	4·2	..	<4·0
International normalised ratio	..	..	1·4	..	..	0·9–1·2
Fibrinogen, mg/dL	..	..	513	..	..	200–393
Ferritin, ng/mL	..	..	..	1501	..	20–200
Triglycerides, mg/dL	..	..	..	162	..	<100

$PaCO_2$=partial pressure of carbon dioxide in arterial blood. PaO_2=partial pressure of oxygen in arterial blood. $ScvO_2$=central venous saturation of oxygen.

Table: **Laboratory results at various timepoints after presentation**

Lancet Child Adolesc Health 2020

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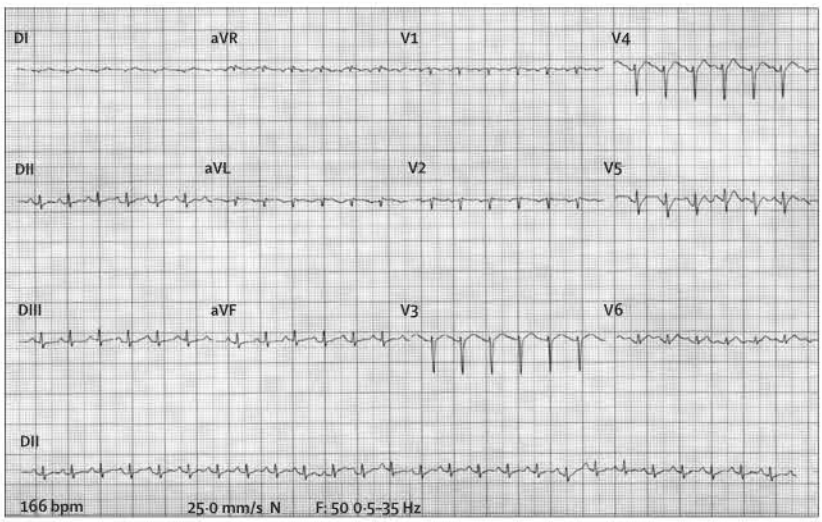

Figure 1: **Electrocardiogram showing sinus tachycardia on admission**

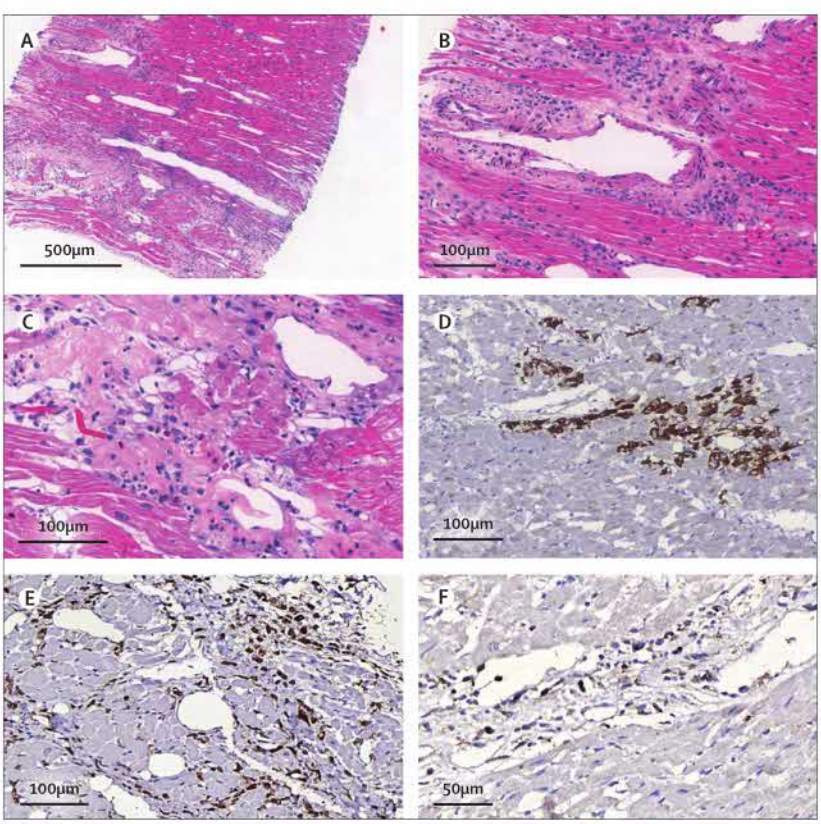

Figure 2: **Post-mortem histological findings**
(A) Diffuse myocardial interstitial inflammation. (B, C) Interstitial and perivascular myocardial inflammation containing lymphocytes, macrophages, a few neutrophils and eosinophils, and foci of cardiomyocyte necrosis. (D) Myocardial necrosis indicated by C4d staining. (E, F) Myocardial interstitial inflammation containing $CD68^+$ (E) and $CD45^+$ (F) cells.

See Online for appendix

estimated with the M-mode Teichholz method in the parasternal short axis view, at the level of the papillary muscles of the mitral valve; substantial myocardial dysfunction was noted, with decreased left-ventricular ejection fraction (31%) and no respiratory collapsibility of the inferior vena cava. The patient received furosemide, and central line and invasive arterial monitoring were established. Initial radiography showed an enlarged cardiac area and bilateral lung opacities (appendix p 1). Chest CT showed multiple ground-glass pulmonary opacities associated with thickening of interlobular septa and sparse bilateral foci of consolidation, predominantly in the peripheral and posterior areas of lower lobes (appendix p 1).

Laboratory results showed high concentrations of markers of systemic inflammation and myocardial injury, including C-reactive protein, interleukin-6, ferritin, triglycerides, D-dimer, troponin, and creatine kinase myocardial band. Moreover, a left-shifted white-blood-cell count and substantial lymphopenia were seen. Blood gas analysis showed hypoxia and acidosis (table).

Mechanical ventilation was implemented during the first hour in the ICU and ventilatory parameters reached a maximum positive end-expiratory pressure of 8 cm H_2O and peak inspiratory pressure of 25 cm H_2O, with an initial fraction of inspired oxygen of 60%. After initiation of mechanical ventilation and use of diuretics, ventilatory parameters could be reduced and less opacification was seen on chest radiography.

The patient had sinus tachycardia throughout the hospital stay (heart rate >200 bpm); the initial electrocardiogram is shown in figure 1. The patient progressed to hyperdynamic vasoplegic shock refractory to volume resuscitation and vasoactive agents. After 28 h of hospital admission, she developed ventricular fibrillation and died.

An ultrasound-guided minimally invasive autopsy was done, with tissue sampling of the heart, lungs, liver, spleen, kidneys, brain, inguinal lymph node, quadriceps muscle, and skin.[1] Post-mortem CT angiography was done before tissue collection and did not show any signs of coronary artery alterations (appendix p 2). Post-mortem ultrasound examination of the heart showed a hyperechogenic and diffusely thickened endocardium (mean thickness 10 mm), a thickened myocardium (18 mm thick in the left ventricle), and a small pericardial effusion. Histopathological examination showed myocarditis, pericarditis, and endocarditis characterised by inflammatory cell infiltration (figure 2A). Inflammation was mainly interstitial and perivascular, associated with foci of cardiomyocyte necrosis (figure 2B, C), and was mainly composed of $CD68^+$ macrophages (figure 2E), a few $CD45^+$ lymphocytes (figure 2F), and a few neutrophils and eosinophils. C4d immunostaining was used for detection of cardiomyocyte necrosis (figure 2D). Analysis of cardiac tissue by electron microscopy identified spherical viral particles of 70–100 nm in diameter, consistent in size and shape with the Coronaviridae family, in the extracellular compartment and within several cell types—

cardiomyocytes, capillary endothelial cells, endocardium endothelial cells, macrophages, neutrophils, and fibroblasts (figure 3). Microthrombi in the pulmonary arterioles (appendix p 3) and renal glomerular capillaries were also noted at autopsy. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated pneumonia was mild, with patchy exudative changes in alveolar spaces and mild pneumocyte hyperplasia (appendix p 3). Lymphoid depletion and signs of haemophagocytosis were noted in the spleen and lymph nodes, indicating secondary haemophagocytic lymphohistiocytosis associated with systemic inflammation. Acute tubular necrosis in the kidneys and hepatic centrilobular necrosis, secondary to shock, were also seen. Brain tissue showed microglial reactivity.

SARS-CoV-2 RNA was detected on a post-mortem nasopharyngeal swab and in cardiac and pulmonary tissues by real time RT-PCR using primers and probes set for E (envelope) gene.[2] Cycle threshold values for lung and heart samples were 35·6 and 36·0, respectively, suggesting a low viral load in both organs.

To investigate a primary immunodeficiency, whole-exome sequencing from genomic DNA extracted from whole blood was done, using a customised Twist Human Core Exome kit (Twist Bioscience, San Francisco, CA, USA) for exon capture, and sequenced in an Illumina NovaSeq platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the reference human genome (GrCh38/hg38 in the University of California Santa Cruz [UCSC] Genome Browser) with Burrows-Wheeler Aligner software. Genotyping was done using the Genome Analysis Toolkit (Broad Institute, Cambridge, MA, USA).[3] No pathogenic, likely pathogenic, or variant of unknown significance was found associated with inborn errors of immunity.

MIS-C is a severe clinical condition that has been described in several paediatric patients diagnosed with COVID-19 and that might be associated with cardiac dysfunction.[4–10] Since the disorder shares similarities with Kawasaki disease, it has also been reported as Kawasaki-like disease or Kawasaki-like multisystem inflammatory syndrome.[4–8] A substantial increase in the incidence of Kawasaki-like disease has been described in several countries with high incidence of COVID-19.[4,5,7] In Italy, the first European country to be affected by the COVID-19 pandemic, Verdoni and colleagues[4] found that, over a period of 1 month, the spread of SARS-CoV-2 was associated with a 30-fold increase in the incidence of Kawasaki-like disease. Compared with classic Kawasaki disease, children with MIS-C are older, have respiratory, gastrointestinal, neurological, and cardiovascular involvement, substantial lymphopenia, thrombocytopenia, and markers of myocarditis.[4,7,8] Although previous studies have reported low mortality among children with MIS-C (<2%), patients presented with cardiogenic shock, acute left-ventricular dysfunction, and signs of myocarditis, indicating a potential risk of a life-threatening condition.[4–10] The mechanism of heart failure in these patients and its relation to SARS-CoV-2 infection is not understood.

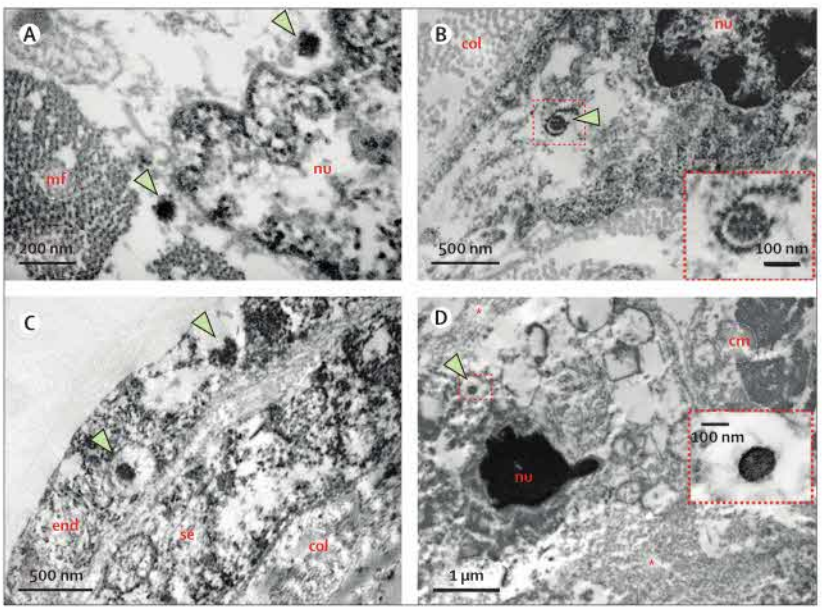

Figure 3: **Post-mortem electron microscopy findings**
(A) Part of a cardiomyocyte, with viral particles (arrows) within a cytoplasmic area close to the nucleus. (B) Part of a fibroblast; arrow points to a viral particle inside a ruptured fragment of the rough endoplasmic reticulum. Inset in (B) corresponds to a higher magnification of the virus. (C) Endothelial lining (endocardium and subendocardium) of the left ventricular lumen; two viral particles (arrows) are present inside the endocardial endothelial cell. (D) Neutrophil in late stages of NETosis; asterisks indicate neutrophil extracellular traps (decondensed and dispersed chromatin); arrow points to a viral particle inside a cytoplasmic vesicle. Inset in (D) shows the viral particle at high magnification. cm=cardiomyocyte. col=collagen fibrils. end=endothelial cell. mf=myofibrils. NET=neutrophil extracellular trap. nu=nucleus. se=subendocardial fibroblast.

Possible mechanisms involved in cardiac dysfunction in children with COVID-19 include myocardial stunning or oedema associated with a severe systemic inflammatory state, direct myocardial injury by SARS-CoV-2, and hypoxia secondary to viral pneumonia.[4–11] Reports of substantial numbers of children presenting with MIS-C or Kawasaki-like disease during the COVID-19 pandemic indicate that SARS-CoV-2 is probably a trigger of this clinical condition, either by eliciting a severe systemic immune response or by direct tissue damage, or both.[4–10]

Our case report shows inflammatory changes in the cardiac tissue of a child with MIS-C related to COVID-19, which led to cardiac failure and death. SARS-CoV-2 could be detected in cardiac tissue by RT-PCR and electron microscopy. Despite the evident systemic inflammation and final progression to multiorgan failure, clinical, echocardiographic, and laboratory findings strongly indicated that heart failure was the main determinant of the fatal outcome. Further, the autopsy showed myocarditis, pericarditis, and endocarditis, with intense and diffuse tissue inflammation, and necrosis of cardiomyocytes. Moreover, the finding of SARS-CoV-2 in heart tissue indicates that myocardial inflammation was

For the **UCSC Genome Browser** see http://genome.ucsc.edu

For more on **Burrows-Wheeler Aligner software** see http://bio-bwa.sourceforge.net/

probably a primary response to the virus-induced injury to cardiac cells. The presence of SARS-CoV-2 in different cell types of cardiac tissue suggests potential mechanisms for heart damage. First, infection of cardiomyocytes probably leads to local inflammation in response to cell injury; both the virus-induced injury and the inflammatory response could lead to necrosis of cardiomyocytes. The finding of viral particles in neutrophils supports the idea of virus-induced inflammation. Also, infection of endothelial cells in the endocardium could result in haematogenous spread of SARS-CoV-2 to other organs and tissues.

Detection of both SARS-CoV-2 RNA by RT-PCR and viral particles by electron microscopy in cardiac tissue has been reported in endomyocardial biopsy specimens from adults with COVID-19.[12,13] Tavazzi and colleagues[13] detected viral particles in cardiac macrophages in an adult patient with acute cardiac injury associated with COVID-19; no viral particles were seen in cardiomyocytes or endothelial cells. Our case report is the first to our knowledge to document the presence of viral particles in the cardiac tissue of a child affected by MIS-C. Moreover, viral particles were identified in different cell lineages of the heart, including cardiomyocytes, endothelial cells, mesenchymal cells, and inflammatory cells.

Two other reports in adolescents with COVID-19 detected myocarditis by MRI or at autopsy.[14,15] In the report from Craven and colleagues,[15] histological analysis of the heart of a 17-year-old boy showed diffuse myocarditis with mixed inflammatory infiltrate, with a predominance of eosinophils. In our case report, cardiac inflammation also included a small number of eosinophils. In these two previous reports,[14,15] common symptoms of COVID-19 were absent, except for fever; pulmonary changes were absent or mild, and there was no multiorgan involvement.

The pulmonary involvement noted in our case report was probably the result of mild pneumonia, cardiogenic oedema, and microthrombi in the pulmonary arteriolar bed, which—associated with the finding of microthrombi in the kidney and the presence of virus in the cardiac capillary endothelium—suggest a SARS-CoV-2-induced endothelial dysfunction that probably involved several organs.

Whole-exome sequencing could not identify any inborn error of immunity in our patient. It is still unclear which host factors could predispose children to MIS-C; further investigation of potential genetic determinants is important to understand the pathogenesis of this syndrome.[10]

In conclusion, our pathological observations support the hypothesis that the direct effect of SARS-CoV-2 infection on cardiac tissue was a major contributor to myocarditis and heart failure in our patient. Hopefully, our findings could help to shed light on the understanding of the complex interaction between SARS-CoV-2 infection, MIS-C, and cardiac dysfunction in children and adolescents with COVID-19.

Contributors

JFF, NVD, AFD, CMF, GNL, RMR, MCS, and WBdC were involved in the care of the patient. MD, RAdAM, AND-N, TM, LFFdS, and PHNS obtained and interpreted autopsy data. KTC did post-mortem CT angiography and interpreted these data. MSG-G and JRRP did molecular analyses and interpreted these data. EGC did electron microscopy and interpreted these data. MD and JFF wrote the report, and all authors reviewed and approved the final version.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was approved by the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) ethics committee (protocol no 3951.904) and written informed consent for publication was obtained from the patient's parent. We thank Jair Theodoro Filho, Kely Cristina Soares Bispo, Reginaldo Silva do Nascimento, Thabata Larissa Luciano Ferreira Leite, Catia Sales de Moura, and Marcelo Alves Ferreira for technical support; Luiz Alberto Benvenuti (Instituto do Coração, HC-FMUSP) for immunohistochemical staining and suggestions on histopathological analysis; Leila Antonangelo and Caroline Silverio Faria (Laboratório de Investigação Médica - 03, HC-FMUSP) for the cytokine profile analysis; and all workers involved in care for patients with COVID-19 and who are part of the HC-FMUSP Coronavirus Crisis Committee. This work was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (2013/17159-2, 2014/50489-9), Bill & Melinda Gates Foundation (INV-002396), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (304987/2017-4). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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From: Richard Killewald
Sent: Mon, 27 Apr 2020 20:40:56 +0000
To: Laura Makaroff; Shulman, Lawrence; Thomas Varghese; Stewart, F. Marc; Dulniak, Craig; CDC IMS 2019 NCOV Response Policy Partnerships; Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE); Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHPSE); Hickner, Hadley (CDC/DDNID/NCCDPHP/DDT); Jessica Sugalski
Subject: COVID-19 and Cancer ECHO for Cancer Care Teams - Information for Tuesday's session at 12:00 ET
Attachments: COVID-19 and Cancer ECHO for Cancer Care Teams.pdf, Cancer Care Teams Preregistration Questions.pdf, COVID-19 and Cancer ECHO for Cancer Care Teams Guide.pdf, COVID-19 and Cancer ECHO for Cancer Care Teams Run of Show.pdf

Hi all! First, I want to welcome Dr. John T. Brooks, MD, Chief Medical Officer, COVID-19 Response for the Centers for Disease Control and Prevention! Dr. Brooks will be joining our expert faculty panel for our ECHO sessions this Tuesday and Thursday. This email contains some important documents and information for tomorrow's session. Please let me know if you have any questions. See you all tomorrow!

Important information

- Time permitting, we'd love to have you join 10 minutes early (11:50 ET) so we can be sure everyone's technology is working.
- If you have not registered as a panelist for tomorrow's session, please let me know ASAP.

Attachment overview

- **COVID-19 and Cancer ECHO for Cancer Care Teams** is a PDF of the slides for tomorrow. Marc, thank you for sharing your draft slides earlier. This version includes those slides and I'll include the final slides when they are available.
- **Cancer Care Teams Preregistration Questions** includes the 11 questions included in the PPT for Tuesday's session, as well as four additional questions available time permitting. We anticipate including some questions coming through the Q&A portal, but this should represent the bulk of questions to be asked.
- **COVID-19 and Cancer ECHO for Cancer Care Teams Guide** is an overview document that provides details on the ECHO model, hub members, and Zoom tips and tricks.
- **COVID-19 and Cancer ECHO for Cancer Care Teams Run of Show** gives a more detailed look at the agenda, but will be of most use for Laura and Rich.

Richard Killewald, MNM
Director, Cancer Control Interventions
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American Cancer Society, Inc.
4550 E Bell Rd Suite 126
Phoenix, AZ 85032
cancer.org | 1.800.227.2345

45 or older? Get screened for colorectal cancer.
Colorectal cancer is one of the leading causes of death, yet with regular screening, it can be prevented or found early. ACS recommends screening starting at age 45.

Welcome to the COVID-19 and Cancer ECHO Series

Use the Q&A portal throughout today's session to submit your questions! Our expert faculty will be answering your questions live.

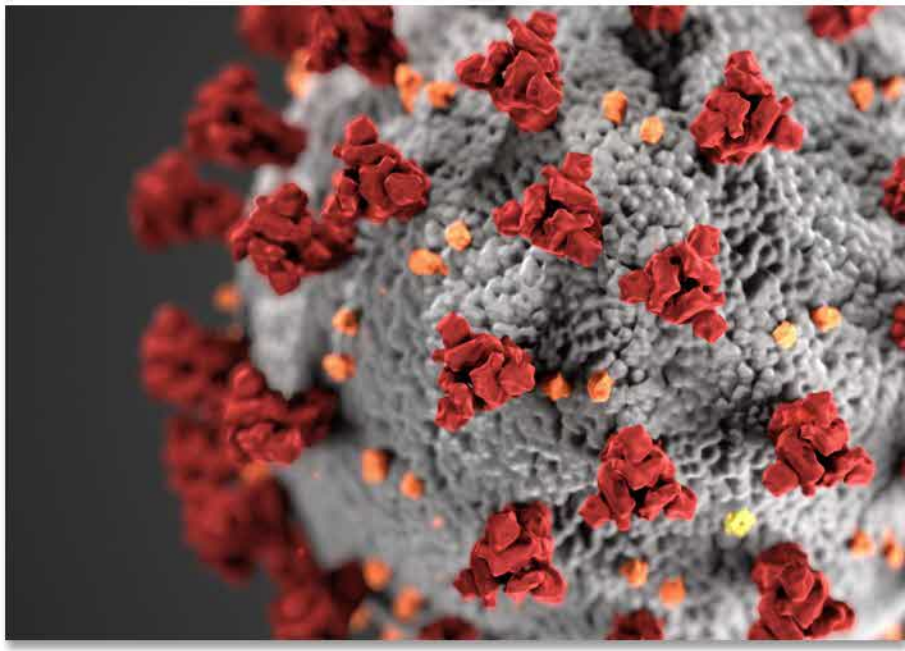
All ECHOs take place on the Zoom platform. Review Zoom's privacy policy at **zoom.us/privacy**. This ECHO will be recorded.

American Cancer Society® | Project ECHO®

NCCN National Comprehensive Cancer Network®

Today's agenda

Introductions	Laura Makaroff, DO 5 minutes
Didactic presentation	F. Marc Stewart, MD 20 minutes
Question and answer session	Expert faculty panel 30 minutes
Wrap-up	Richard Killewald, MNM 5 minutes



Introductions

INTRODUCTIONS

Expert faculty panel

John T. Brooks, MD

Chief Medical Officer, COVID-19 Response
Centers for Disease Control and Prevention

Lawrence N Shulman, MD, MACP, FASCO

Professor of Medicine
Deputy Director for Clinical Services
Director, Center for Global Cancer Medicine
Abramson Cancer Center at the University of Pennsylvania

F. Marc Stewart, MD

Medical Director and Senior Vice President
Seattle Cancer Care Alliance

Thomas K. Varghese Jr. MD, MS, FACS

Executive Medical Director and Chief Value Officer
Huntsman Cancer Institute – University of Utah

Didactic presentation

DIDACTIC PRESENTATION

Today's presenter

F. Marc Stewart, MD

Medical Director and Senior Vice President

Seattle Cancer Care Alliance

COVID-19 and Cancer ECHO For Cancer Care Teams

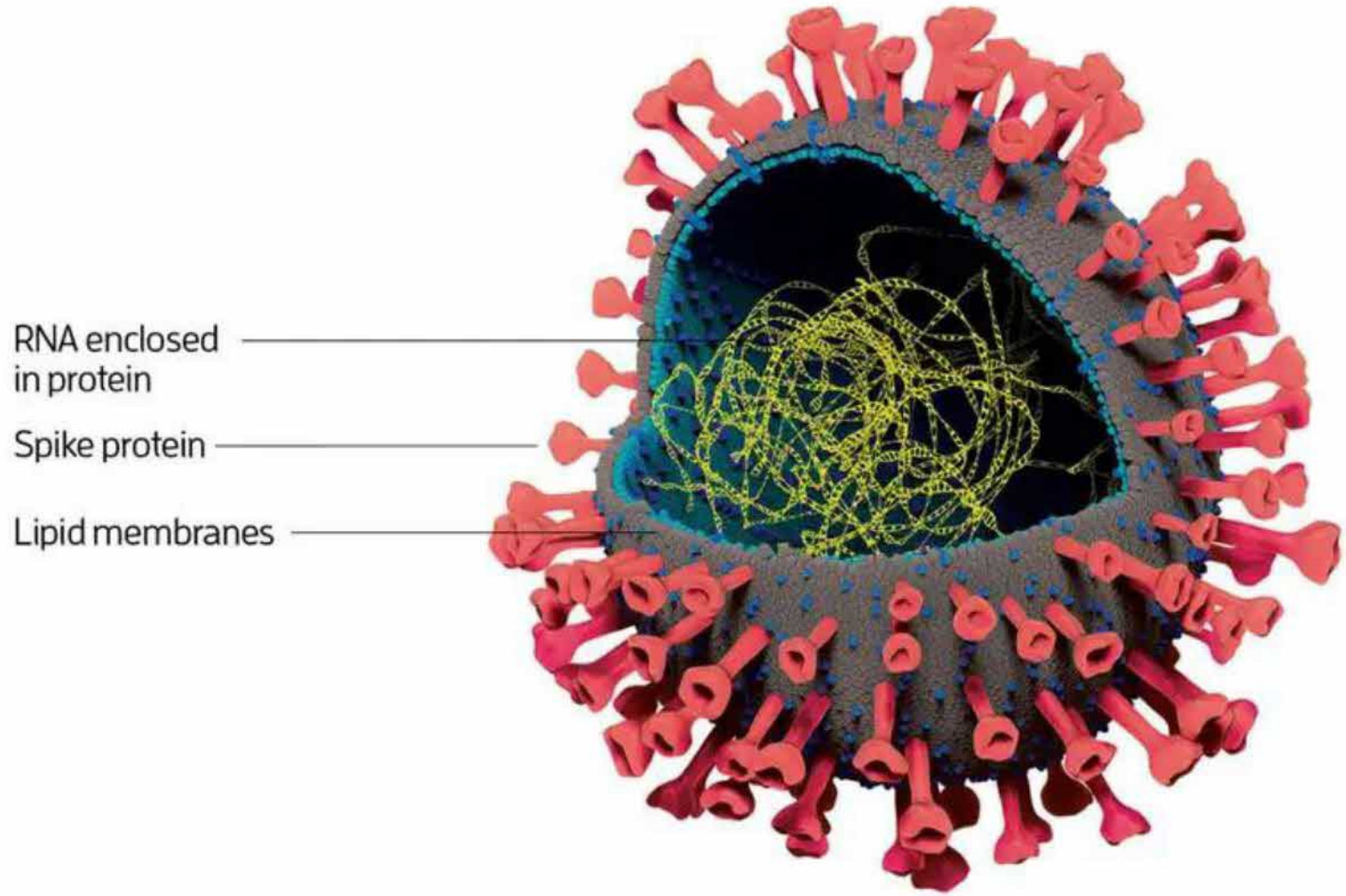
F. Marc Stewart MD
NCCN Best Practices Committee
American Cancer Society

Disease

Coronavirus disease (COVID-19)

Virus

Severe acute respiratory syndrome coronavirus 2
(SARS-CoV-2)



Origin

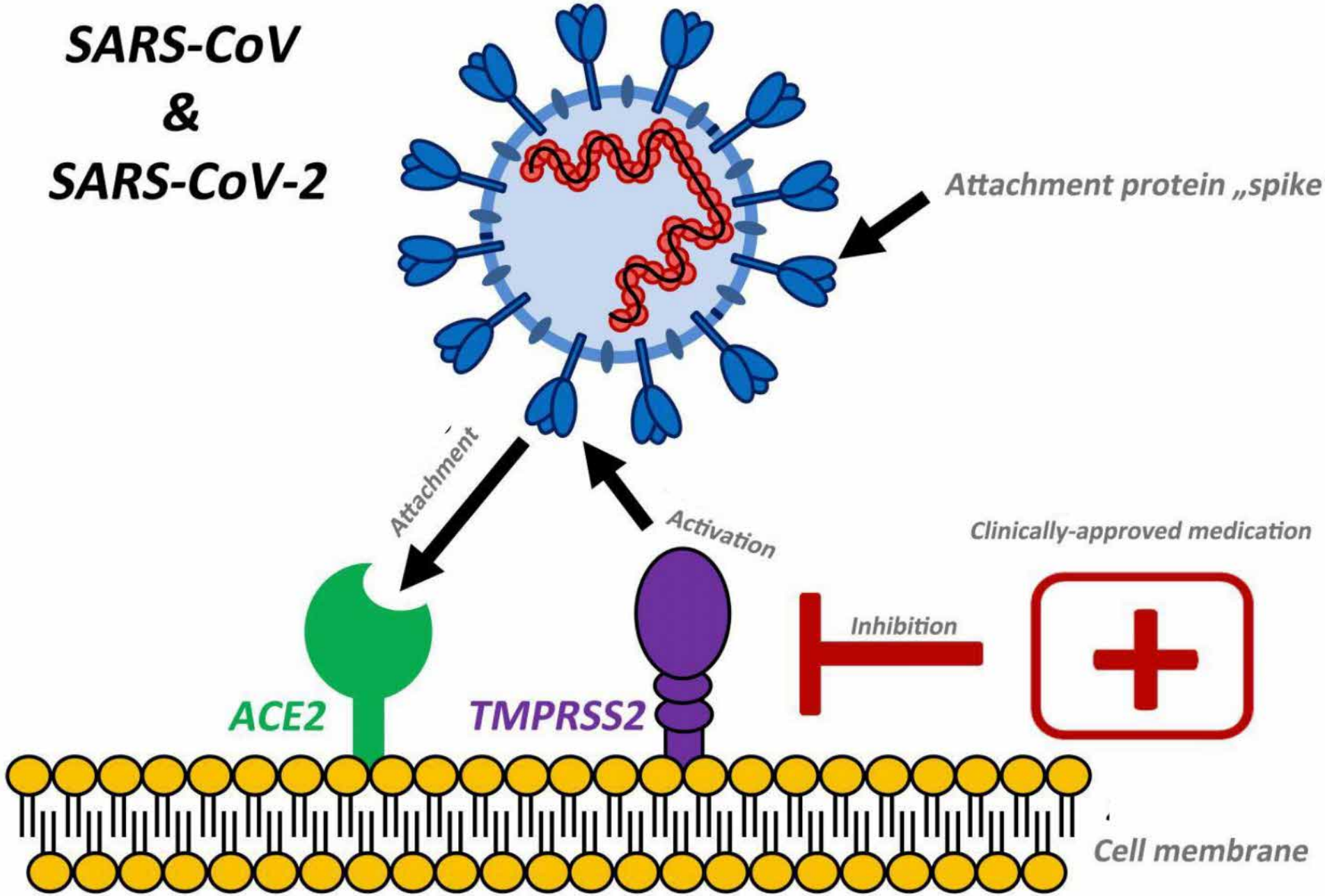
- Animal Source: bats
- Wet market in Wuhan, China.
- ? Virology Institute in Wuhan, China.
- Carl T. Bergstrom, professor of biology at the University of Washington: "There is strong evidence that the SARSCoV2 coronavirus is NOT an engineered bioweapon. That said, it's important to be upfront that we do not have sufficient evidence to exclude entirely the possibility that it escaped from a research lab..."
- Transmitted by droplet, found in feces but no documentation for transmission fecal-oral transmission.
- Persists on surfaces for hours to days.

Disease	Year	Contagious	Mortality
Severe Acute Respiratory Syndrome (SARS)	2002	8,000 cases (and 774 deaths).	9.6%
Middle East Respiratory Syndrome (MERS)	2012	2,519 cases (and 866 deaths).	34.4%
Coronavirus Disease (COVID-19)	2019	To date: 2,995,456 cases (and 207,583 deaths).	2-4% ?

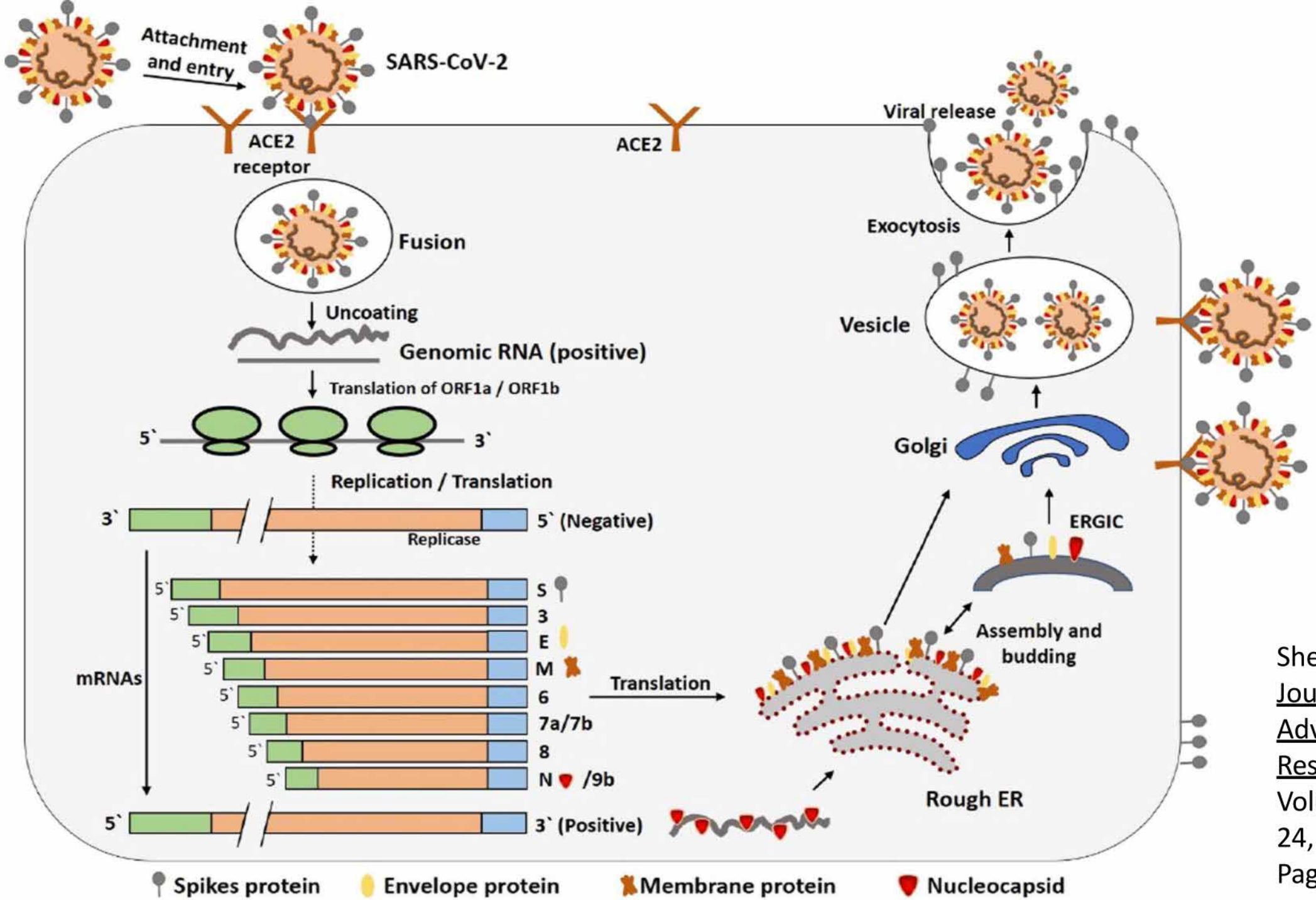
World Health Organization:

1.Suspect case of COVID19: a person with acute respiratory illness and having been in contact with confirmed or probable COVID 19 case in the last 14 days.

2. Confirmed case SARS CoV-2: lab confirmation with or without symptoms.

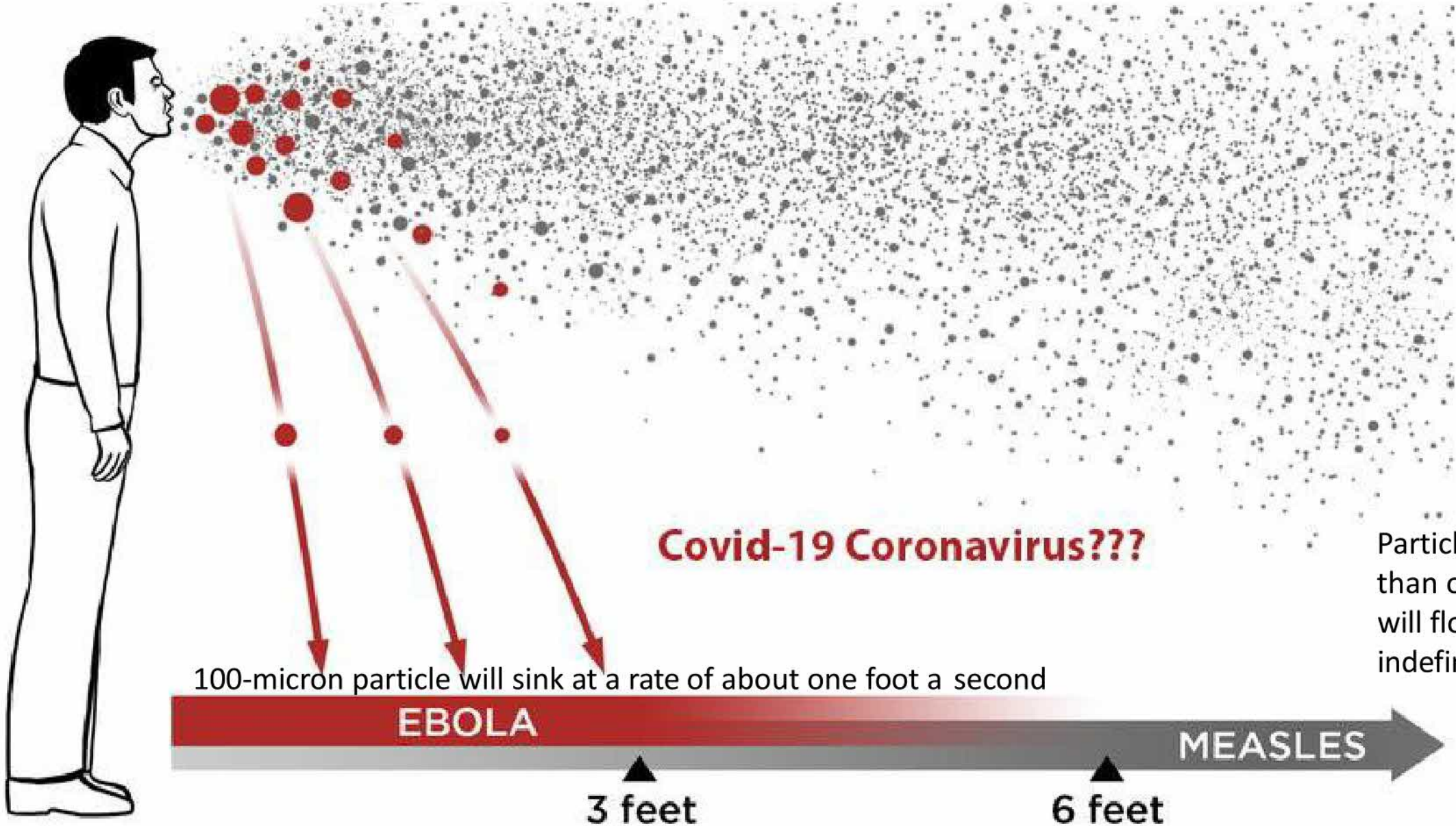


Incubation: 2-14 days

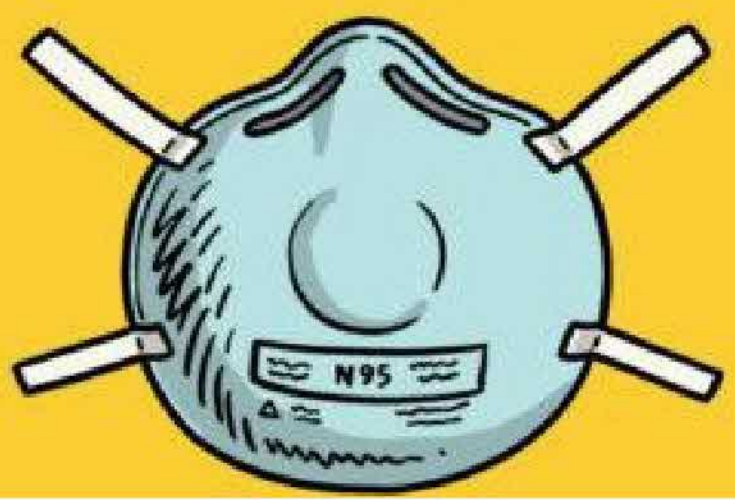


Shereen MA: Journal of Advanced Research Volume 24, July 2020, Pages 91-98

Launch Particles sized at 80 to 300 microns at speeds of 50 miles an hour to 100 miles an hour



Particles less than one micron will float indefinitely.



N95 Mask	Surgical Mask	Homemade/Cloth Mask
Electrostatic charge Non woven material Wear when caring for COVID+ patients	Non woven material Wear in hospital care setting	Porous, woven material Wear in public places.
Reduces wearer's exposure to large, intermediate and small particles (less than 100 microns)	Fluid resistant, protects wearer against large droplets, splashes. Protects patient from wearer's respiratory emissions.	Not fluid resistant. Protects patient from wearer's respiratory emissions
Reusable	Not reusable	Reusable
Difficult to breathe	Breathable	Breathable, may get warm
Tight fit	Loose fit	Loose fit

Precautions for Public and Healthcare Workers

- Hand hygiene:
  - Wet hands
  - Wash hands for 20 sec with soap and water
  - Dry with paper towel.
  - Or use alcohol-based protection (> 60%).
- Maintain social distancing:
  - ? Work from home, ? stay home, maintain six feet;
- Avoid touching eyes, nose, mouth.
- Cover with elbow/cloth if cough or sneeze.
- Clean surfaces (counters, tables, etc.) with disinfectants, UV light.
- Clean shopping carts (packaged food likely safe).
- Wear masks in public.
- For healthcare workers, patients and family members: review proper donning and doffing techniques, proper disposal of PPE.

Asymptomatic and Pre-symptomatic Carriers

- The median incubation period, from exposure to symptom onset, is approximately 4 to 5 days.
- 97.5% of patients who are symptomatic will have symptoms within 11.5 days after infection.
- Pre-symptomatic patients may be infectious 1 to 6 days before symptom onset.
- Up to 40 to 50% of cases may be attributable to transmission from asymptomatic or pre-symptomatic people.
- Just before/soon after symptom onset, patients have high nasopharyngeal viral levels, which then fall over the course of approximately 1 week.
- Patients with severe disease may shed the virus for longer periods.

“Achilles Heel”: Asymptomatic and Pre-symptomatic Carriers

- Seattle Skilled Nursing Facility
- Twenty-three days after identifying the first resident with SARS-CoV-2 infection, Facility A had a 64% prevalence of Covid-19 among residents, with a case fatality rate of 26% despite early adoption of infection-control measures.
- Covid-19 was diagnosed in 26 members of the staff (19%).
- More than half of the residents with positive tests were asymptomatic at the time of testing.
- Transmission from asymptomatic residents infected with SARS-CoV-2 most likely contributed to the rapid and extensive spread of infection to other residents and staff.
- Close quarters probably played a role.
- Symptom-based infection-control strategies were not sufficient to prevent transmission after the introduction of SARS-CoV-2 into this skilled nursing facility.

Arons M et al. N Engl J Med April 25, 2020
Gandhi M et al. N Engl J Med April 25, 2020

Clinical Considerations:

- Risks associated with mortality:
  - Over age 60 (Distribution of age in COVID+ patients: age <10=<1%, age 10-19 =8%, age 20-29 = 8%, age 30-79=87%, age >80= 3%)
  - Presence of cardiovascular disease, hypertension
  - Underlying condition: diabetes, COPD, obesity, ? Cancer chemotherapy/radiation, others.
- Symptoms:
  - Fever 88%, Dry Cough 67%, Fatigue 38%, Phlegm 33%, SOB 19%, Muscle pain 15%, Sore throat 14%, Headache 14%, Confusion.
- Findings:
  - Chest CT: ground glass opacities; lungs: hyaline membranes, exfoliation of pneumocytes.
  - Lymphopenia (CD4 and CD8)
  - Increased Procalcitonin (may indicate superimposed bacterial infection)
- Serology for COVID-19: (documentation of immunity)

	Timing of antibody	Percent COVID+ pts with antibody
IgM	3-6 days	85.4% (not recommended for acute diagnosis)
IgA	3-6 days	92.7% (not recommended for acute diagnosis)
IgG	10-18 days	77.9% (documenting immune response)

Less Common Symptoms/Conditions:

- “Covid toes”
- Anosmia
- “Pink Eye” (follicular conjunctivitis)
- Diarrhea/nausea
- Chest pain/Myocarditis/Infarction
- Thrombosis
- Renal failure
- Guillian Barre

Cancer Screening

- Most situations including ‘high risk’ genetics allow for three months delay without harm in otherwise asymptomatic patients or patients without objective findings.
- American Cancer Society recommends no one be required to undergo routine mammograms, screening colonoscopies', PAP/pelvic exams, rectal exams, CT scans.
- Breast lumps (new): evaluate
- Lung nodules: delay the evaluation of pulmonary nodules detected incidentally or by screening that have a low probability of cancer or are likely to be an indolent cancer (solid nodules measuring <8 mm in average diameter, pure ground glass opacities of any size, and part-solid nodules in which the solid component measures 6-8 mm in average diameter)
- Prostate: Risks of a delay in diagnosis of up to 6 to 12 months are minimal for most prostate cancers. (NCCN) Invasive cancer diagnoses require prompt attention.
- Many elective visits (wellness, survivorship) may be accomplished with telehealth visits.

Controversies

- Do we know the true incidence and mortality of COVID-19? *
  - USC and the Los Angeles Department of Public Health concluded that between 2.8% and 4.6% of the adult population in Los Angeles County has an antibody to the virus.
  - This translates to between 221,000 and 442,000 adults — an estimate that is 28 to 55 times higher than the roughly 8,000 confirmed cases that the county had in early April, when the study was conducted.
  - Stanford study: mortality rate in Santa Clara County is between 0.12% and 0.2%. (In contrast, the county's mortality rate based solely on official cases and deaths as of last Friday, April 17, was 3.9%.).
  - New York (April 20) has collected around 3,000 samples from 40 locations in 19 counties across the state so far.
  - In New York City, around 21% of randomly sampled people had antibodies against the coronavirus; on Long Island, about 16.7% had antibodies; in Westchester and Rockland around 11.7% had antibodies; and in the rest of the state 3.6% had antibodies.
- As we gain knowledge about coronavirus incidence, how does it fit into the context of what we "sacrifice"?
  - 8000 persons die in the US per day.
  - 6% from accidents, 23% from heart disease, 2% from flu and pneumonia.
  - These deaths are allowed but not from coronavirus even at the cost of economic ruin for millions.
- Are other models worthy of consideration e.g., Sweden?

Palo Alto online, April 21, 2020
Jenkins HW: The lockdowns were the Black Swan WSJ April 24, 2020
Rodgers TJ: WSJ, April 26, 2020

* Caution about accuracy/relevance of antibody studies correlating with exposure and immunity

Question and answer session

Use the Q&A portal to submit your questions

QUESTION AND ANSWER SESSION

Question 1

Are their certain types of cancer that puts patients at a higher risk of contracting COVID-19 than others?

QUESTION AND ANSWER SESSION

Question 2

How do you decide whether to initiate a new treatment or hold off during a pandemic?

QUESTION AND ANSWER SESSION

Question 3

I am a breast cancer patient with a low WBC level. I am also a health care professional. When is it safe for me to see patients?

QUESTION AND ANSWER SESSION

Question 4

When a cancer survivor is still undergoing treatment and is working, what extra precautions should they take for home and work?

QUESTION AND ANSWER SESSION

Question 5

Should all survivorship programming be virtual or at least keeping survivors 6 feet apart for the near future?

QUESTION AND ANSWER SESSION

Question 6

What should a protocol look like for patients receiving second opinions out of our geographic area (ie. quarantine 14 days?)

QUESTION AND ANSWER SESSION

Question 7

What are your recommendations for what a visitor policy might look like?

QUESTION AND ANSWER SESSION

Question 8

How do you think COVID-19 will affect cancer centers' CoC accreditation?

QUESTION AND ANSWER SESSION

Question 9

What actions and recommendations do you suggest to stress the importance of preventative screening in today's medical environment?

QUESTION AND ANSWER SESSION

Question 10

Why are we hearing that we will see a surge of cases in the Fall 2020?

QUESTION AND ANSWER SESSION

Question 11

How do you recommend we support patients during social isolation?

QUESTION AND ANSWER SESSION

Questions received through Q&A portal

Use the Q&A portal to submit your questions

Wrap up

WRAP UP

Resources

For more information and COVID-19 resources, visit:

cancer.org

nccn.org/covid-19

cdc.gov

For more about what Project ECHO is doing to respond to COVID-19, visit **echo.unm.edu/covid-19**

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WRAP UP

Join us this Thursday at 12:00 ET

Thomas K. Varghese Jr. MD, MS, FACS
Executive Medical Director and Chief Value Officer
Huntsman Cancer Institute – University of Utah

Topics will include:

- How cancer patients can mitigate risk
- Potential modifications in treatment plans
- What is the reasonable timeframe to delay follow-up testing or treatment and how to guide patients?

Complete the **post-survey evaluation** and ask your questions of our expert faculty panel

Email **echo@cancer.org** with any questions

AMERICAN CANCER SOCIETY

COVID-19 AND CANCER ECHO FOR CANCER CARE TEAMS

PREREGISTRATION QUESTIONS

Questions included in PPT for Tuesday, April 28

1. Are their certain types of cancer that puts patients at a higher risk of contracting COVID-19 than others?
2. How do you decide whether to initiate a new treatment or hold off during a pandemic?
3. I am a breast cancer patient with a low WBC level. I am also a health care professional. When is it safe for me to see patients?
4. When a cancer survivor is still undergoing treatment and is working, what extra precautions should they take for home and work?
5. Should all survivorship programming be virtual or at least keeping survivors 6 feet apart for the near future?
6. What should a protocol look like for patients receiving second opinions out of our geographic area (ie. quarantine 14 days?)
7. What are your recommendations for what a visitor policy might look like?
8. How do you think COVID-19 will affect cancer centers' CoC accreditation?
9. What actions and recommendations do you suggest to stress the importance of preventative screening in today's medical environment?
10. Why are we hearing that we will see a surge of cases in the Fall 2020?
11. How do you recommend we support patients during social isolation?

Time permitting questions for Tuesday, April 28

1. Is it advisable for patients to stock up on drugs? What happens to continuous monitoring by oncologist in a lockdown situation?
2. Should patients who do not have cancer, but are in need a mammogram screening still get one or wait?
3. Are Leukemia patients more predisposed to Covid 19 than other people?
4. What needs to be in place for an organization to start up screenings and vaccinations again?

Raw questions as submitted

1. Is it wise for patients to be delaying treatment because of the pandemic? Won't this decrease their chances of better outcomes? Hold for Thursday, April 30 session
2. what things need to be in place at an organization for them to start up screenings and vaccinations again...recommendations? Tuesday, April 28 session time permitting
3. How and when will we restart our road to recovery program? Not appropriate
4. How can the American Cancer Society support hospital systems? Not appropriate
5. 1. Procedure for patients receiving 2nd opinions out of geographic area (ie. quarantine 14 days?) Tuesday, April 28 session 2. Visitor policy? Tuesday, April 28 session
6. When would it be safe to return back to work, offices, hospital, etc? Not appropriate
7. Should all survivorship programming be virtual or at least keeping survivors 6 feet apart for the near future? Tuesday, April 28 session
8. How do you decide whether to initiate a new treatment or hold off during a pandemic? Hold for Thursday, April 30 session
9. When a cancer survivor is still tasking treatment and is working what extra precautions should she take for home and work. Tuesday, April 28 session
10. How should we prepare for the new environment post COVID-19 from possible late stage Dx to raising awareness in a different way? Hold for Tuesday, May 5 session
11. Why are we hearing that we will see a surge of cases in the Fall 2020 Tuesday, April 28 session
12. 1) when to resume chemo when still shedding virus? 2) when to resume immunotherapy when still shedding virus? Hold for Thursday, April 30 session
13. What actions and recommendations are you making to stress the importance of Preventative Screening in today Medical environment? Tuesday, April 28 session
14. solutions to colon cancer screening during covid
15. How can a program encourage screening for the community that will overcome the fears of going to a healthcare facility?
16. Has there been a move toward at-home screening tests (FIT, FIT-DNA) in the current environment with COVID 19?
17. how to support patients during social isolation Tuesday, April 28 session
18. What's the projected time of hoping to end this pandemic Not appropriate
19. Is it advisable for patients to stock up on drugs? What happens to continuous monitoring by oncologist in a lockdown situation? Tuesday, April 28 session time permitting
20. How do you think COVID-19 will affect cancer centers' CoC accreditation? Tuesday, April 28 session
21. Should patients who do not have cancer, but are in need a mammogram screening still get one or wait? Tuesday, April 28 session time permitting
22. Are there standard measures that should be taken to minimize exposure of cancer patients who are on treatment? Hold for Thursday, April 30 session
23. Are Leukemia patients more predisposed to Covid 19 than other people? Tuesday, April 28 session time permitting
24. How do we balance between maintaining treatment plan and ensuring safety in a congested environment? Hold for Thursday, April 30 session
25. Are their certain types of cancer that puts patients at a higher risk of contracting COVID-19 than others? Tuesday, April 28 session
26. What advice to you have for breast centers planning to add back screening appointments?

27. I am a breast cancer patient with a low WBC level. I am also a health care professional. When is it safe for me to see patients? Tuesday, April 28 session
28. What is the vision moving forward for cancer screening?

AMERICAN CANCER SOCIETY

COVID-19 AND CANCER ECHO FOR CANCER CARE TEAMS

ECHO GUIDE

The COVID-19 and Cancer ECHO for Cancer Care Teams is a partnership between the American Cancer Society and the National Comprehensive Cancer Network to deliver up-to-date information to interdisciplinary cancer care teams about how the COVID-19 pandemic impacts cancer patients and other high-risk individuals.. This document is an overview and "how to" guide for American Cancer Society staff and external partners engaged in the project.

ECHO OVERVIEW

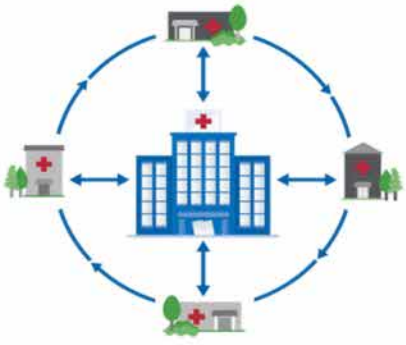
Project ECHO (Extension for Community Healthcare Outcomes) is a hub-and-spoke knowledge sharing network, led by expert teams (faculty) who use multi-point videoconferencing to conduct virtual telementoring sessions with community providers. Founded in 2003 by Dr. Sanjeev Arora at the University of New Mexico, Project ECHO uses the ECHO model to address the needs of the most vulnerable populations by equipping communities with the right knowledge, at the right place, at the right time.

An ECHO session is, essentially, a virtual learning collaborative. Stakeholders from multiple locations connect at regularly scheduled times with a team of specialists using Zoom, a videoconferencing tool offered at no cost.

During traditional ECHO sessions, participants present patient and/or system-related cases centered around COVID-19 to expert teams to brainstorm ways to help them. "Cases" will be collected during the pre-registration process in the form of questions to asked of the panelists for the COVID-19 and Cancer ECHOs. These case-based discussions are supplemented with short didactic presentations to improve content knowledge and share evidence-informed best practices. These expert teams serve as mentors, training participants to address issues.

Move knowledge, not participants

Each online ECHO session includes case-based and didactic learning to create a collaborative sharing of information. It's led by expert faculty from across the United States.



Hub-and-spoke knowledge-sharing creates a learning loop:

- Non-paid caregivers, health works, and ACS staff share and learn from each other and experts
- Faculty specialize in issues impacting non-paid caregivers
- Best practices emerge and can be shared for wider use.

For more information on ECHO,

- Changing the World, Fast: Dr. Sanjeev Arora at TEDxABQ
- Project ECHO: A Revolutionary Model for Expanding Access to Specialized Care

MEET THE ECHO HUB TEAM

The following individuals represent the COVID-19 and Cancer ECHO for Cancer Care Teams Hub Team.

Richard Killewald, MNM
ECHO Coordinator and IT Support
Director, Cancer Control Intervention
American Cancer Society

Richard Killewald is a nonprofit professional with over 20 years in-sector experience using data to change lives. As the director of cancer control interventions at the American Cancer Society, Rich works to design, administer, evaluate, and support quality improvement projects at community health centers nationwide.

Rich has a Masters of Nonprofit Management degree from Regis University in Denver and lives in Phoenix, Arizona with his wife, Lauren, and two children.

John T. Brooks, MD
ECHO Faculty
Chief Medical Officer, COVID-19 Response
Centers for Disease Control and Prevention

Dr John T. Brooks, MD is a medical epidemiologist with the Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Dr. Brooks is a nationally known expert on using public health research to improve the prevention and treatment of HIV infection. In addition to his work on HIV/AIDS, he has devoted many hours to working on national and global disasters including working on surveillance for infectious diseases during Hurricane Katrina in 2005, leading domestic surveillance for SARS during the 2003 outbreak, and assisting with clinical monitoring during the anthrax bioterrorism events of 2001. Most recently, Dr. Brooks led the 2014 Ebola Response Medical Care Task Force during the period when the epidemic was accelerating in West Africa and the first cases were diagnosed in the United States.

Laura Makaroff, DO
ECHO Facilitator
Senior Vice President, Prevention and Early Detection
American Cancer Society

Dr. Laura Makaroff is a family physician and Senior Vice President of Prevention and Early Detection at the American Cancer Society. In this role, she provides strategic and clinical leadership for a range of cancer control initiatives addressing primary prevention, secondary prevention, and screening and early detection. Prior to joining ACS, Dr. Makaroff served as a Senior Clinical Advisor for the Office of Quality Improvement, Bureau of Primary Health Care at the Health Resources Services Administration (HRSA).

Dr. Makaroff completed a fellowship in health policy at Georgetown University and The Robert Graham Center in Washington, DC. Dr. Makaroff spent the early part of her career in solo family medicine and also has clinical experience in community health centers and integrated delivery systems. She completed her residency in family medicine at the University of Colorado Hospital and was awarded the Colorado Academy of Family Physician's Resident of the Year Award and the Larry Green, MD award.

Lawrence N Shulman, MD, MACP, FASCO
ECHO Faculty
Professor of Medicine
Deputy Director for Clinical Services
Director, Center for Global Cancer Medicine
Abramson Cancer Center at University of Pennsylvania

Lawrence N. Shulman, M.D., is the Deputy Director for Clinical Services of the Abramson Cancer Center at the University of Pennsylvania, and Director of their Center for Global Cancer Medicine. He has a leadership role in the strategic development of cancer services for the Cancer Center and its affiliated hospitals and ambulatory cancer centers.

Dr. Shulman is currently Chair of the Commission on Cancer and serves on the National Cancer Policy Forum of the National Academy. He is the former Chair of the American Society of Clinical Oncology Quality of Care Committee and the Commission on Cancer's Quality Integration Committee.

Dr. Shulman serves as Senior Oncology Advisor to the non-profit organization Partners In Health (PIH). The PIH mission includes the establishment of national cancer treatment programs with the Ministries of Health in Rwanda and Haiti, programs for which he plays a seminal leadership role. He sits on the Vice Chancellor's Advisory Council for Rwanda's University for Global Health Equity. In addition, he helps to lead the development of the national oncology program in Botswana through the Botswana-UPenn Partnership. Dr. Shulman is a former member of ASCO's International Affairs Committee and their Task Force on Global Oncology as an Academic Career. He led the World Health Organization's review and revision of their Essential Medicines for Cancer from 2014-2017.

A specialist in the treatment of patients with breast cancer, his research includes development of new cancer therapies, and implementation of cancer treatment programs in low-resource settings.

He received his MD from Harvard Medical School, and trained in Hematology and Oncology at the Beth Israel Hospital in Boston, MA.

F. Marc Stewart, MD
ECHO Faculty
Medical Director and Senior Vice President
Seattle Cancer Care Alliance

As the medical director and vice president of Seattle Cancer Care Alliance, oncologist Dr. Marc Stewart oversees SCCA outpatient clinics. Over the past decade, his research has focused on the optimal use of advanced practice providers, drug safety in oncology and clinical productivity. Previously Dr. Stewart studied the basic biology of non-myeloablative stem cell transplants, sometimes called “mini-transplants,” a type of transplant which does not require wiping out bone marrow to the degree of traditional blood stem cell transplants.

In addition to serving on the board of directors for the National Comprehensive Cancer Network, Dr. Stewart is also co-chair of its best practices committee. In this role, Dr. Stewart helped launch a patient-safety campaign focused on the administration of the chemotherapy drug vincristine.

Thomas K. Varghese Jr. MD, MS, FACS
ECHO Faculty
Executive Medical Director and Chief Value Officer
Huntsman Cancer Institute – University of Utah

Dr. Thomas Varghese Jr. is the Executive Medical Director and Chief Value Officer at Huntsman Cancer Institute, Head of the Section of General Thoracic Surgery, Program Director of the Cardiothoracic Surgery Fellowship, and an Associate Professor (Tenure-track) in the department of Surgery at the University of Utah (promotion to Professor [Tenure-track] effective July 1, 2020). Dr. Varghese holds national leadership positions in the Society of Thoracic Surgeons (STS), Thoracic Surgery Directors Association (TSDA), American College of Surgeons (ACS), Society of University Surgeons, and the National Cancer Care Network (NCCN). On the NCCN he serves as a member of the Board of Directors and Best Practices Committee. He is a health services researcher who helped create the American College of Surgeons Strong for Surgery program and is a co-PI on the National Cancer Institute RO1-funded clinical trial on the role of Precision Exercise Prescription (PEP) for elective lung cancer surgical resection. Tom spends his free time with his family, as well as actively engaging on social media.

Social Media Handles
Twitter: @tomvarghesejr
Linked-In: http://www.linkedin.com/in/tomvarghesejr

University of Utah Academic Website:
https://healthcare.utah.edu/fad/mddetail.php?physicianID=u6001828

AGENDA

The following agenda outlines how a typical ECHO session will flow including roles and responsibilities for ECHO Hub members.

Agenda Item	Allotted Time	Hub Roles & Responsibilities
Housekeeping and introductions	5	**Coordinator** welcomes everyone and covers general housekeeping items **Facilitator** introduces all faulty and welcomes participants
Didactic	15	**Faculty/subject matter expert** delivers brief presentation on the didactic topic
Didactic Q&A	5	**Facilitator** shares any questions that have come through the chat
Q&A	30	**Facilitator** poses questions received during pre-registration to faculty **Facilitator** poses questions received via Q&A portal, time permitting
Wrap-up	5	**Coordinator** shares next didactic topic and post-session survey

ZOOM: START-UP AND TROUBLESHOOTING

This section provides important information to get you started on the Zoom videoconferencing platform. The ECHO team will be available on Zoom 10 minutes before each session for additional troubleshooting, if necessary. Additionally, contact echo@cancer.org with any Zoom-related questions or concerns.

Getting started

- Download and install Zoom Client For Meetings at the Zoom Download Center. Consider downloading mobile apps, if interested.
- Join a test meeting to confirm your microphone, speaker, and videos are working correctly and to familiarize yourself with the Zoom application. Review this resource if you run into any issues.

Tips and tricks

- Zoom allows for multiple layout options. View this resource to learn about the options, including how to maximize your layout during a screenshare. If you are using dual monitors, take a look at this.
- If you are joining the ECHO by phone, be sure to enter the Participant ID (displayed in Zoom) so your audio and video feeds will be connected within Zoom. Click here for more information.
- This video from ManyCam offers 11 tips on looking better on video calls, including tips on background, lighting, internet connection, and camera angle.

Troubleshooting

If your video or camera isn't working, please review these troubleshooting tips. If you are using an Lenovo device, start here. If you are using Windows 10, start here.

These one-minute videos may be particularly useful in addressing some frequently asked questions:

- Joining a Meeting
- Meeting Controls
- Joining & Configuring Audio & Video
- Sharing Your Screen

The Zoom Help Center includes resources to help you get started on a desktop or mobile device, and to address issues related to audio, video, or screen sharing.

VIDEO CONFERENCE ETIQUITTE

The recommended practices and what to avoid have been adopted from a resource provided by the ECHO Institute at the University of New Mexico.

Recommended practices

- Test your equipment before the ECHO. ECHO staff will be on Zoom at least 10 minutes early. Join early if you'd like to test your equipment live.
- Eliminate or reduce environmental distractions (i.e. turn off cell phones, avoid rustling papers, turn off loud fans) that may be picked up by your microphone.
- Make eye contact with the camera when you are speaking.

- Speak clearly and in a conversational tone.
- Use respectful and appropriate language.

What do avoid

- Disclosing protected health information (PHI) or personally identifiable information (PII)
- Engaging in side conversations
- Talking over other people

DISCLOSURES

This section includes important disclosures surrounding the ECHO.

Recording

- As a reminder, all ECHO sessions are recorded. The recording may be posted on a dedicated ECHO website which will be viewable by the general public. If you do not wish to have your image recorded, please turn off the video option.
- Please remember not to share personal information of any patient or study participant.
- All ECHOs take place on the Zoom platform. You can review Zoom's privacy policy here.

Project ECHO Data Usage Statement

In order to support the growth of the ECHO movement, Project ECHO collects participation data for each ECHO program. This data allows Project ECHO to measure, analyze, and report on the movement's reach. It is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.

AMERICAN CANCER SOCIETY

COVID-19 AND CANCER ECHO FOR CANCER CARE TEAMS

RUN OF SHOW

Date: Tuesday, April 28
Session #: 1
Didactic presenter: F. Marc Stewart, MD

Step	Allotted Time	Notes
Housekeeping and introductions	5	**Rich** to handle housekeeping • Use Q&A portal to submit questions • Zoom privacy policy and reminder that call will be recorded **Laura** to facilitate, will introduce all faulty • **John T. Brooks, MD**, Chief Medical Officer, COVID-19 Response, Centers for Disease Control and Prevention Dr. John T. Brooks, MD is a medical epidemiologist with the Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Dr. Brooks is a nationally known expert on using public health research to improve the prevention and treatment of HIV infection. In addition to his work on HIV/AIDS, he has devoted many hours to working on national and global disasters including working on surveillance for infectious diseases during Hurricane Katrina in 2005, leading domestic surveillance for SARS during the 2003 outbreak, and assisting with clinical monitoring during the anthrax bioterrorism events of 2001. Most recently, Dr. Brooks led the 2014 Ebola Response Medical Care Task Force during the period when the epidemic was accelerating in West Africa and the first cases were diagnosed in the United States. • **Lawrence N Shulman, MD, MACP, FASCO**, Professor of Medicine, Deputy Director for Clinical Services, Director, Center for Global Cancer Medicine, Abramson Cancer Center at University of Pennsylvania Lawrence N. Shulman, M.D., is the Deputy Director for Clinical Services of the Abramson Cancer Center at the University of Pennsylvania, and Director of their Center for Global Cancer Medicine. He has a leadership role in the strategic development of cancer services for the Cancer Center and its affiliated hospitals and ambulatory cancer centers. Dr. Shulman is currently Chair of the Commission on Cancer and serves on the National Cancer Policy Forum of the National Academy. He is the former Chair of the American Society of Clinical Oncology Quality of Care Committee and the Commission on Cancer's Quality Integration Committee.

		• **F. Marc Stewart, MD**, Medical Director and Senior Vice President, Seattle Cancer Care Alliance As the medical director and vice president of Seattle Cancer Care Alliance, oncologist Dr. Marc Stewart oversees SCCA outpatient clinics. Over the past decade, his research has focused on the optimal use of advanced practice providers, drug safety in oncology and clinical productivity. Previously Dr. Stewart studied the basic biology of non-myeloablative stem cell transplants, sometimes called "mini-transplants," a type of transplant which does not require wiping out bone marrow to the degree of traditional blood stem cell transplants. In addition to serving on the board of directors for the National Comprehensive Cancer Network, Dr. Stewart is also co-chair of its best practices committee. In this role, Dr. Stewart helped launch a patient-safety campaign focused on the administration of the chemotherapy drug vincristine. • **Thomas K. Varghese Jr. MD, MS, FACS**, Executive Medical Director and Chief Value Officer, Huntsman Cancer Institute – University of Utah Dr. Thomas Varghese Jr. is the Executive Medical Director and Chief Value Officer at Huntsman Cancer Institute, Head of the Section of General Thoracic Surgery, Program Director of the Cardiothoracic Surgery Fellowship, and an Associate Professor (Tenure-track) in the department of Surgery at the University of Utah (promotion to Professor [Tenure-track] effective July 1, 2020). Dr. Varghese holds national leadership positions in the Society of Thoracic Surgeons (STS), Thoracic Surgery Directors Association (TSDA), American College of Surgeons (ACS), Society of University Surgeons, and the National Cancer Care Network (NCCN). **Rich** to share screen, advance slides, and record call
Didactic presentation	15	**Laura** to hand off to **F. Marc Stewart**
Didactic Q&A	5	**Laura** to ask questions relevant to didactic presentation received through Q&A portal
Q&A session	30	**Laura** asks questions received through preregistration process **Laura** to ask additional questions that have come through Q&A portal
Wrap up	5	**Rich** • Review next didactic topic • Please complete post-session survey • Email echo@cancer.org with questions

From: McKay, Susannah (CDC/DDID/NCEZID/DHQP)
Sent: Wed, 24 Jun 2020 16:30:44 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Subject: RE: ACIP
Attachments: COVID-01-Brooks-508.pdf

PDFs are posted on the website. Attached.

From: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Sent: Wednesday, June 24, 2020 12:29 PM
To: McKay, Susannah (CDC/DDID/NCEZID/DHQP) <nra2@cdc.gov>
Subject: RE: ACIP

BTW did they send out PPT or PDF?

John T. Brooks, MD
Chief Medical Officer, CDC COVID-19 Response
Email: zud4@cdc.gov
Apologies for errors in my messages that may be due to my need to dictate.

http://intranet.cdc.gov/library/covid19/index.html

From: McKay, Susannah (CDC/DDID/NCEZID/DHQP) <nra2@cdc.gov>
Sent: Wednesday, June 24, 2020 11:04 AM
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Subject: ACIP

John,

Your ACIP slides are BEAUTIFUL! Graphic, straightforward, clear. Everyone will be so happy for a break from the 3-bullet slide (or worse, >3 bullet slides). I'm making notes for my future presentations.

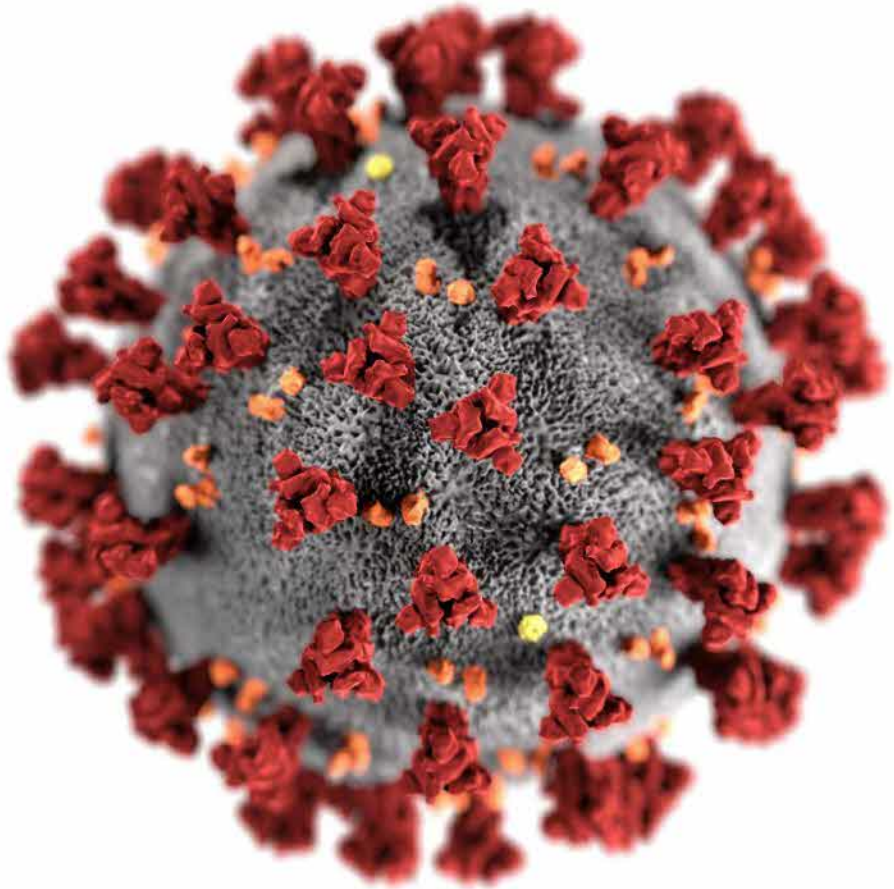
Good luck!

-best,
Susannah

Susannah L. McKay, PhD, MPH (*she/her/hers*)
Deputy Associate Director
Office of Scientific Innovation and Integration
Clinical and Environmental Microbiology Branch
Division of Healthcare Quality Promotion | CDC
Building 17
Phone: 404-718-7636
Email: nra2@cdc.gov, smckay@cdc.gov

COVID 19
CORONAVIRUS DISEASE

Overview of COVID-19 Disease



John T. Brooks MD – Chief Medical Officer
CDC, Division of HIV/AIDS Prevention
CDC, COVID-19 Response

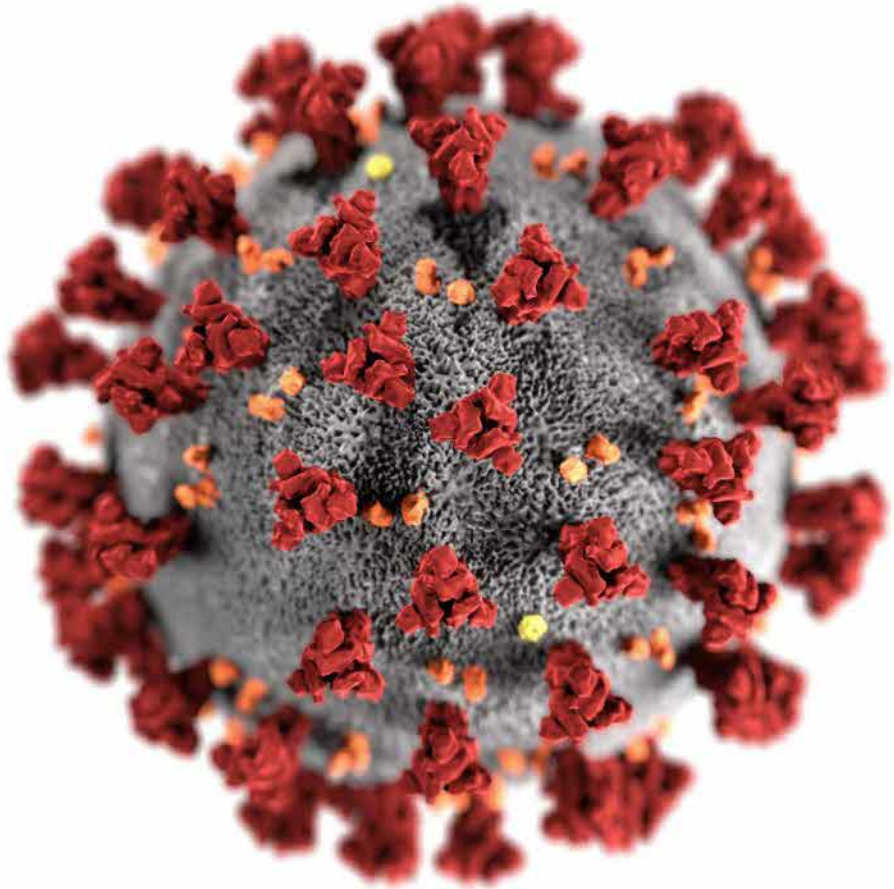
ACIP 2020 – June 24, 2020

For more information: **www.cdc.gov/COVID19**

Valid as of June 20, 2020

COVID 19
CORONAVIRUS DISEASE

Dr. Brooks has no relevant financial affiliations to disclose



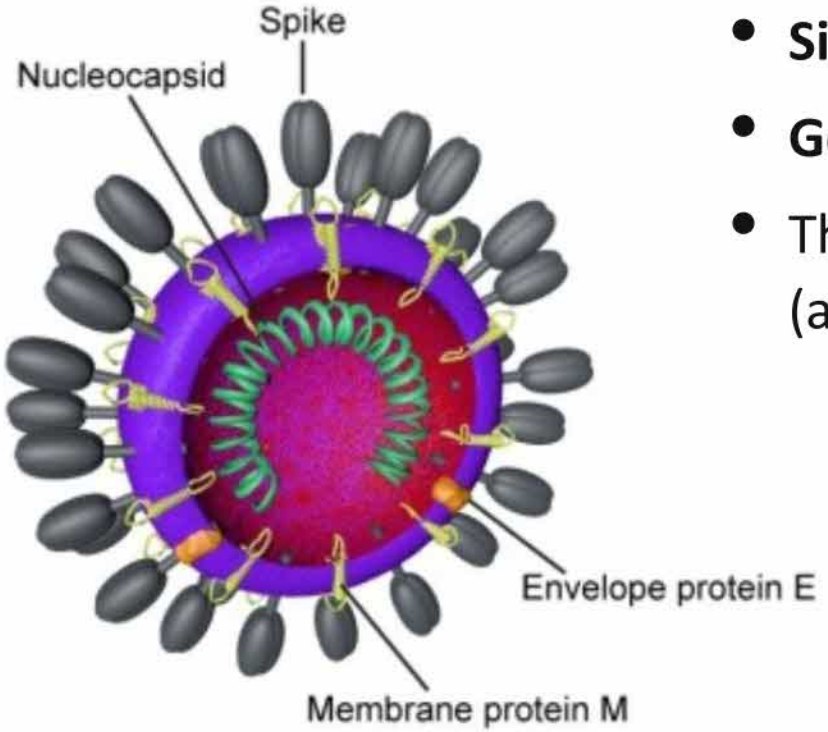
For more information: **www.cdc.gov/COVID19**

Valid as of June 20, 2020

COVID-19 Virology

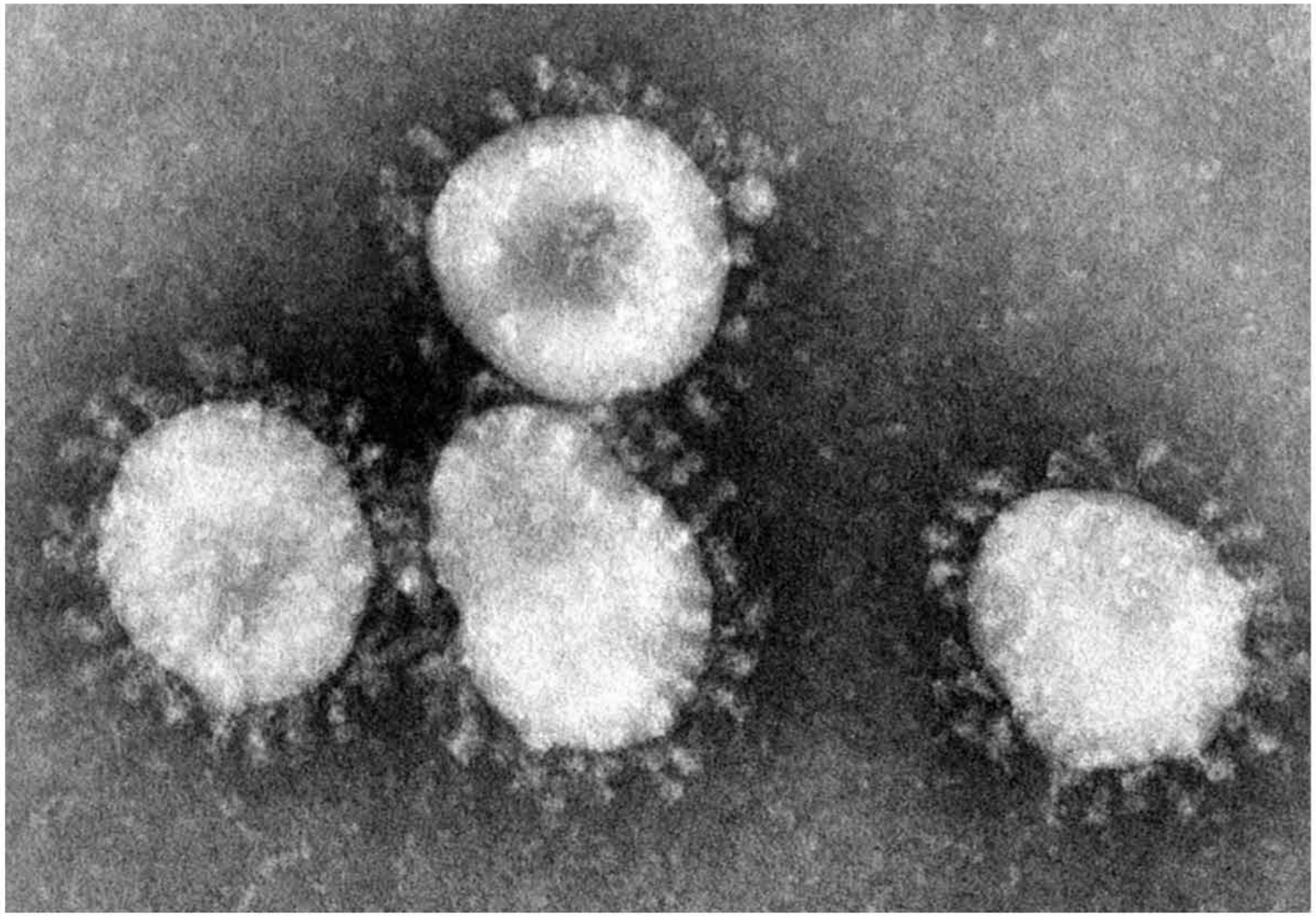
Valid as of June 20, 2020

Basic Structure of *Coronavirinae*



- **Single-stranded RNA viruses**
- **Genomes range from 25 to 32 kilobases**
- The coronaviral genome encodes **four major structural proteins** (all are required to produce a structurally complete viral particle)
  - Spike (S) protein: *binding*
  - Nucleocapsid (N) protein: *RNA synthesis*
  - Membrane (M) protein: *organization/assembly*
  - Envelope (E) protein: *organization/assembly*

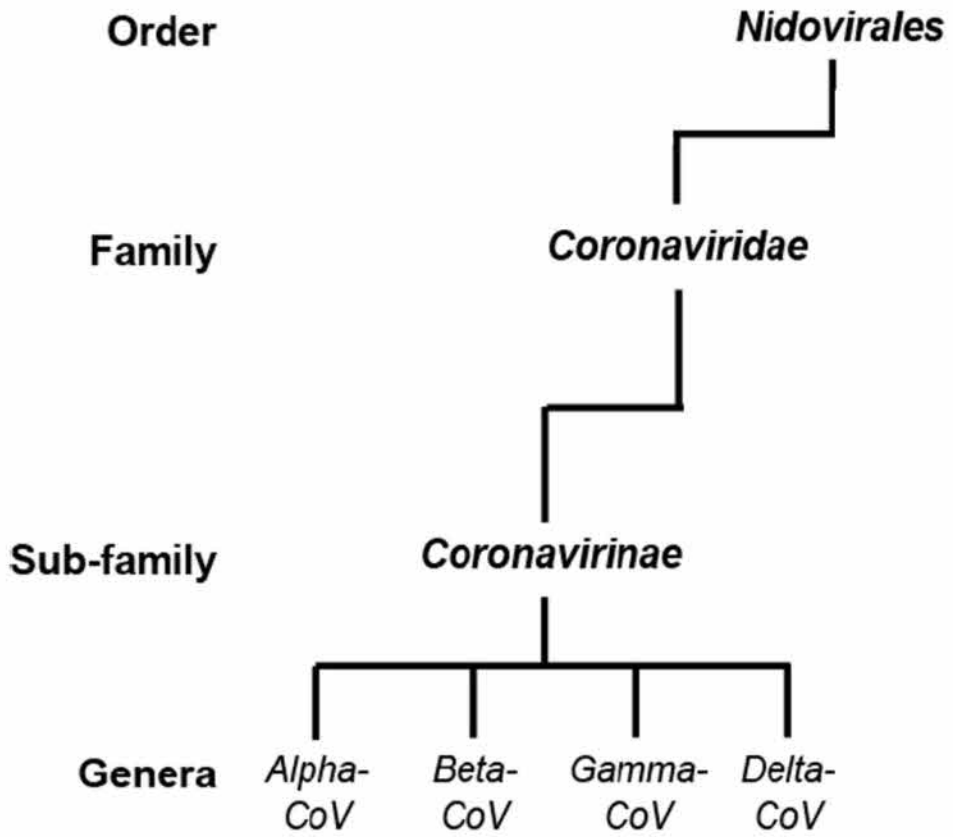
Electron Micrograph of Coronavirus Virions



Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #4814.

Valid as of June 20, 2020

Coronaviridae/-virinae Belong to Order Nidovirales



Infect a wide variety of mammals and birds

- Alpha and beta: "mammals"
  - flying bats to beluga whales
- Gamma and delta: "birds"
  - sparrows to ostriches

Cause a variety of lethal diseases, with well-studied impact on the agricultural sector

- Illness is usually **respiratory or enteric**

Cong 2017, Viruses 9(182), doi:10.3390/v9070182

Seven Human Coronaviruses (HCoVs)

- **Common HCoVs (lower pathogenicity):**
  - HCoV-229E (alpha)
  - HCoV-NL63 (alpha)
  - HCoV-OC43 (beta)
  - HCoV-HKU1 (beta)
- **Other HCoVs (higher pathogenicity):**
  - SARS-CoV-1 (beta)
  - MERS-CoV (beta)
  - **SARS-CoV-2** (beta)

The illness COVID-19 is caused by SARS-CoV-2, which is more like SARS-CoV than MERS-CoV

Song 2019, Viruses 11, 59; doi:10.3390/v11010059
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

Seven Human Coronaviruses (HCoVs)

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- **Other HCoVs (higher pathogenicity):**
  - SARS-CoV-1 (beta)
  - MERS-CoV (beta)
  - **SARS-CoV-2** (beta)

Palm civit cat

Dromedary camel

?

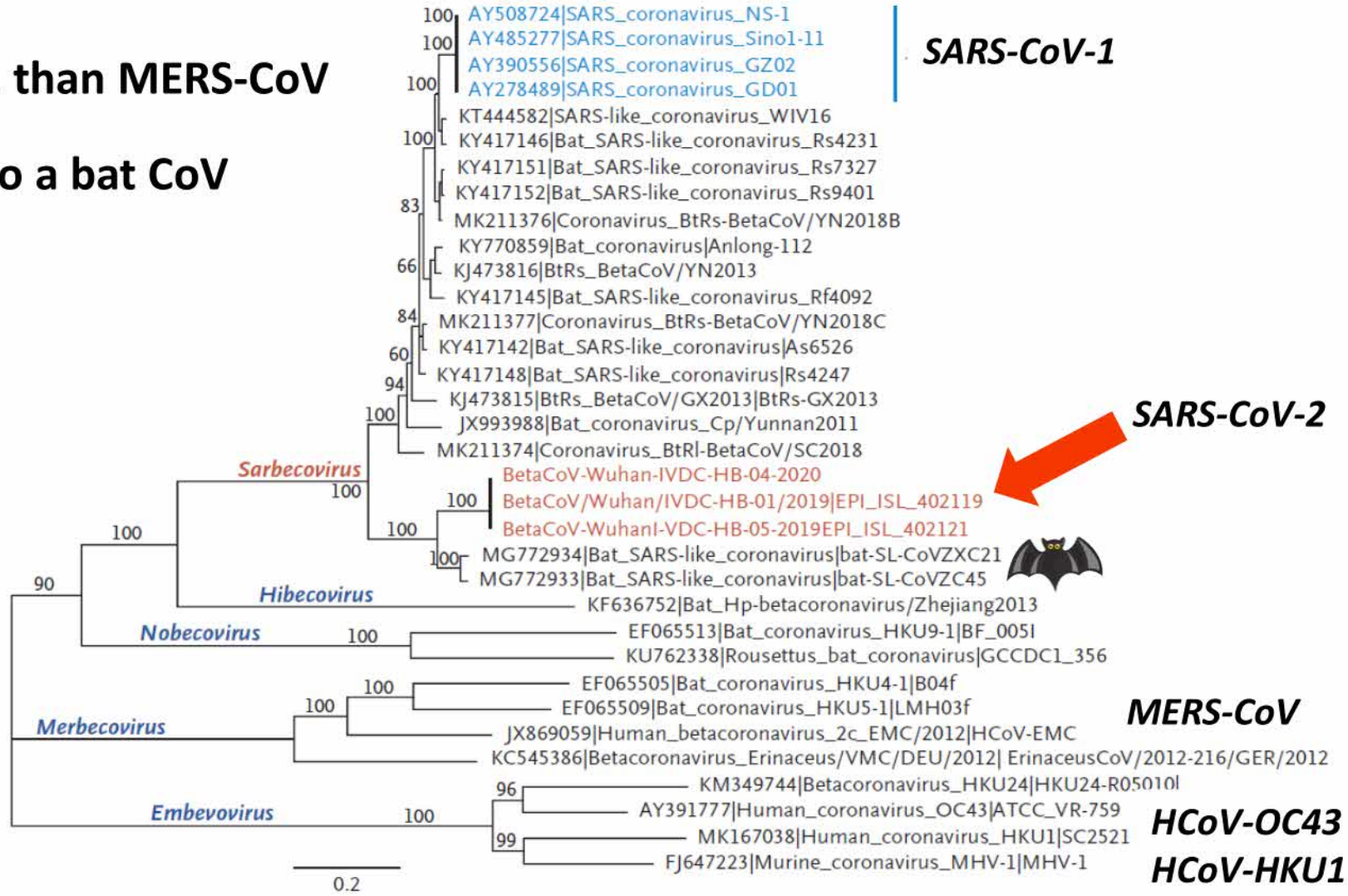
Song 2019, Viruses 11, 59; doi:10.3390/v11010059

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

Valid as of June 20, 2020

Phylogenetic Analysis of COVID-19 and Other Betacoronavirus Genomes

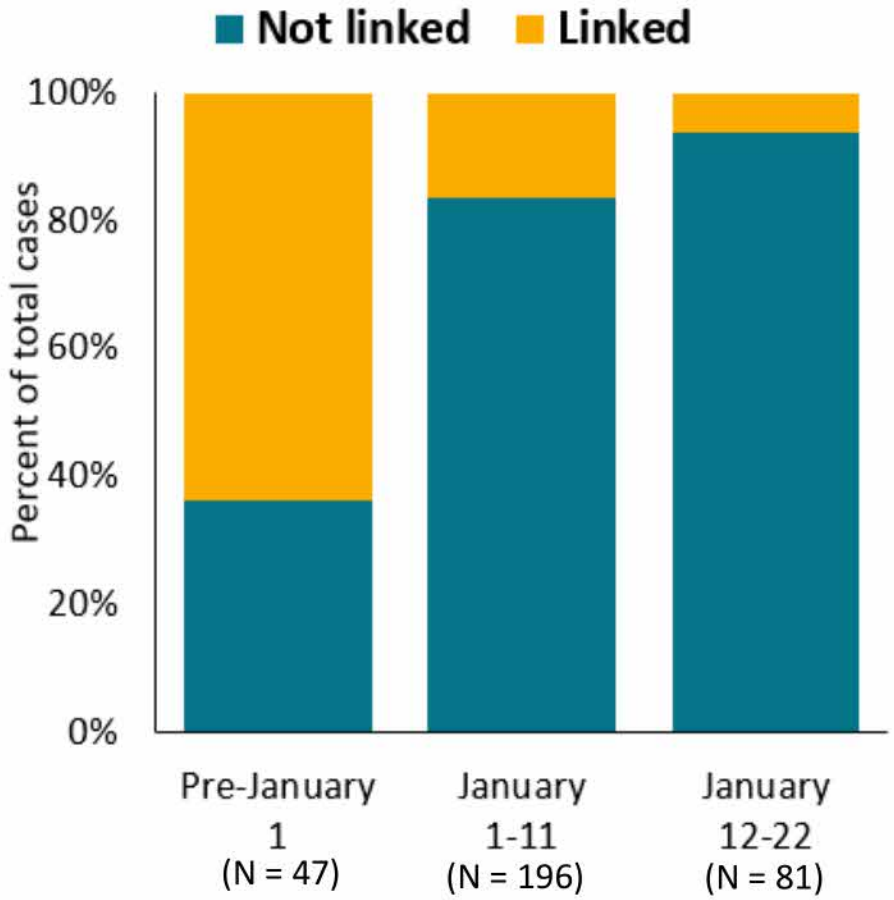
- More like SARS-CoV-1 than MERS-CoV
- Most closely related to a bat CoV



COVID-19 Transmission

Valid as of June 20, 2020

Linkage of Early COVID-19 Cases* to Huanan Seafood Wholesale Market – Wuhan, China



https://www.healthpolicy-watch.org/

Adapted from Li 2020, N Engl J Med; DOI: 10.1056/NEJMoa2001316.
* Total N=324 persons with complete exposure histories among 425 total cases

Valid as of June 20, 2020

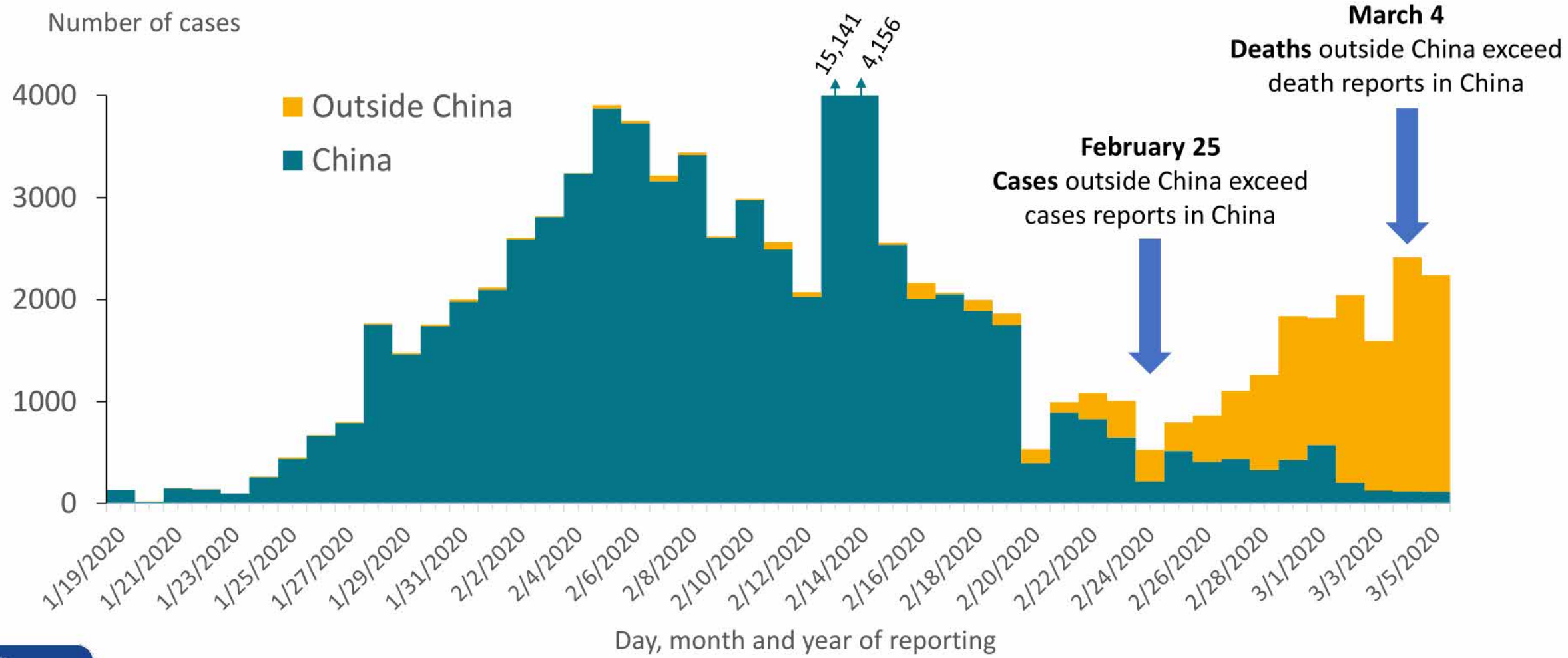
Early Distribution of Cases:

China as of 20-Jan-2020

CNN Source: National Health Commission of the PRC. Data correct as of January 26, 08:30 P.M. ET
Graphic: Natalie Leung and Henrik Pettersson, CNN

Valid as of June 20, 2020

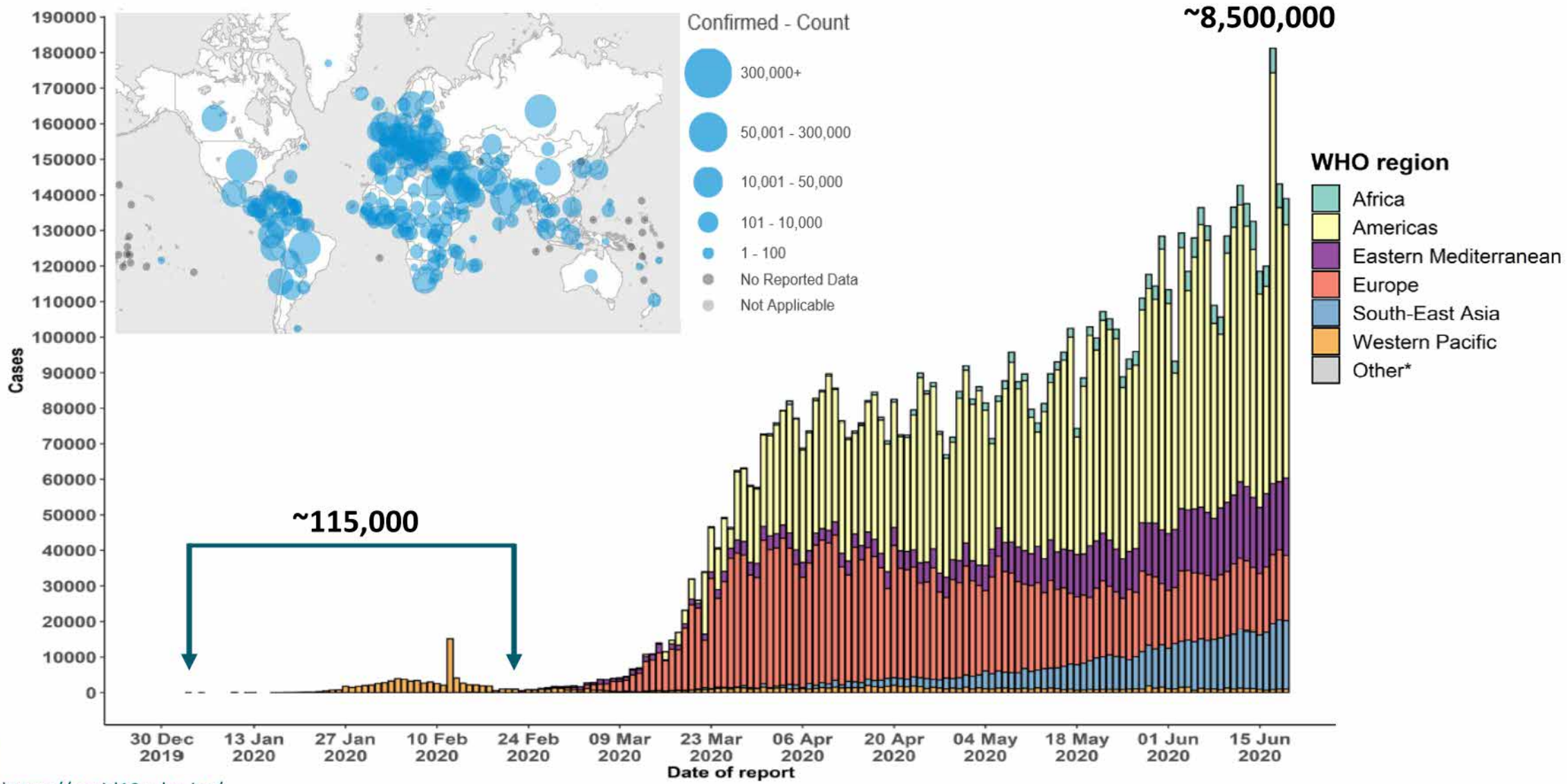
Distribution of COVID-19 cases in accordance with the applied case definitions in the affected countries, as of 05 March 2020



Courtesy of European CDC

Valid as of June 20, 2020

Number of confirmed COVID-19 cases, by date of report and WHO region, 30 December through 20 June



https://covid19.who.int/

Valid as of June 20, 2020

Transmission Dynamics of Pathogenic Human *Coronavirinae* (CoV)

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Incubation period, median (range)	4-6 days (up to 16)	4-6 days (range 2-14)	5 days (range 2-14)
Serial interval (days)	> Incubation (8)	> Incubation (12-14)	**< incubation (4)**
Infectious before ill	No	No	**Yes**

SARS-CoV-2

- Peak infectiousness days before symptom onset (***pre-symptomatic***) and shortly thereafter
- A substantial fraction of infections, **estimated 30-35%, are *asymptomatic***

Lauer 2020, Ann Intern Med; doi:10.7326/M20-0504. Du 2020, Emerg Infect Dis; doi.org/10.3201/eid2606.200357.
Nichiura 2020, Int J Infect Dis; doi.org/10.3201/eid2606.200357. Lipsitch 2003, Science;300(5627):1966-70.
Park 2018, BMC Public Health; doi.org/10.1186/s12889-018-5484-8

SARS-CoV-2 in Human Samples and Transmission

Sample	Mode of transmission	Detected by PCR	Isolated by culture	Observed mode of transmission
Nasopharyngeal swab	RESPIRATORY	Yes	Yes	Yes
Oropharyngeal swab		Yes	Yes	Yes
Sputum		Yes	Yes	Yes
Stool	FECAL	Yes	Yes but likely rare	Not yet reported
Urine	URINARY	No	Not yet reported	Not yet reported
Blood/serum	TRANSFUSION	Not reliably	No	Not yet reported
Amniotic fluid	PERINATAL	No	Not yet reported	Not yet reported
Umbilical cord blood		No	Not yet reported	Not yet reported
Breast milk		Not reliably	No	Not yet reported
Cervicovaginal fluid		No	Not yet reported	Not yet reported
Semen	SEXUAL	Yes, but likely rare	Not yet reported	Not yet reported

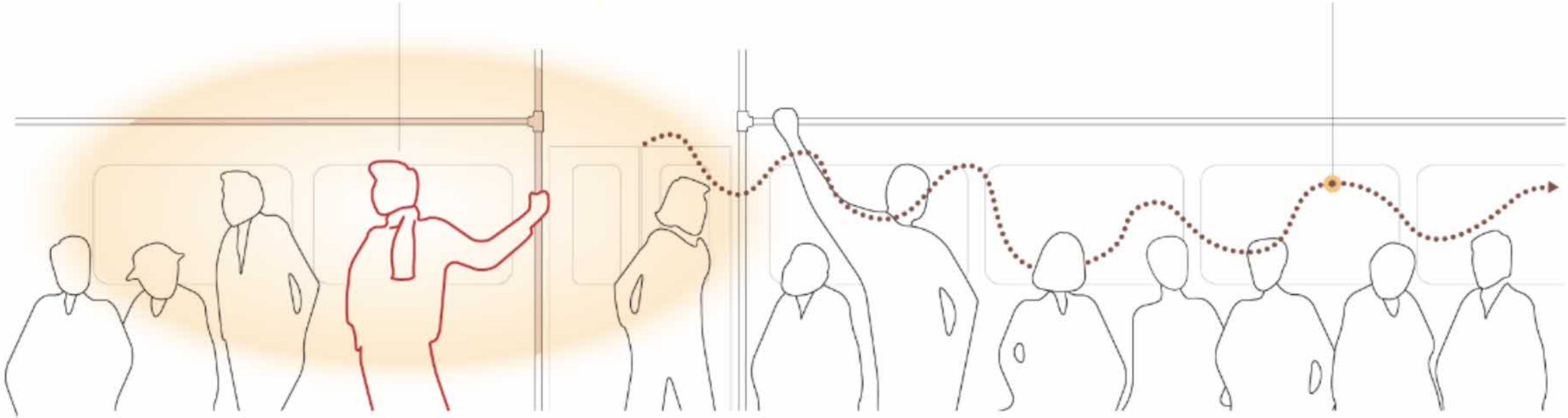
Zou 2020, N Engl J Med; DOI: 10.1056/NEJMc2001737. Pan 2020, Lancet Infect Dis; https://doi.org/10.1016/S1473-3099(20)30113-4. Zhang 2020; China CDC Weekly: http://weekly.chinacdc.cn/en/article/id/ffa97a96-db2a-4715-9dfb-ef662660e89d. Chen 2020; Lancet: https://doi.org/10.1016/ S0140-6736(20)30360-3. Zhu 2020l Transl Pedtr: http://dx.doi.org/10.21037/tp.2020.02.06. Li 2020, JAMA Network Open; doi:10.1001/jamanetworkopen.2020.8292. Yu 2020, Lancet Infect Dis; doi.org/10.1016/S1473-3099(20)30320-0

Valid as of June 20, 2020

How Far Can SARS-CoV-2 Travel?

Respiratory droplets
About 6 feet (2 meters)

Airborne/aerosolized
Many meters



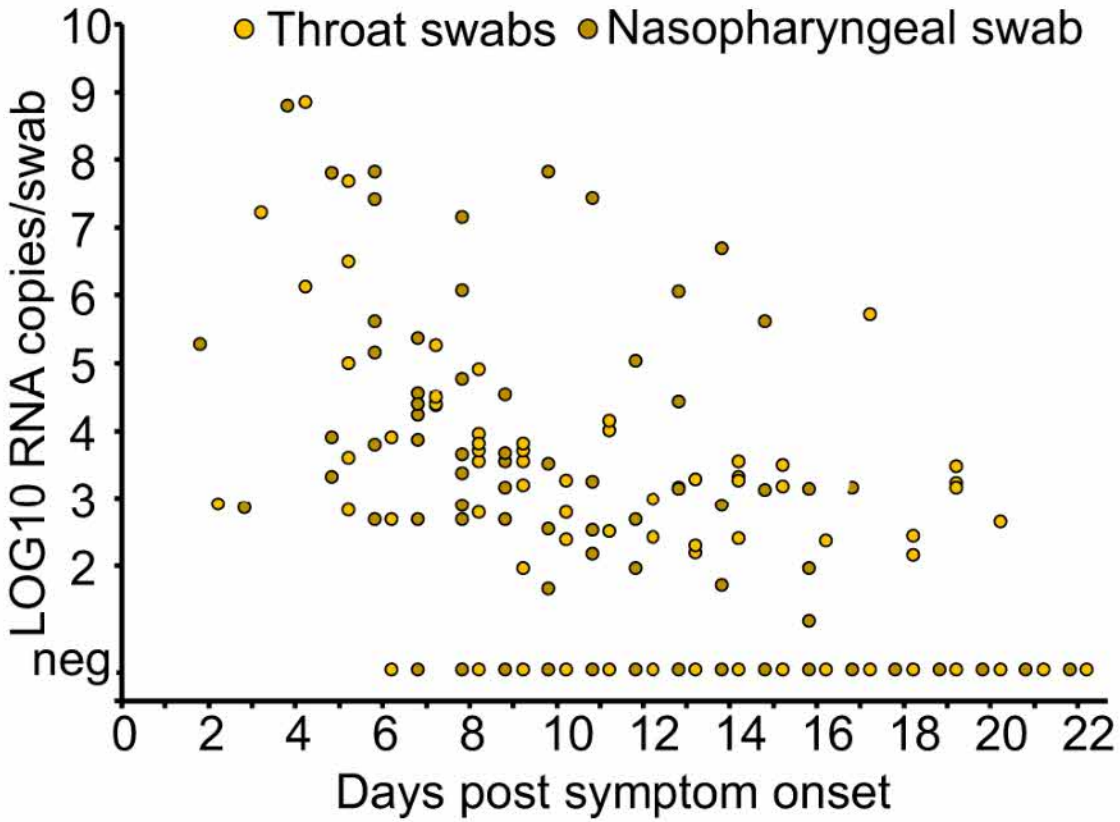
New York Times, January 31, 2020

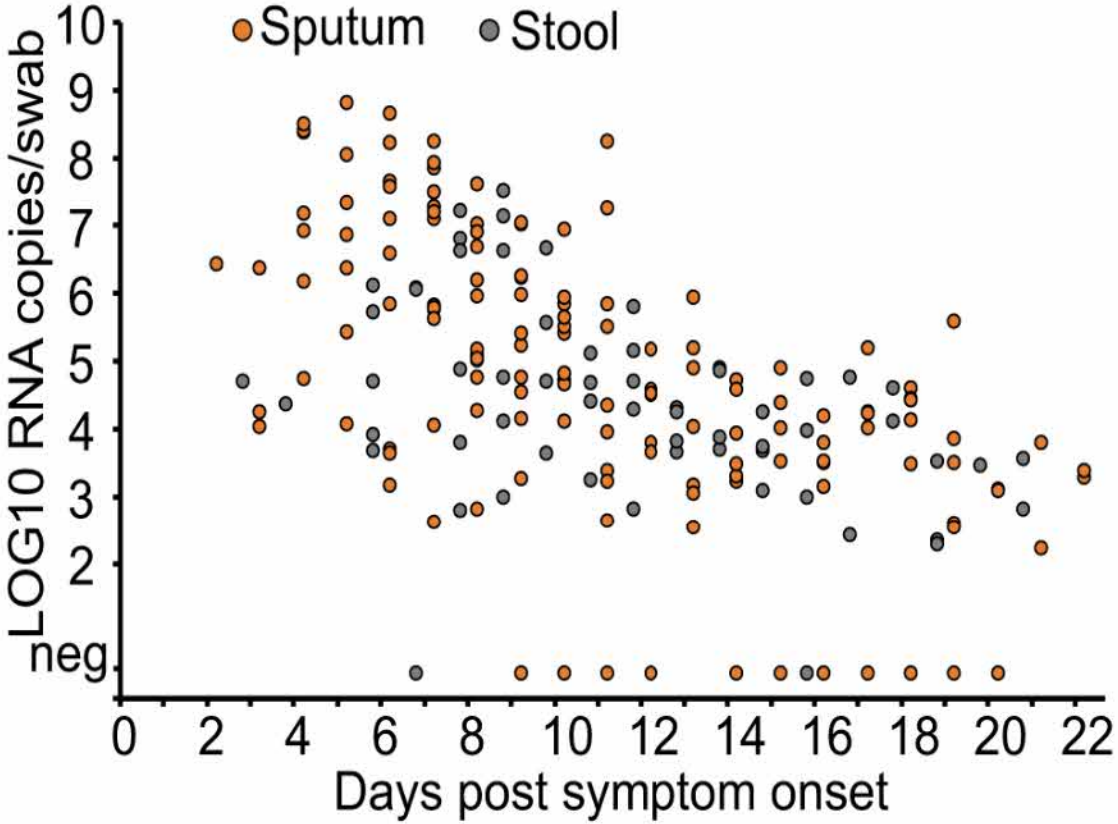
Valid as of June 20, 2020

COVID-19
Response to Infection

Valid as of June 20, 2020

Viral Burden Declines Steadily After Illness Onset

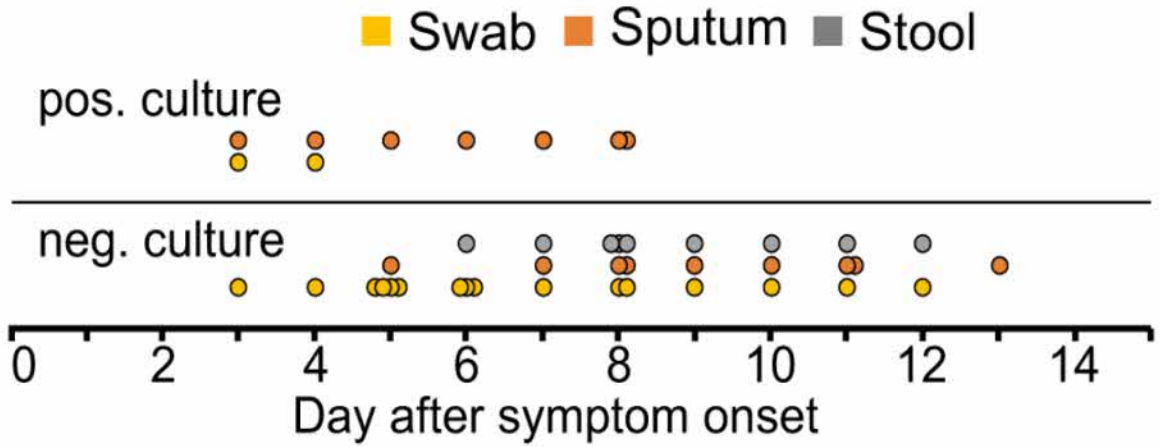




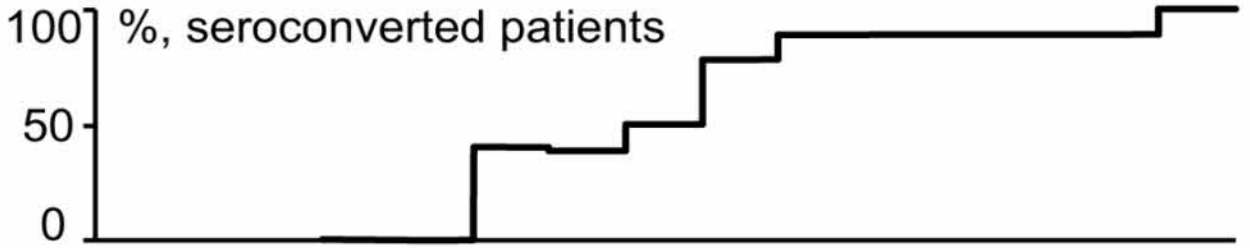
Wölfel2020, Nature; doi.org/10.1038/s41586-020-2196-x.

Valid as of June 20, 2020

Ability to Culture Virus from Specimens Declines as Serologic Response to Infection Grows



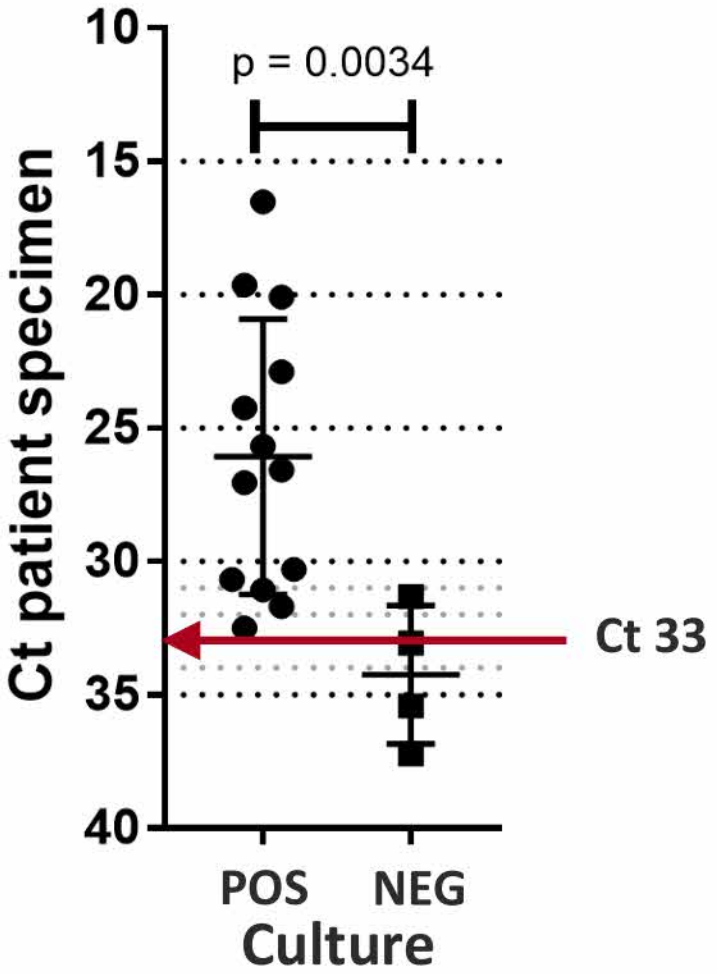
- After 8-10 days, replication-competent virus can no longer be recovered from respiratory tract specimens, in otherwise healthy persons with mild to moderate illness.
- In severely ill and immunocompromised persons, shedding of culturable virus may persist up to 20 days



- Within days after symptom onset, patients being to develop serologic response to infection that includes IgM, IgG, and IgA.
- IgG response includes neutralizing antibodies.

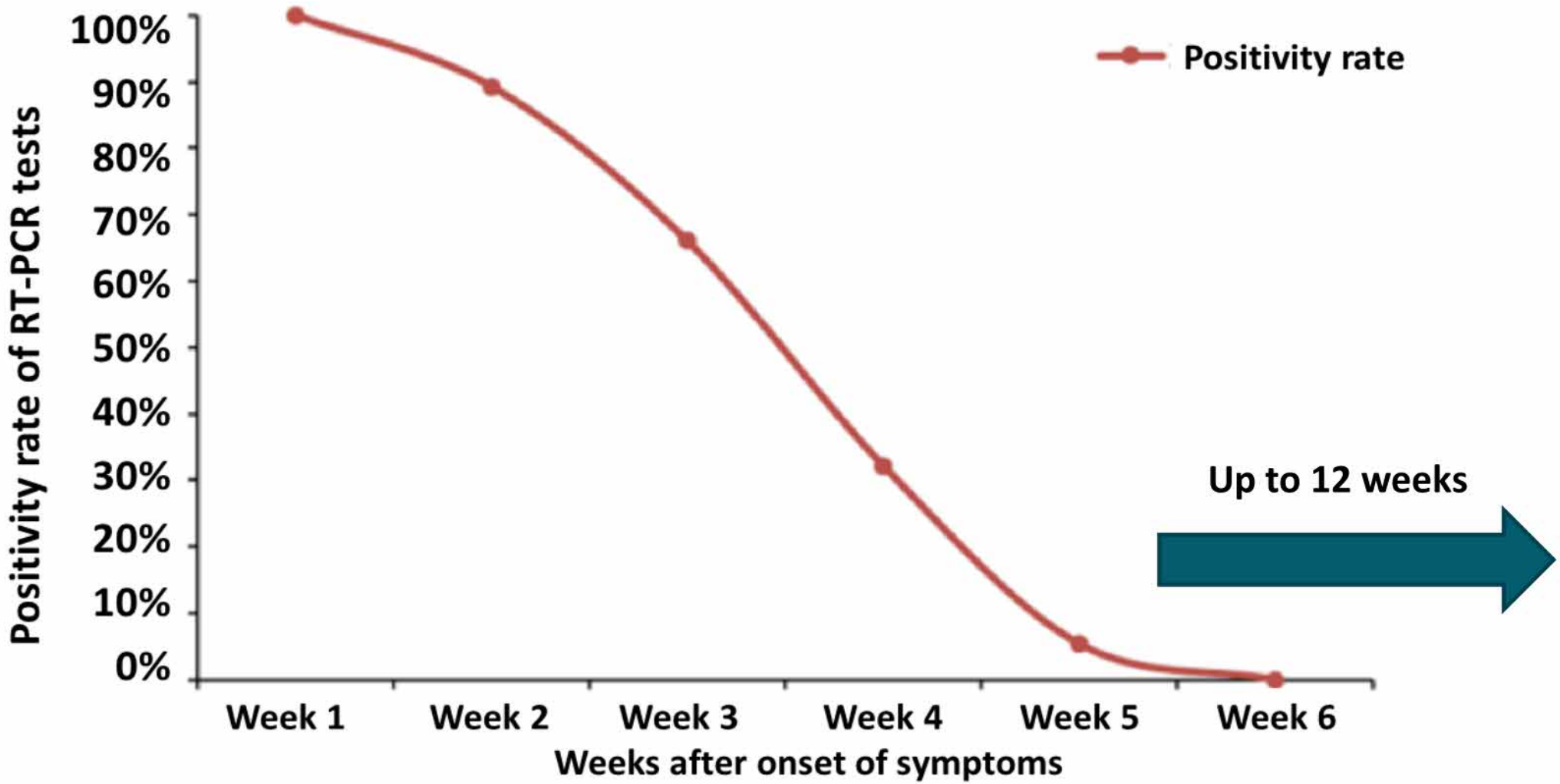
Wölfel2020, Nature; doi.org/10.1038/s41586-020-2196-x. van Kampen 2020, medRxiv; doi.org/10.1101/2020.06.08.20125310

Ability to Culture Virus from Specimens Declines with Decreasing Viral Burden



CDC, unpublished data.

PCR Can Remain Positive for Weeks After Recovery



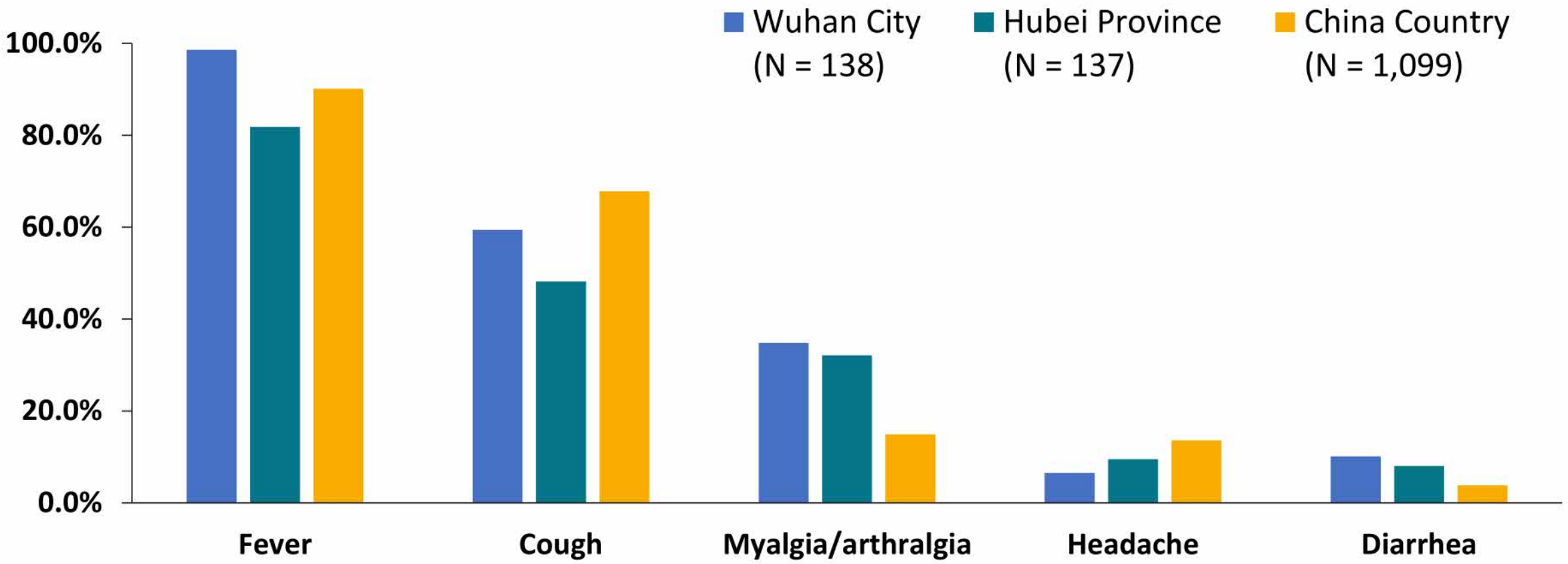
Xiao 2020, Clin Infect Dis; doi.org/10.1093/cid/ciaa460. Li 2020, J Med Virol; doi: 10.1002/jmv.25952.

Valid as of June 20, 2020

COVID-19
Clinical Epidemiology

Valid as of June 20, 2020

Signs/Symptoms of COVID-19



Liu 2020, Chinese Med J; DOI: 10.1097/CM9.0000000000000744. Wang 2020, JAMA; doi:10.1001/jama.2020.1585.
Guan 2020, N Engl J Med; DOI: 10.1056/NEJMoa2002032.

Valid as of June 20, 2020

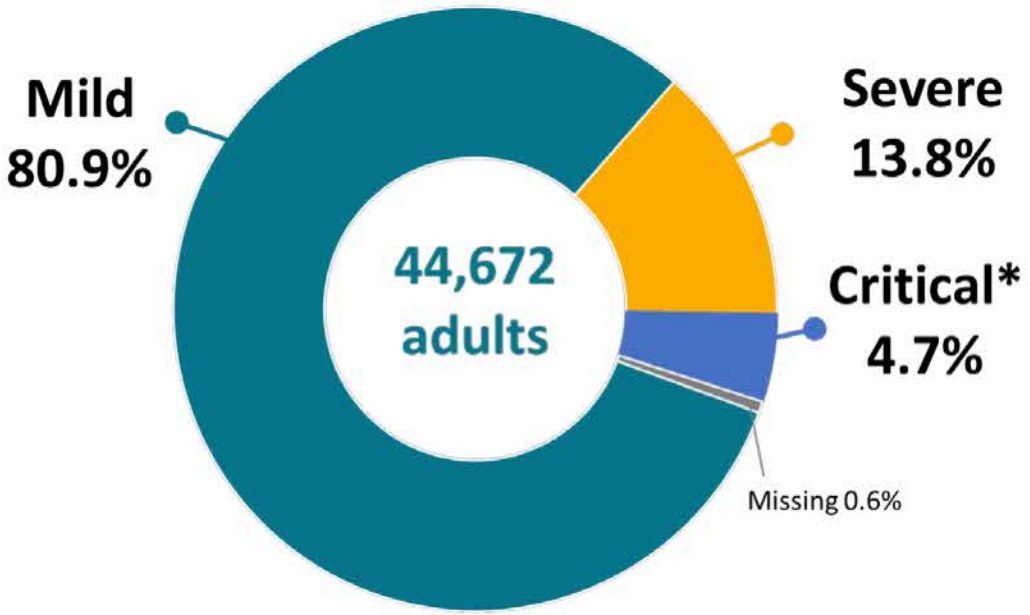
Signs/Symptoms of COVID-19

- No particular set of signs or symptoms can reliably discriminate COVID-19 from other respiratory viral illnesses such as influenza
  - Anosmia/dysgeusia
- Most people will recover spontaneously with supportive care
- Typical complications include pneumonia, respiratory failure, multiorgan system failure, and death

Liu 2020, Chinese Med J; DOI: 10.1097/CM9.0000000000000744. Wang 2020, JAMA; doi:10.1001/jama.2020.1585.
Guan 2020, N Engl J Med; DOI: 10.1056/NEJMoa2002032.

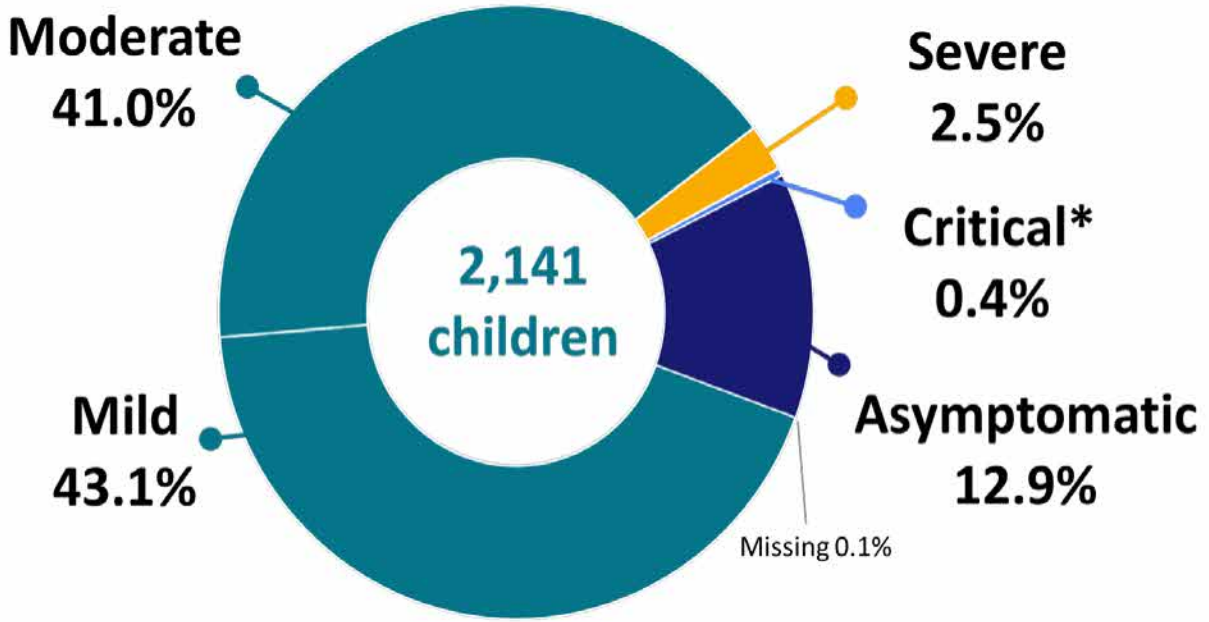
Illness Severity in Adults and Children with COVID-19, China

Severity of Illness, Adult COVID-19 (N = 44,672 confirmed cases)



* 1,023 (49%) deaths among 2,087 critically ill adults

Severity of Illness, Pediatric COVID-19 (N = 2,141 confirmed cases)



* 1 deaths among critically ill children

adapted from Zhang 2020, China CDC Weekly Report; 2(8):113-122 and Dong 2020, Pediatrics; doi 10.1542/peds.2020-0702.

Valid as of June 20, 2020

Unique Complications of COVID-19

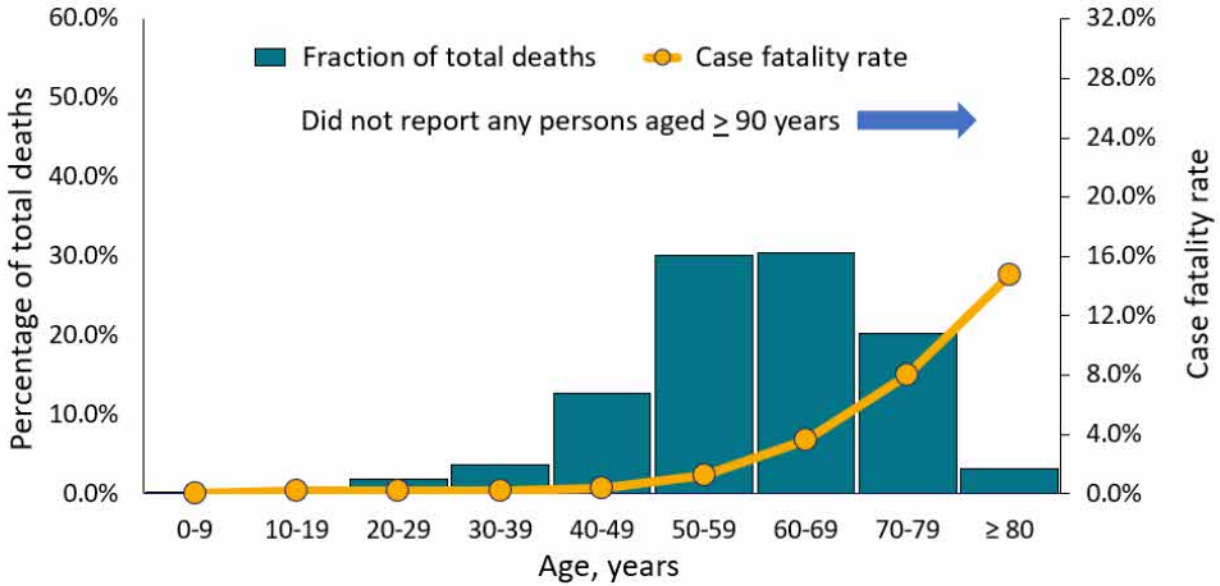
- Diffuse endotheliitis (viral tropism)
- Hypercoagulability
  - Both local and embolic
  - ARDS complicated by thromboembolic disease
- Peri- and post-infectious hyperimmune reaction
  - Myocarditis
  - Multiorgan inflammatory syndrome in children (MIS-C)

Varga 2020, Lancet; doi.org/10.1016/S0140-6736(20)30937-5. Fox 2020, Lancet Resp Med; doi.org/10.1016/S2213-2600(20)30243-5. Belot 2020, Euro Surveill;25(22):pii=2001010. Carsana 2020, Lancet Infect Dis; doi.org/10.1016/S1473-3099(20)30434-5. Riphagen 2020, Lancet; doi.org/10.1016/S0140-6736(20)31094-1 Lax 2020, Ann Intern Med; doi:10.7326/M20-2566. Verdoni 2020, Lancet; doi.org/10.1016/S0140-6736(20)31103-X

Age Structure Contributes to Observed Case Fatality Rate

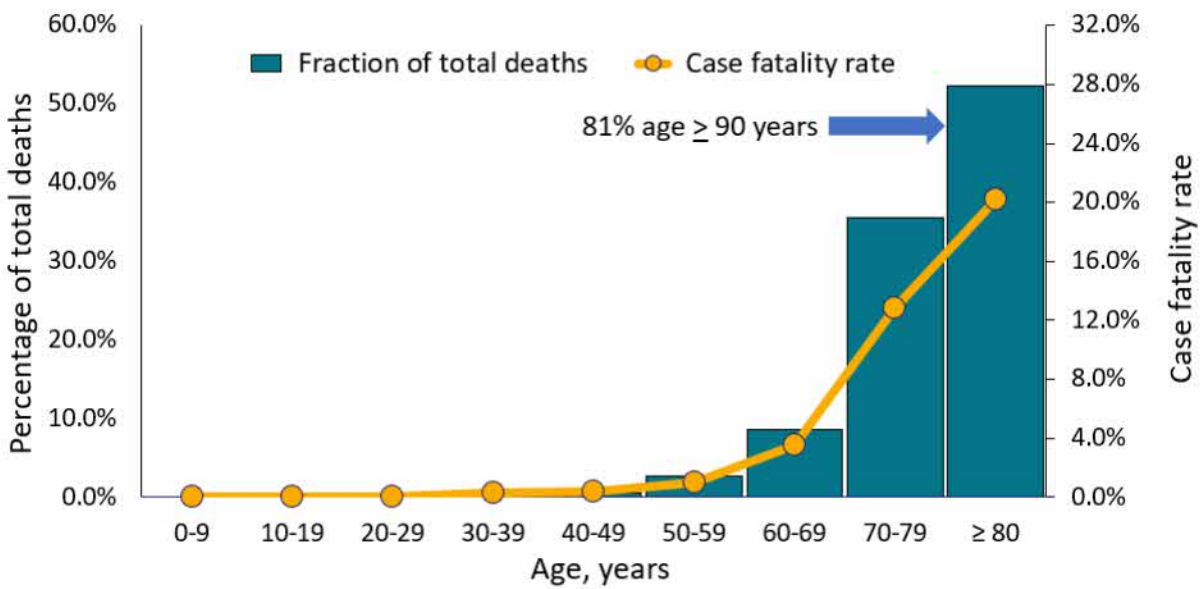
Death Distribution and Case Fatality Rate
China, (N = 44,672) through 11 FEB 2020

2.3% overall CFR



Death Distribution and Case Fatality Rate
Italy, (N = 22,512) through 17 MAR 2020

7.2% overall CFR



adapted from Zhang 2020, China CDC Weekly Rep; 2(8):113-122. adapted from Onder 2020, JAMA; doi:10.1001/jama.2020.4683.

Valid as of June 20, 2020

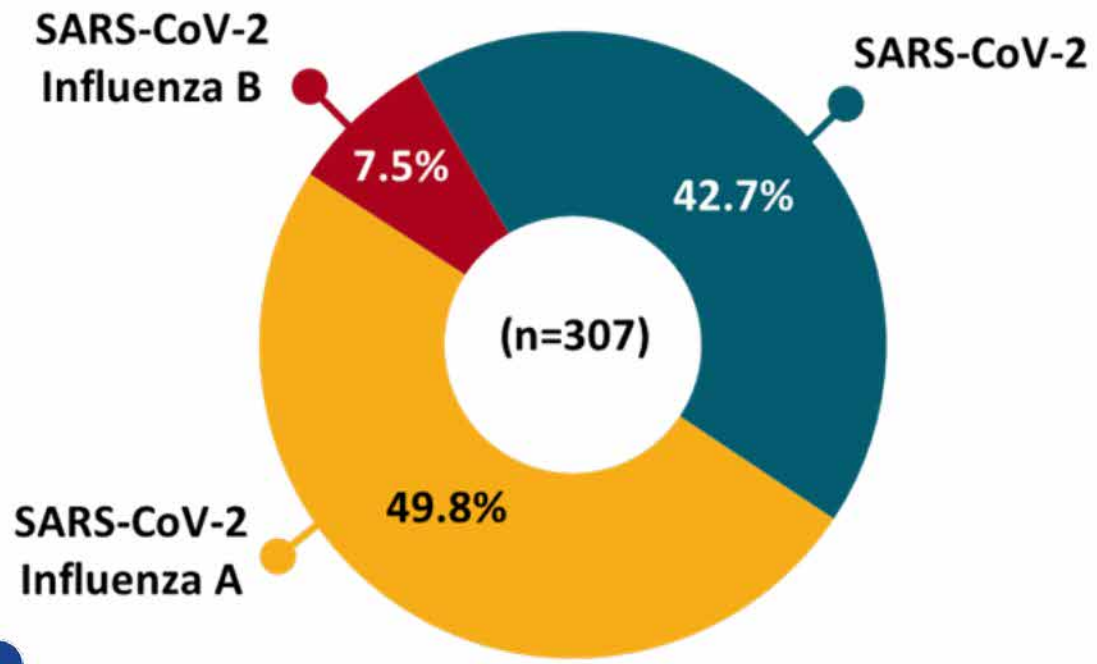
COVID-19 in High-Risk Groups

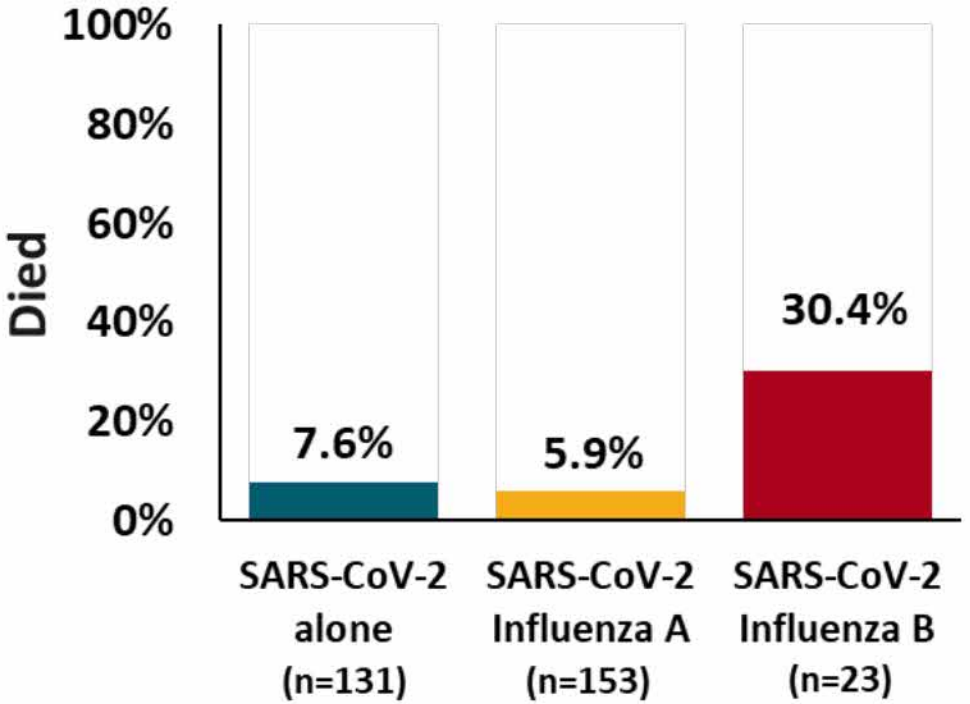
- **Comorbidity and advanced age increase risk for severe illness and death**
  - Cardiovascular disease, diabetes, chronic respiratory disease
- **Immunocompromised (medical, acquired) – emerging data reassuring**
  - For persons with HIV, risk likely greatest at low CD4 cell counts or not virally suppressed
  - No definitive evidence that cancer therapy worsens outcomes (incl. immnuosuppresives)
- **Pregnancy**
  - Maternal morbidity similar to that of uninfected women in COVID-19
  - No definitive evidence infection transmitted perinatally

Zhang 2020, China CDC Weekly Report; 2(8):113-122 Rasmussen 2020; Am J Obstet Gynecol: https://doi.org/10.1016/j.ajog.2020.02.017
Lee 2020, Lancet; doi.org/10.1016/S0140-6736(20)31173-9

SARS-CoV-2 and Influenza Coinfection, Coinfection with Influenza B More Deadly

- Patients from a single hospital outbreak in Wuhan during Jan-Feb 2020
- Diagnoses made by assaying SARS-CoV-2 RNA and influenza IgM
- No significant differences in age (median 50's-60's), sex (M:F), illness severity





Yue 2020, J Med Virol; doi:10.1002/jmv.26163.

Valid as of June 20, 2020

Valid as of June 20, 2020

From: Kirkcaldy, Bob (CDC/DDID/NCHHSTP/DSTDP)
Sent: Wed, 15 Apr 2020 14:38:54 +0000
To: Allison, Robert (CDC/DDPHSIS/CGH/GID)
Cc: Brooks, John T. (CDC/DDID/NCHHSTP/DHP); King, Brian a. (CDC/DDNID/NCCDPHP/OSH)
Subject: FW: Just and FYI er; HCQ/CQ Special Edition
Attachments: Lane 2020 - meta-analysis assoc HCQ and AZITHRO with outcomes in persons taking for non-COVID indication - medRxiv.pdf, Borba 2020 - chloroquine study stopped due to cardiac toxicity - medRxiv.pdf

Hi Rob -- sharing

From: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Sent: Wednesday, April 15, 2020 10:37 AM
To: King, Brian a. (CDC/DDNID/NCCDPHP/OSH) <iyn3@cdc.gov>
Cc: Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHPSE) <geo5@cdc.gov>; Kirkcaldy, Bob (CDC/DDID/NCHHSTP/DSTDP) <hgl8@cdc.gov>
Subject: Just and FYI er; HCQ/CQ Special Edition

Just noting two papers that we would want to include in any update of Special Edition #1 about HCQ/CQ

Although non-peer reviewed now, keep an eye for publication. They look like solid studies that should move to publication relatively quickly…

-john

John T. Brooks, MD
Chief Medical Officer, CDC COVID-19 Response
Email: zud4@cdc.gov
Apologies for errors in my messages that may be due to my need to dictate.


KEEP
CALM
AND
WASH
YOUR
HANDS
CDC

Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study

Jennifer C.E.Lane MRCS*[1], James Weaver MSc*[2], Kristin Kostka MPH[3] , Talita Duarte-Salles PhD[4], Maria Tereza F. Abrahao PhD[5], Heba Alghoul MD[6], Osaid Alser MD[7], Thamir M Alshammari PhD[8], Patricia Biedermann MSc[9], Edward Burn MSc[1,4], Paula Casajust MSc[10], Mitch Conover[2], Aedin C. Culhane PhD[11], Alexander Davydov MD[12], Scott L. DuVall PhD[13,14], Dmitry Dymshyts MD[12], Sergio Fernandez-Bertolin MSc[2], Kristina Fišter MD[15], Jill Hardin PhD[2], Laura Hester PhD[2], George Hripcsak MD[16,17], Seamus Kent PhD[18], Sajan Khosla MSc[19], Spyros Kolovos PhD[1], Christophe G. Lambert PhD[20], Johan van der Lei PhD[21], Ajit A. Londhe MPH[22], Kristine E. Lynch PhD[13,14], Rupa Makadia PhD[2], Andrea V. Margulis ScD[23], Michael E. Matheny MD[13,24], Paras Mehta BA[25], Daniel R. Morales PhD[26], Henry Morgan-Stewart PhD[3], Mees Mosseveld MSc[21], Danielle Newby PhD[27], Fredrik Nyberg PhD[28], Anna Ostropolets MD[16], Rae Woong Park MD[29], Albert Prats-Uribe MPH[1], Gowtham A. Rao MD[2], Christian Reich MD[3], Jenna Reps PhD[2], Peter Rijnbeek PhD[21], Selva Muthu Kumaran Sathappan MSc[30], Martijn Schuemie PhD[2], Sarah Seager BA[3], Anthony Sena [2], Azza Shoaibi PhD[2], Matthew Spotnitz MD[16], Marc A. Suchard MD[31], Joel Swerdel PhD[2], Carmen O. Torre MSc[3], David Vizcaya PhD[32], Haini Wen MSc[33], Marcel de Wilde BSc[21], Seng Chan You MD[29], Lin Zhang MD[34], Oleg Zhuk MD[12], Patrick Ryan PhD[2]**, and Daniel Prieto-Alhambra PhD[1,4]; on behalf of OHDSI-COVID-19 consortium.

*equal contribution

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** Corresponding author: Patrick Ryan, Janssen Research & Development, Titusville, NJ, USA

ryan@ohdsi.org, 919.609.2723

Keywords: hydroxychloroquine, chloroquine, covid-19, coronavirus, SARS-CoV-2, safety, epidemiology, international, serious adverse event, rheumatoid arthritis, azithromycin

ABSTRACT

Background Hydroxychloroquine has recently received Emergency Use Authorization by the FDA and is currently prescribed in combination with azithromycin for COVID-19 pneumonia. We studied the safety of hydroxychloroquine, alone and in combination with azithromycin.

Methods New user cohort studies were conducted including 16 severe adverse events (SAEs). Rheumatoid arthritis patients aged 18+ and initiating hydroxychloroquine were compared to those initiating sulfasalazine and followed up over 30 days. Self-controlled case series (SCCS) were conducted to further establish safety in wider populations. Separately, SAEs associated with hydroxychloroquine-azithromycin (compared to hydroxychloroquine-amoxicillin) were studied. Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate calibrated hazard ratios (CalHRs) according to drug use. Estimates were pooled where I2<40%.

Results Overall, 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin were included. No excess risk of SAEs was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. SCCS confirmed these findings. However, when azithromycin was added to hydroxychloroquine, we observed an increased risk of 30-day cardiovascular mortality (CalHR2.19 [1.22-3.94]), chest pain/angina (CalHR 1.15 [95% CI 1.05-1.26]), and heart failure (CalHR 1.22 [95% CI 1.02-1.45])

Conclusions Short-term hydroxychloroquine treatment is safe, but addition of azithromycin may induce heart failure and cardiovascular mortality, potentially due to synergistic effects on QT length. We call for caution if such combination is to be used in the management of Covid-19.

Trial registration number: Registered with EU PAS; Reference number EUPAS34497 (http://www.encepp.eu/encepp/viewResource.htm?id=34498). The full study protocol and analysis source code can be found at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine.

Funding sources

This research received partial support from the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and Senior Research Fellowship (DPA), US National Institutes of Health, Janssen Research & Development, IQVIA, and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea [grant number: HI16C0992]. Personal funding included Versus Arthritis [21605] (JL), MRC-DTP [MR/K501256/1] (JL), MRC and FAME (APU). The European Health Data & Evidence Network has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 806968. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. No funders had a direct role in this study. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Clinician Scientist Award programme, NIHR, NHS or the Department of Health, England.

INTRODUCTION

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic exerts an unprecedented pressure on health care systems worldwide, there remains a paucity of evidence surrounding the safety and effectiveness of potential treatments.[1] Several existing drugs have been postulated to be effective against SARS-CoV-2. These include conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), which are most commonly used as the first line treatment of autoimmune diseases such as rheumatoid arthritis (RA) and systematic lupus erythematosus (SLE).[2,3] Hydroxychloroquine (HCQ) has been proposed as potential treatment options for COVID-19 based on its mechanism of action. Accumulating in the acid vesicles (endosome, Golgi vesicles, lysosomes), HCQ causes alkalinisation, leading to enzyme dysfunction and preventing endosome mediated viral entry to the cell. [3-6] It is also suggested in vitro that HCQ can prevent glycosylation of virus cell proteins including the ACE2 receptor, inhibiting virus entry and replication, and that similar compounds like chloroquine can specifically inhibit SARS-Cov-2.[5,7-9] In clinical studies, the addition of HCQ has shown increased early virological response to treatment for chronic hepatitis C, and reduced viral load in patients with HIV infection, compared to placebo. [10,11] Treatment with HCQ also lowered IL-6 level in HIV patients, suggesting the agent may have immunosuppressive properties helpful in the prevention or treatment of cytokine storm associated with severe COVID-19 disease.[12,13]

As of 28th March 2020, there are over 21 registered ongoing clinical trials and 3 prophylactic studies assessing the efficacy of hydroxychloroquine HCQ for the treatment of SARS-Cov-2.[14-20] Early results from randomised controlled trials conducted in China have shown reduced severity and course of the disease with hydroxychloroquine HCQ, compared with placebo, without detecting serious adverse effects, although others have suggested no difference in outcome from conventional treatment.[21,22] Of those studies that have reported more detailed results and received significant media attention, HCQ

has been proposed at higher doses than used in the treatment of auto-immune disorders and alongside azithromycin (AZM), a macrolide antibiotic.[23 24] Results from this open label observational study suggest that the combination of HCQ and azithromycin AZM might lead to a faster recovery and reductions in viral load in the treatment of COVID-19. However, many authors have criticised the study due to lack of low power, limited follow-up, confounding by indication, and lack of adherence to the allocated treatment arm.[25] The efficacy of HCQ in combination with AZM is therefore yet to be established, but approval for compassionate use by regulators and media attention will likely lead to an increase in use of this combined therapy for the management of COVID-19 worldwide.

In preparation for our study, we systematically searched the literature (PubMed, Embase), clinical trial registries (Clinicaltrials.gov, ICTRP and Chinese Clinical Trial Registry) and preprint servers (bioRxiv and medRxiv) from inception until 27/03/2020 (Supplementary appendix section 11). No contemporary large-scale evidence was found to identify the real-world comparative safety of HCQ compared to other first line DMARDs, especially in combination with macrolide antibiotics such as AZM that are being considered for use in treating COVID-19.

Sepriano *et al.* led a systematic review to inform EULAR 2019 recommendations for the safety of RA medications, but little high-level evidence focussed on HCQ.[26] Another recent review of the comparative risks of non-serious and serious adverse events (SAEs) associated with DMARDs predominantly focussed upon biologic therapies.[27] There is little good high quality evidence quantifying SAEs risk in the literature with several studies suggesting no increased infection risk with any nonbiologic DMARDs, including HCQ.[28,29] The safety profile of HCQ is described in its summary of products characteristics, with adverse drug reactions including severe cardiac disorders as QT segment prolongation that could lead to arrhythmia, myocardial arrest or cardiovascular death.[30] Azithromycin (AZM, and macrolides in general)

are known to induce cardiotoxicity when used alone, and to also increase the risk of other drugs that prolong QTc interval.[31-34] It is therefore of utmost importance that we understand the safety implications of the proposed combination of HCQ and azithromycin AZM before this becomes standard practice in the management of COVID-19 globally.

In light of the current global pandemic, information regarding the safety of HCQ in worldwide real-world practice is vital to inform policy.[35,36] We aimed to assess the safety of hydroxychloroquine (HCQ) alone and in combination with AZM to help guide decisions in the face of the growing COVID-19 pandemic.

METHODS

Study design

Two study designs were developed and executed across a multinational, distributed database network. First, new user cohort studies were used to estimate the safety of HCQ compared to sulfasalazine (SSZ), and to assess the risks associated with the addition of AZM compared to amoxicillin (AMX) amongst users of HCQ in patients with rheumatoid arthritis (RA). SSZ and AMX were chosen as active comparators as they have similar indications as the target treatments (HCQ and AZM respectively). As a secondary analysis, self-controlled case series (SCCS) was used to estimate the safety of HCQ in the wider population, including uses for non-RA indications.

Data sources

Electronic health records and administrative claims databases from primary care and secondary care containing participants from Germany, Japan, Netherlands, Spain, the UK, and the USA were analysed in a distributed network, and are detailed in the Supplementary Appendix, Table S1.

Observational healthcare databases mapped to the Observational Medical Outcomes Partnership (OMOP) common data model collaborated in an international effort with the Observational Health Data Science and Informatics (OHDSI) community.[37,38] De-identified or pseudonymised data were obtained from routinely collected records from clinical practice in Germany, Spain, the UK, Japan, and the USA. Studies were performed locally and no patient level data shared using the following databases: IQVIA Disease Analyser Germany EMR (ambulatory EMR from Germany); JMDC (Japanese claims); IPCI (primary care EMR from Netherlands); SIDIAP (primary care EMR from Spain); CPRD and IMDR (primary care EMRs from UK); and CCAE, Optum, MDCR, MDCD, PanTher, IQVIA OpenClaims, Veteran Affairs (VA), and IQVIA US Ambulatory EMR (USA). SCCS were conducted on a subset of these as a secondary analysis: CCAE, CPRD, Optum, MDCD, and MDCR. Rather than pooling these data assets, all analyses were conducted in a distributed network, where analysis code was sent to participating sites and only aggregate summary statistics were returned, with no sharing of patient-level data between organizations.

Study Period and Follow-up

The study period started from 01/09/2000 and ended at the latest available date for all data sources in 2020. Follow-up for each of the cohorts started at an index date defined by the first dispensing or prescription of the target/comparator drug as described in the cohort definitions (Supplementary Table 2.1). Two periods were considered to define time-at-risk. First, for an *intention-to-treat analysis*, follow-up started one day after the index date and continued up until the first of: outcome of interest, loss to follow-up, or 30 days after the index date to resemble the likely duration of COVID-19 treatment regimens.[23] Secondly, for an *on-treatment analysis*, follow-up started one day after the index date and continued until the earliest of: outcome of interest, loss to follow-up, or discontinuation, with an added

washout time of 14 days. Continued use of a same treatment was inferred by allowing up to 90-day gaps between dispensing or prescription records.

In the HCQ versus SSZ study, the index event was defined as the first recorded dispensing or prescription of the drug in a patient's history. For the study of HCQ combined with AZM, follow up started when the second of the two co-administered treatments was initiated while still exposed to the first treatment (e.g. when AZM started during a period of HCQ use, or when HCQ started during a period of AZM use). HCQ use was assumed to be chronic in the management of RA, and AZM was assumed an acute prescription for infection treatment, and therefore inferred persistent exposure to AZM was assessed by allowing up to 30 days between dispensing or prescription records. Cohorts of combined HCQ and amoxicillin were generated using these same rules as an active comparator.

For SSCS, periods of inferred persistent exposure to HCQ were generated by allowing up to 90-day gaps between dispensing or prescription records. Individual SCCS analyses were executed separately for each of the proposed study outcomes, including both safety events and negative control outcomes. Patients were followed for their entire observation time (e.g. from enrolment to disenrollment in each database), and incidence rates of each of the study outcomes calculated in periods of inferred persistent exposure to HCQ and non-exposure periods.

Participants

For the new user cohorts, participants included those with a history of RA (a condition occurrence or observation indicating RA any time before or on the same day as therapy initiation), aged 18 years or over at the index event, with at least 365 days of continuous observation time prior to index event. Inclusion and start of follow-up started at the time one of the drugs of interest (HCQ, SSZ, or addition of

AZM or AMX amongst users of HCQ) was initiated after a diagnosis of RA. For the SCCS study, all prevalent users of HCQ were included, regardless of RA history or indication for HCQ therapy.

Participants were identified using pre-specified code lists reviewed by a core team of clinicians, epidemiologists, vocabulary experts, and health data scientists with extensive expertise in the use of the OMOP CDM and the OHDSI tools. The code lists in the OMOP CDM used to identify participants are listed in Supplementary Table 2.2.

Exposures, outcomes and confounders

The proposed code lists for the identification of the study population and for the study exposures were created by clinicians with experience in the management of RA using ATLAS, and reviewed by 4 clinicians and 1 epidemiologist (Supplementary Table 2.1).[39]

A total of 16 severe adverse events (SAEs) were analysed. Hospital-based events, not available in primary care records (CPRD, IMRD and SIDIAP), included gastrointestinal bleeding, acute renal failure, acute pancreatitis, myocardial infarction, stroke, transient ischaemic attack, and cardiovascular events (composite). Additionally, angina/chest pain, heart failure, cardiac arrhythmia, bradycardia, venous thromboembolism, end stage renal disease, and hepatic failure were analysed from both primary and secondary care data. Mortality outcomes were obtained only from data sources with reliable information on death date (CPRD, IMRD, IPCI, Optum, SIDIAP, VA) and cardiovascular events preceding death records (CPRD, IMRD, Optum, VA), with the former contributing to informing all-cause mortality, and the latter also used to assess to cardiovascular death. All codes for the identification of the 16 proposed study outcomes were based on a previously published paper, and are detailed in Supplementary Table 2.2.[40] Face validity for each of the outcome cohorts was further reviewed by

exploring age- and sex-specific incidence rates compared to previous clinical knowledge and/or existing literature.

Two active comparator analyses were conducted in the cohort studies: first, incident users of HCQ were compared to new users of SSZ; second, new use of AZM amongst prevalent users of HCQ was compared to incident use of AMX during ongoing HCQ use.

Exposure commenced on the first day of dispensing or prescription recorded with at least 365 days of prior observation period to increase confidence that the exposure was incident. Exposure interval gaps of ≤90 days (HCQ and SSZ) and of ≤30 days (AZM and AMX) between drug dispensing or prescription records were allowed and inferred as persistent exposure. Drug discontinuation was considered in the HCQ study if a patient switched from one study drug to another. Patients who switched from target exposure to comparator exposure, or vice versa, contributed follow-up time to the exposure cohort that they entered first, and were censored at the time of switching in the 'on treatment' analysis.

A list of negative control outcomes was also assessed for which there is no known causal relationship with any of the drugs of interest. These outcomes were identified using a semi-automatic process based on data extracted from literature, product labels, and spontaneous reports, and confirmed by manual review by 2 clinicians.[41] A full list of codes used to identify negative control outcomes can be found in Supplementary Table 3, and details on covariate/confounder identification are provided in Supplementary Table 4.

Study size

This study was undertaken using routinely collected data and all patients meeting the eligibility criteria above during the study observation period were included. No *a priori* sample calculation was performed; instead, a minimum detectable rate ratio (MDRR) was estimated for each drug-outcome pair

in each of the available databases. The MDRRs for each of the databases for each drug pair-outcome analysis, as well as sample size for each of the comparisons are reported in full in an interactive web app (https://data.ohdsi.org/Covid19EstimationHydroxychloroquine/. Only analyses with 0 counts in either treatment group were excluded based on power, with all others contributing to meta-analytic estimates where applicable.

Statistical methods

PS stratification was used as the analytical strategy to adjust for imbalance between exposure cohorts in a comparison, using a large-scale regularized logistic regression [36] fitted with a LASSO penalty and with the optimal hyperparameter determined through 10-fold cross validation. Baseline patient characteristics were constructed for inclusion as potentially confounding covariates.[42] From this large set of tens of thousands of covariates, key predictors of exposure classification were selected for the propensity score. The predictor variables included were based on all observed patient characteristics and covariates available at each data source, including conditions, procedures, visits, observations and measurements. All covariates that occur in fewer than 0.1% of patients within the target and comparator cohorts were excluded prior to propensity score model fitting for computational efficiency. Patients in the target and comparator cohorts were stratified into 5 propensity score quintiles.

Plotting the propensity score distribution and assessment of covariate balance expressed as the standardized difference of the mean was undertaken for every covariate before and after propensity score adjustment. A standardized difference > 0.1 indicated a non-negligible imbalance between exposure cohorts.[43] The target and comparator cohort were compared using a univariate Cox proportional hazards model conditioned on the propensity score strata with treatment allocation as the sole explanatory variable. Negative control outcomes analyses and empirical calibration were used to

further minimise potential unresolved confounding with calibrated HRs (CalHRs) and 95% confidence intervals estimated.[44,45]

For SCCS, safety of HCQ therapy was assessed separately as a secondary analysis, regardless of indication, comparing exposed and unexposed time periods within the same individuals. The method is self-controlled in that it makes within-person comparisons of event rates during periods of hypothesized increase risk with other periods of baseline risk, with eliminates all time-invariant confounding. Because we do not compare between persons, the SCCS is robust to between-person differences, even including unmeasured differences (like genetics). However, the method is vulnerable to time-varying confounders: the time of exposure may be incomparable to the time when not exposed. To adjust for this, we included many time-varying co-variates in the models, including age, season, and other drug exposures. The effects of age and season were assumed constant within each calendar month and were modelled using bicubic splines with 5 knots. A conditional Poisson regression was used to fit the outcome model using the Cyclops package, with a hyperparameter selected through 10-fold cross-validation.[46]

Study diagnostics (power, propensity score distribution, covariate balance, empirical null distribution) were evaluated by clinicians and epidemiologists to determine which database-target-comparator-outcome-analysis variants could produce unbiased estimates. Database-target-comparator-analysis variants with zero event outcomes in the time-at-risk window or contained analyses with baseline covariate with standardized mean difference>0.1 after stratification were excluded from analysis. Study diagnostics for all database-target-comparator-outcome-analysis will be provided as part of study, regardless of which effect estimation results are unblinded. All the proposed analyses were conducted for each database separately, with estimates combined in fixed effects meta-analysis methods where I2

is <=40%. No meta-analysis was conducted where I2 for a given drug-outcome pair is >40%. Of note, when running analysis in a distributed network, it was not possible to link across datasets, and to know the extent of overlap between data.

All analytical code is available at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine, with study diagnostics considered prior to the unblinding of estimation results. All study diagnostics are available for exploration at https://data.ohdsi.org/Covid19EstimationHydroxychloroquine/. All statistical analyses were conducted using tools previously validated by the OHDSI community. For the cohort analysis, the CohortMethod package was used (https://ohdsi.github.io/CohortMethod/) using a large-scale propensity score (PS) constructed through the Cyclops package (https://ohdsi.github.io/Cyclops).[46] All SCCS were run using the freely available package (https://ohdsi.github.io/SelfControlledCaseSeries/).[47]

RESULTS

Participants

A total of 956,374 HCQ and 310,350 SSZ users were identified, with 323,122 and 351,956 contributing to the analyses of combination therapy of HCQ with AZM compared to HCQ with AMX respectively. Participant counts in each data source are provided in Appendix S5.

Users of HCQ were more likely female (e.g. 82.0% vs 74.3% in CCAE) and less likely to have certain comorbidities like inflammatory bowel disease (e.g. prevalence of Crohn's disease 0.6% vs 1.8% in CCAE) or psoriasis (e.g. 3.0% vs 8.9% in CCAE). All these differences were however minimised after propensity score stratification, with all reported analyses balanced on all identified confounders including socio-demographics, comorbidities and concomitant drug/s use. Similarly, users of combination HCQ+AZM differed from those of HCQ+AMX, with a prevalence of acute respiratory disease appearing higher

amongst azithromycin users (62.5% vs 50.7% in CCAE). Again, propensity score methods resolved these differences, and comparison groups became balanced for all observed confounders after stratification. Detailed baseline characteristics for HCQ vs SSZ and for HCQ+AZM vs HCQ+AMX after propensity score stratification in CCAE are detailed in Table 1 for illustrative purposes, and similar tables with a more complete list of features for each included database and comparing before and after propensity score stratification are provided as Supplementary Tables 6.1.1 to 6.1.14 for HCQ vs SSZ, and Supplementary Tables 6.2.1 to 6.2.13 for HCQ+AZM vs HCQ+AMX.

Propensity score distribution plots showing overlap between groups and figures depicting all covariate balance and empirical null distribution plots based on negative controls can be found in Supplementary Tables 9.1 to 9.14 (Evidence evaluation diagnostics), and interactive versions of these are available at https://data.ohdsi.org/Covid19EstimationHydroxychloroquine/

Table 1. Baseline characteristics of users of HCQ compared to SSZ, and HCQ+AZM vs HCQ+AMX after propensity score stratification in CCAE

	HCQ vs SSZ			AZM vs AMX		
	HCQ	SSZ		AZM	AMX	
Characteristic	%	%	Std. diff	%	%	Std. diff
15-19	0.6	0.6	0.00	0.5	0.5	0.00
20-24	1.8	2.0	-0.01	1.4	1.4	0.00
25-29	2.5	2.7	-0.01	2.2	2.2	0.00
30-34	4.5	4.4	0.00	4.0	3.9	0.01
35-39	7.1	7.1	0.00	6.8	6.7	0.00
40-44	9.7	9.5	0.01	9.3	9.3	0.00
45-49	13.6	13.4	0.00	13.2	13.3	0.00
50-54	18.2	18.0	0.01	18.1	18.0	0.00
55-59	20.8	20.8	0.00	21.5	21.8	-0.01
60-64	19.4	19.8	-0.01	21.1	21.1	0.00
65-69	1.8	1.6	0.01	2.0	2.0	0.00
Gender: female	80.1	79.7	0.01	86.3	86.2	0.00
Medical history: General						
Acute respiratory disease	35.1	34.8	0.01	58.0	57.5	0.01
Chronic obstructive lung disease	4.3	4.5	-0.01	5.0	5.2	-0.01
Depressive disorder	13.3	13.5	0.00	14.7	14.8	0.00
Diabetes mellitus	13.6	13.8	-0.01	13.2	13.1	0.00
Hyperlipidaemia	31.2	31.4	0.00	30.4	30.3	0.00
Pneumonia	4.0	4.0	0.00	5.7	5.5	0.01
Renal impairment	3.0	2.8	0.01	4.2	4.1	0.00
Urinary tract infectious disease	11.6	11.5	0.00	14.0	13.9	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	1.4	1.3	0.01	1.7	1.8	0.00
Cerebrovascular disease	2.8	2.9	-0.01	3.1	3.2	-0.01
Coronary arteriosclerosis	4.4	4.6	-0.01	5.0	4.9	0.00
Heart disease	15.5	15.4	0.00	17.8	17.9	0.00
Heart failure	1.9	2.0	0.00	2.5	2.4	0.01
Ischemic heart disease	3.0	3.1	-0.01	3.3	3.1	0.01
Medication use						
Agents acting on the renin-angiotensin system	24.5	24.6	0.00	27.1	26.9	0.00
Antidepressants	36.3	36.5	0.00	43.0	42.8	0.00
Drugs for obstructive airway diseases	29.5	29.5	0.00	41.1	40.7	0.01
Immunosuppressants	43.4	43.6	0.00	51.1	51.2	0.00
Opioids	39.0	39.3	-0.01	41.4	41.2	0.00
Psycholeptics	33.4	33.3	0.00	38.2	38.1	0.00

HCQ= hydroxychloroquine; **SSZ**= sulfasalazine;
AZM vs AMX = combination of HCQ+ azithromycin (AZM) vs HCQ + amoxicillin (AMX)

Outcome Data

We report here (Table 2) on database-specific counts and rates of key outcomes (cardiovascular mortality, chest pain/angina and heart failure) observed in the proposed 30-day *intention-to-treat* analysis.

Table 2. Event occurrence

Comparison T vs C	Outcome	Database	30-day follow-up						On-treatment follow-up					
			Patients		Events		IR		Patients		Events		IR	
			T	C	T	C	T	C	T	C	T	C	T	C
HCQ vs SSZ	CV-related mortality	CPRD							9,127	11,398	7	25	0.39	0.94
		Optum	51,280	17,389	16	<5	3.85	<3.54	51,280	17,389	234	25	4.39	2
		VA	32,028	14,349	9	<5	3.43	<4.25	32,028	14,349	315	65	5.69	3.71
		Meta-analysis	83,308	31,738	25	<10	3.68	<3.86	92,435	43,136	556	115	4.39	2.03
	Chest pain or angina	AmbEMR	57,140	15,268	122	31	26.04	24.76	57,140	15,268	451	112	24.44	19.89
		CCAE	65,935	22,173	440	143	82.41	79.62	65,935	22,173	3,354	810	55	58.8
		CPRD	9,114	11,388	10	17	13.4	18.22	9,114	11,388	260	422	14.99	16.78
		DAGermany	3,884	5,045	<5	5	<15.69	12.07	3,884	5,045	31	36	12.36	10.26
		IMRD	8,843	8,452	9	10	12.45	14.46	8,843	8,452	235	293	14	16.25
		MDCD	7,982	2,177	80	23	123.5	130.43	7,982	2,177	467	100	87.34	85.81
		MDCR	15,690	5,150	129	49	101.25	117.43	15,690	5,150	1,178	279	71.38	75.12
		OpenClaims	617,628	182,776	2,674	804	52.83	53.68	617,628	182,776	31,161	6,198	38.59	38.11
		Optum	50,698	17,221	396	166	96.62	119.34	50,698	17,221	3,185	829	66.13	72.48
		PanTher	76,844	21,549	629	143	101.46	82.23						
		VA	31,824	14,276	130	54	49.89	46.2	31,824	14,276	1,822	611	35.88	37.31
		Meta-analysis	945,582	305,475	<4,624	1,445	<59.86	57.9	868,738	283,926	42,144	9,690	40.36	37.07
	Heart failure	AmbEMR	57,383	15,305	42	10	8.92	7.96	57,383	15,305	182	53	9.76	9.37
		CCAE	66,604	22,370	30	5	5.55	2.75	66,604	22,370	305	74	4.64	5.07
		CPRD	9,126	11,397	<5	<5	<6.69	<5.35	9,126	11,397	16	36	0.89	1.36
		DAGermany	3,885	5,042	<5	<5	<15.68	<12.08	3,885	5,042	11	22	4.29	6.22
		IMRD	8,852	8,460	<5	<5	<6.91	<7.22	8,852	8,460	15	21	0.86	1.11
		MDCD	8,072	2,195	15	<5	22.81	<27.99	8,072	2,195	118	28	20.55	23.02
		MDCR	15,808	5,171	39	19	30.3	45.22	15,808	5,171	586	141	33.13	36.29
		OpenClaims	620,244	183,350	749	214	14.71	14.22	620,244	183,350	12,246	2,246	14.36	13.22
		Optum	51,204	17,356	84	25	20.23	17.76	51,204	17,356	915	207	17.55	16.9
		PanTher	77,813	21,768	237	50	37.64	28.39						
		VA	31,895	14,307	56	17	21.42	14.49	31,895	14,307	897	296	16.75	17.42
		Meta-analysis	950,886	306,721	<1,267	<360	<16.28	<14.34	873,073	284,953	15,291	3,124	13.85	11.43
AZM vs AMX	CV-related mortality	Optum	23,597	24,521	9	6	4.7	3.02	23,597	24,521	96	82	5.56	5.58
		VA	6,234	8,005	46	18	90.6	27.49	6,234	8,005	157	115	14.6	10.2
		Meta-analysis	29,831	32,526	55	24	22.7	9.08	29,831	32,526	253	197	9.03	7.59
	Chest pain or angina	AmbEMR	13,093	12,028	32	21	29.8	21.29	13,093	12,028	142	119	25.69	25.31
		CCAE	32,165	32,229	241	211	92.76	80.98	32,165	32,229	1,402	1,145	60.46	60.54
		MDCD	3,712	3,764	30	37	99.97	121.56	3,712	3,764	129	113	60.05	63.39
		MDCR	7,991	9,195	81	85	125.6	114.2	7,991	9,195	517	498	74.83	71.25
		OpenClaims	214,494	231,851	1,050	888	59.76	46.74	214,494	231,851	8,348	7,223	36.24	36.37
		Optum	23,206	24,254	244	203	130.28	103.7	23,206	24,254	1,019	887	70.33	70.28
		PanTher	18,039	16,191	218	134	150.01	102.42						
		VA	6,121	7,912	58	50	116.96	77.52	6,121	7,912	340	371	38.48	39.87
		Meta-analysis	318,821	337,424	1,954	1,629	75.13	59.12	300,782	321,233	11,897	10,356	40.82	40.95
	Heart failure	AmbEMR	13,152	12,053	16	16	14.83	16.18	13,152	12,053	61	49	10.44	9.96
		CCAE	32,586	32,496	30	23	11.36	8.73	32,586	32,496	177	126	6.58	5.82
		MDCD	3,796	3,795	16	9	52.08	29.21	3,796	3,795	65	48	26.26	24.83
		MDCR	8,085	9,239	45	33	68.88	43.97	8,085	9,239	322	295	41.61	38.34
		OpenClaims	215,732	232,725	472	370	26.68	19.38	215,732	232,725	4,352	3,714	17.5	17.43
		Optum	23,541	24,468	65	49	34.08	24.73	23,541	24,468	337	317	20.33	22.63
		PanTher	18,054	16,298	99	60	67.77	45.45						
		VA	6,164	7,959	79	31	158.53	47.73	6,164	7,959	280	229	28.17	21.64
		Meta-analysis	321,110	339,033	822	591	31.32	21.32	303,056	322,735	5,594	4,778	17.58	17.44

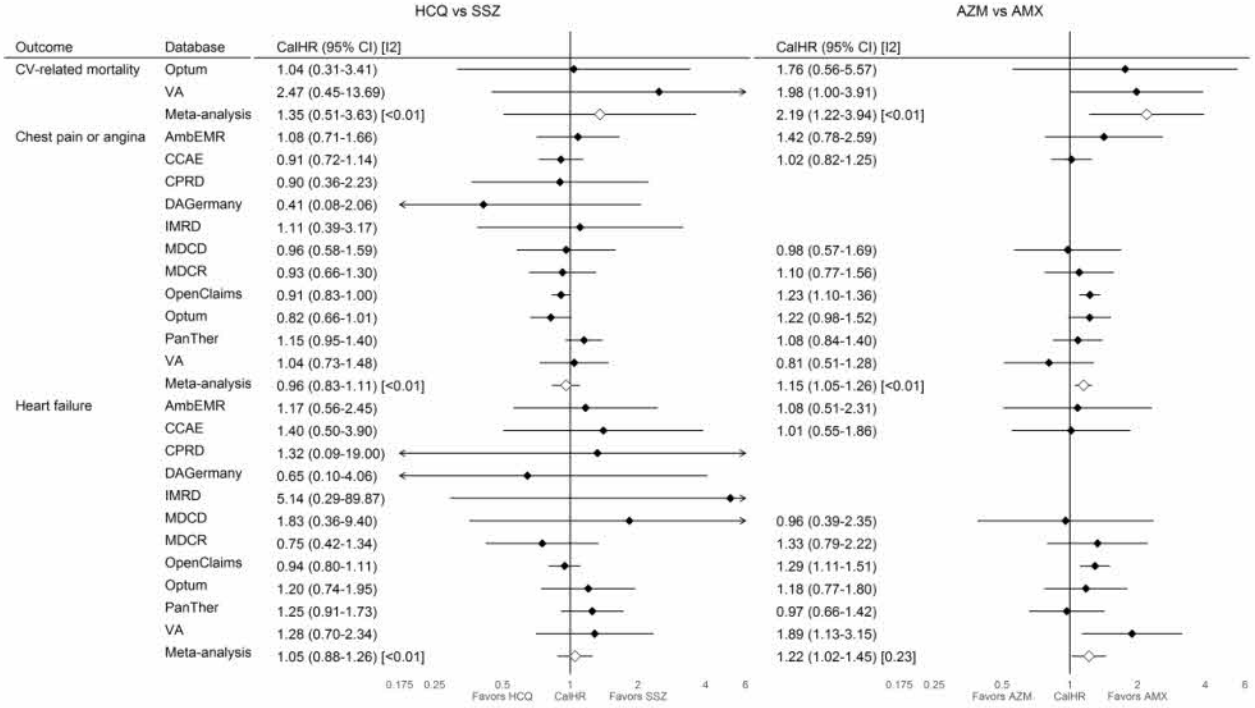
T = target therapy; C= comparator therapy. IR= incidence rate. CV-related mortality = cardiovascular-related mortality
HCQ= hydroxychloroquine; SSZ= sulfasalazine. AZM= HCQ+ Azithromycin; AMX = HCQ + amoxicillin.
AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; CPRD=Clinical Practice Research Datalink, DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; Optum=Optum Clinformatics Datamart; PanTher=Optum PanTherapeutic Electronic Health Record; VA=Veteran's Health Administration Database

Database-specific counts, incidence rates (IR) of all study outcomes stratified by drug use are detailed in full in Supplementary Table S7. Least common outcomes included bradycardia (e.g. IR 0.92/1,000

person-years (py) amongst HCQ users in CCAE) and end-stage renal disease (e.g. IR <0.92/1,000 py amongst HCQ users in CCAE), whilst most common ones were chest pain/angina (e.g. IR 82.41/1,000 py amongst HCQ users in CCAE) and composite cardiovascular events (e.g. IR 17.96/1,000 py amongst HCQ users in CCAE). As expected, most IRs appeared higher in data sources which included older populations (e.g. IR of composite cardiovascular events in HCQ users in MDCR of 91.39/1,000 py). Mortality rates ranged from 4.81/1,000 person-years in HCQ users in Optum to 17.13/1,000 py amongst HCQ users in VA, with cardiovascular-specific mortality ranging from IR 3.43/1,000 py in HCQ users in VA to <4.25/1,000 person-years in SSZ users in the same data source.

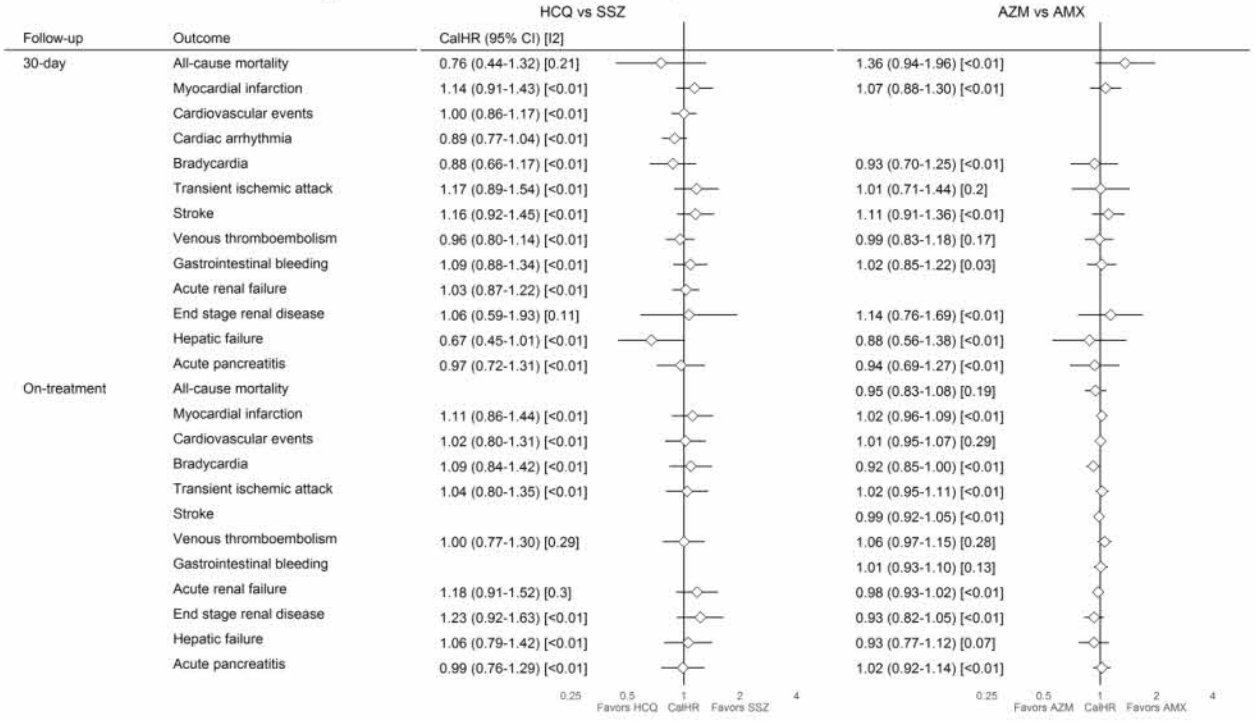
Database and outcome-specific HRs (uncalibrated as well as calibrated) are reported in full in the form of forest plots (Supplementary Figure Sections 8.1 and 8.2). None of the SAEs appeared consistently increased with the short-term use of HCQ (vs SSZ) in the *intention-to-treat* analyses (Figure 1), with meta-analytic calibrated HRs (CalHRs and 95%CI) ranging from 0.67 (0.45-1.01) for hepatic failure to 1.35 (0.51-3.63) for cardiovascular mortality (Figure 2).

Figure 1. Source-specific and meta-analytic cardiovascular risk estimates for hydroxychloroquine vs sulfasalazine and azithromycin vs amoxicillin new users during 30-day follow-up



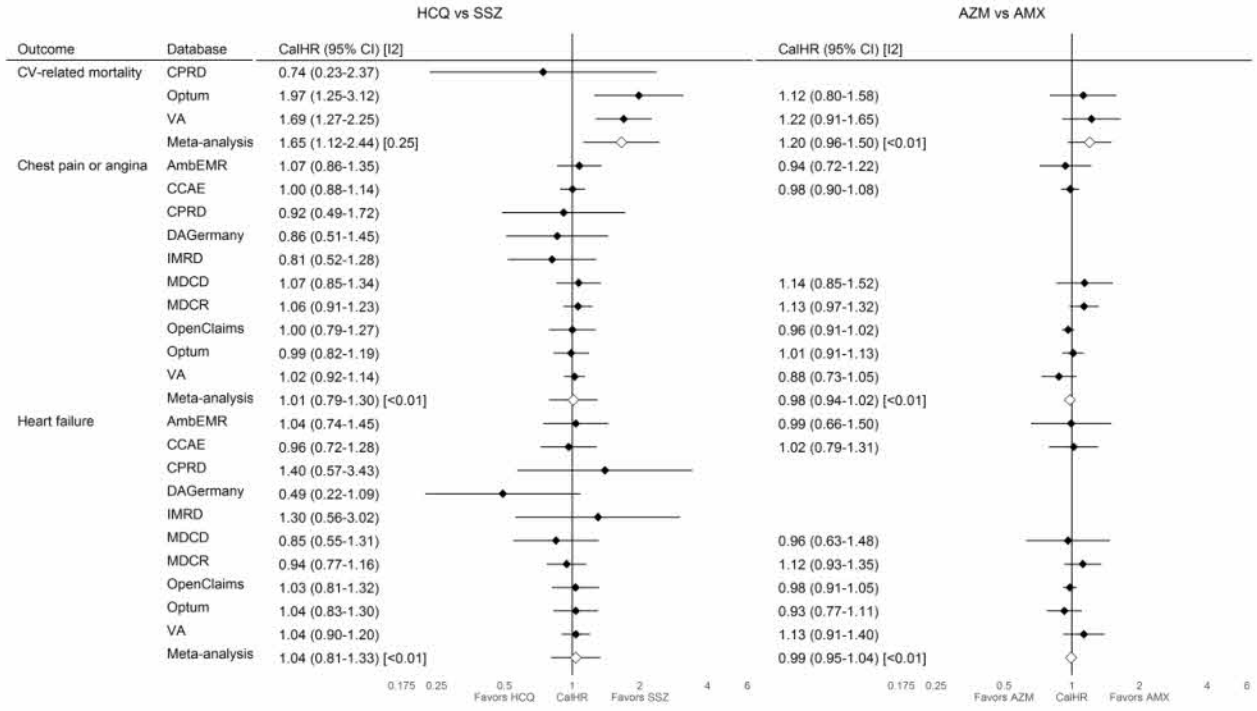
HCQ=hydroxychloroquine; SSZ=sulfasalazine; AZM=azithromycin (plus concurrent hydroxychloroquine exposure); AMX=amoxicillin (plus concurrent hydroxychloroquine exposure); CalHR=calibrated hazard ratio; CI=confidence interval; I2=estimate heterogeneity statistic. Meta-analytic estimates reported where I2<0.4. All database-specific estimates are reported in Appendix Table S7. AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; CPRD=Clinical Practice Research Datalink, DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; Optum=Optum Clinformatics Datamart; PanTher=Optum PanTherapeutic Electronic Health Record; VA=Veteran's Health Administration Database

Figure 2. Meta-analytic risk estimates for hydroxychloroquine vs sulfasalazine and azithromycin vs amoxicillin new users during on-treatment during 30-day and on-treatment follow-up



HCQ=hydroxychloroquine; SSZ=sulfasalazine; AZM=azithromycin (plus concurrent hydroxychloroquine exposure); AMX=amoxicillin (plus concurrent hydroxychloroquine exposure); CalHR=calibrated hazard ratio; CI=confidence interval; I2=estimate heterogeneity statistic.

Figure 3. Source-specific and meta-analytic cardiovascular risk estimates for hydroxychloroquine vs sulfasalazine and azithromycin vs amoxicillin new users during on-treatment follow-up



HCQ=hydroxychloroquine; SSZ=sulfasalazine; AZM=azithromycin (plus concurrent hydroxychloroquine exposure); AMX=amoxicillin (plus concurrent hydroxychloroquine exposure); CalHR=calibrated hazard ratio; CI=confidence interval; I2=estimate heterogeneity statistic; AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; CPRD=Clinical Practice Research Datalink, DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; Optum=Optum Clinformatics Datamart; PanTher=Optum PanTherapeutic Electronic Health Record; VA=Veteran's Health Administration Database. AZM vs AMX comparisons in CPRD, DAGermany, and IMRD did not meet study diagnostic criteria so estimates are not reported. On-treatment follow-up information was not available in the PanTher database.

Consistent findings were seen with the long-term (*on treatment*) use of HCQ vs SSZ (Figure 3), with the exception of cardiovascular mortality, which appeared inconsistent in the available databases, but overall increased in the HCQ group when meta-analysed: pooled CalHR 1.65 (1.12-2.44).

Similar results were obtained in SCCS analyses, which looked at the effect of HCQ use (on- vs off-treatment) on all outcomes except mortality regardless of indication, and therefore included non-RA patients (Tables S10.1 to 10.6 for database-specific results).

All the obtained database- and outcome-specific calHRs for the association between short-term (1 month) use HCQ+AZM vs HCQ+AMX are depicted in the form of Forest plots in Supplementary Figure

Sections 8.1 and 8.2. Three SAEs appeared increased with the short-term (30-day fixed follow-up) use of HCQ+AZM: chest pain/angina (meta-analytic CalHR 1.15 (1.05-1.26), heart failure (meta-analytic CalHR 1.22 (1.02-1.45)), and cardiovascular mortality (meta-analytic CalHR 2.19 (1.22-3.94) (Figure 1).

DISCUSSION

Despite a lack of evidence on efficacy, HCQ and HCQ+AZM have become the most popular treatment/s for COVID-19. This is the largest ever analysis of the safety of such treatments worldwide, examining over 900,000 HCQ and more than 300,000 HCQ+AZM users respectively.

The results on the risk of SAEs associated with short-term (1 month) HCQ treatment as proposed for COVID-19 therapy are reassuring, with no excess risk of any of the considered safety outcomes compared to an equivalent therapy (SSZ). However, long-term treatment with HCQ as used for RA is associated with a 65% increase in cardiovascular mortality.

Worryingly, significant risks are identified for combination users of HCQ+AZM even in the short-term as proposed for COVID19 management, with a 15-20% increased risk of angina/chest pain and heart failure, and a two-fold risk of cardiovascular mortality in the first month of treatment.

A systematic review of the cardiac side effects of chloroquine and HCQ identified 86 articles reporting short series or individual cases.[39] In the 127 included patients, cardiac side effects occurred in mainly women (65.4%) who had a median age of 56 years. Conduction disorders were the main side effect reported (85%), with heart failure (26.8%), ventricular hypertrophy (22%), hypokinesia (9.4%), valvular dysfunction (7.1%) and pulmonary arterial hypertension (3.9%) being the other reported side effects. When drugs were withdrawn, 44.9% of patients recovered normal cardiac function; 12.9% sustained irreversible damage, and 30% died. It should be noted that cardiac toxicity was induced by a high cumulative dose of chloroquine or HCQ in most patients, although some studies identified by this

systematic review mentioned complications even in patients with a low cumulative dose. Furthermore, interrogation of the Food and Drug Administration's adverse event reporting database FAERS from 2004-2019 Q4 saw 357 adverse events reported.[48] 20% of the events reported were cardiac, with the median age of patients included being 39, and a male to female ratio of 0.60. The cardiovascular SAEs reported appear similar to those included in the review by Chatre *et al.,* with complete AV block 1.8%; cardiac arrest 1.8% ventricular fibrillation 1.09%, cardiogenic shock 0.6%; heart failure 1.4%; cardiomyopathy 1.6% reported as the most likely cardiovascular SAEs.

Our results suggest that long-term use of HCQ leads to an increased risk of cardiovascular mortality, with no observable excess risk of major cardiovascular events or diagnosed bradycardia. Considering the current evidence, this may relate to cumulative effects of HCQ leading to an increased risk of QT lengthening or relate to the moderately increased risk of angina and heart failure seen. However, as the strong association observed with cardiovascular death is not observed with diagnosed arrhythmia or bradycardia in this study, sudden cardiovascular death here is more likely due to QT lengthening and undetected and/or sudden torsade-de-pointes. Although long-term treatment with HCQ is not expected for the management of COVID-19, some research suggests that higher doses as prescribed for COVID-19 can, even in the short-term, lead to equivalent side effects given the long half-life of HCQ.[49]

QT lengthening is a known effect of all macrolides including AZM and physicians already use caution when prescribing macrolides concurrently with other medications that can also increase the QT interval.[32-34] In this study, the elevated risk of cardiovascular death with combined HCQ +AZM therapy may arise through their synergistic effects of inducing lethal arrhythmia.

As with all observational data, this study is limited by its ability to appropriately identify exposure and outcome. Due to the nature of sudden cardiac death, capturing the true cause of cardiovascular related mortality is difficult. We therefore have explored cardiovascular related outcomes other than mortality to determine if deterioration in these pathophysiological processes led to increased mortality. Since this is not seen, and sudden cardiac death in association with prolonged QT interval is described in the literature, our conclusions are drawn from these assumptions. It should be acknowledged that misclassification can occur due to non-adherence or non-compliance with exposure medication, and incomplete lack of recording of SAEs may lead to underestimation of these outcomes.

Another potential limitation in this study is the potential for patients to be included in more than one dataset in the US. Whilst we ran meta-analysis, which assume populations are independent, we wish to highlight we are likely to under-estimate variance in our meta-analytic estimates.

The comparative new user cohort studies are anchored in patients using HCQ for RA, who therefore are likely to be using HCQ at a lower dose than is currently being proposed for use in the treatment of COVID-19. We have taken into consideration that patients with RA taking HCQ may also have further auto-immune conditions such as systemic lupus erythematosus (SLE) and therefore generate the potential for confounding by indication.[50] We therefore ensured that when investigating covariate balance after propensity score stratification and matching and before unblinding study results, that we did not see unbalanced proportions of patients with a diagnosis of SLE between the groups. Negative control outcome analyses also did not identify any residual unobserved confounding in the PS analysis. Whilst patients with RA may have greater levels of comorbidities than the general population, the age and demographic profile of patients developing cardiovascular complications described in both the systematic review and FAERS database suggests that complications are not only restricted to those with

multimorbidity.[48] However, absolute risk in our study should be interpreted cautiously since patients with RA are likely different from those with COVID-19.

As the world awaits the results of clinical trials for the anti-viral efficacy of HCQ in the treatment of SARS-Cov2 infection, this large scale, international real-world data network study enables us to consider the safety of the most popular drugs under consideration. HCQ appears to be largely safe in both direct and comparative analysis for short term use, but when used in combination with AZM this therapy carries double the risk of cardiovascular death in patients with RA. Whereas we used the collective experience of a million patients to build our confidence in the evidence around the safety profile, the current evidence around efficacy of HCQ+AZI in the treatment of covid-19 is quite limited and controversial.

ETHICAL APPROVAL

All data partners received IRB approval or waiver in accordance to their institutional governance guidelines.

Database	Statement
AmbEMR	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
CCAE	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
CPRD	Approval for CPRD was provided by the Independent Scientific Advisory Committee (ISAC). This study is based in part on data from the Full Feature General Practice Research Database obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However the interpretation and conclusions contained in this report are those of the author/s alone. The protocol for this study (20_059R) was approved by the Independent Scientific Advisory Committee (ISAC).

DA Germany	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
IMRD	The present study is filed and under review for Scientific Review Committee for institutional adjudication. Due to the public health imperative of information related to these data, approval is provided for this publication.
IPCI	The present study was approved by the Scientific and Ethical Advisory Board of the IPCI project (project number: 4/2020).
JMDC	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Open Claims	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
Optum	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
PanTher	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
SIDIAP	The use of SIDIAP data base was approved by the SIDIAP Scientific Committee and the IDIAPJGol Clinical Research Ethics Committee.
VA	The use of VA data was reviewed by the Department of Veterans Affairs Central Institutional Review Board (IRB) and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization. The VA Privacy Office certified the release of aggregate analysis results for the meta-analysis.

DECLARATION OF INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure_.pdf

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Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (*CloroCovid-19 Study*)

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Research in context

Evidence before this study

Before the CloroCovid-19 trial began, to our knowledge, there were no published reports of robust clinical studies on the safety and/or efficacy of chloroquine (CQ) and/or hydroxychloroquine (HCQ) for the treatment of COVID-19 during the recent 2020 pandemic. We searched PubMed and also MedRxiv.org (pre-print server for health sciences, without peer review), without any language restrictions and including Chinese publications, for studies published between Dec 2019 and April 5, 2020, using the search terms 'COVID-19, coronavirus, SARS-Cov-2'. We found three non-randomized studies with limited sample sizes in which (1) HCQ use led to a decrease in SARS-Cov-2 detected in respiratory secretions five days after treatment, together with azithromycin (France, 36 patients); (2) HCQ use shortened time to clinical recovery (China, 62 patients); and (3) CQ was superior to control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, and promoting virus-negative conversion and shortening the disease course (China, 100 patients). We found no published studies comparing different dosages of CQ/HCQ and their thorough safety assessment.

Added value of this study

In a larger patient population, we found that a higher dose of CQ for 10 days presented toxicity red flags, particularly affecting QTc prolongation. The limited sample size recruited so far does not allow to show any benefit regarding treatment efficacy, however the trend towards higher fatality associated with the higher dose by day 6 of follow-up resulted in a premature halting of this arm. This is the first double-blinded, randomized clinical trial addressing different dosages of CQ for the treatment of severe patients with COVID-19 in the absence of a control group using placebo. Due to the impossibility of not using the drug recommended at the national level, we used historical data from the literature to infer comparisons for lethality endpoints. Follow-up until day 28 is ongoing with a larger sample size, in which long-term lethality will be better estimated.

Implications of all the available evidence

The preliminary findings from CloroCovid-19 trial suggest that the higher dosage of CQ (12 g total dose over 10 days) in COVID-19 should not be recommended because of safety

concerns regarding QTc prolongation and increased lethality, in the Brazilian population, and more often in older patients in use of drugs such as azithromycin and oseltamivir, which also prolong QTc interval. Among patients randomized to the lower dosage group (5 days of treatment, total dose 2.7 g), given the limited number of patients so far enrolled, it is still not possible to estimate a clear benefit of CQ in patients with severe ARDS. Preliminary data on viral clearance in respiratory secretions in our confirmed cases are also indicative of little effect of the drug at high dosage. More studies initiating CQ prior to the onset of the severe phase of the disease are urgently needed.

Summary

Background

There is no specific antiviral therapy recommended for the disease caused by SARS-CoV-2 (COVID-19). Recent publications have drawn attention to the possible benefit of chloroquine (CQ). Our study aimed to comprehensively evaluate the safety and efficacy of two different CQ dosages in patients with established severe COVID-19.

Methods

We performed a parallel, double-blinded, randomized, phase IIb clinical trial, aiming to assess safety and efficacy of two different CQ dosages as adjunctive therapy of hospitalized patients with SARS in Manaus, Brazilian Amazon. Eligible participants were allocated to receive orally or via nasogastric tube high dose CQ (600mg CQ twice daily for 10 days or total dose 12g); or low dose CQ (450mg for 5 days, twice daily only on the first day, or total dose 2.7g). In addition, all patients received ceftriaxone and azithromycin. This study was registered with ClinicalTrials.gov, number NCT04323527.

Findings

Out of a pre-defined 440 patients sample size, 81 patients were enrolled. The high dose CQ arm presented more QTc>500ms (25%), and a trend toward higher lethality (17%) than the lower dosage. Fatality rate was 13.5% (95%CI=6.9–23.0%), overlapping with the CI of historical data from similar patients not using CQ (95%CI=14.5-19.2%). In 14 patients with paired samples, respiratory secretion at day 4 was negative in only one patient.

Interpretation

Preliminary findings suggest that the higher CQ dosage (10-day regimen) should not be recommended for COVID-19 treatment because of its potential safety hazards. Such results forced us to prematurely halt patient recruitment to this arm. Given the enormous global push for the use of CQ for COVID-19, results such as the ones found in this trial can provide robust evidence for updated COVID-19 patient management recommendations.

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INTRODUCTION

Coronaviruses, first discovered in the 1960s, are a family of RNA viruses that typically cause respiratory and intestinal infections in birds and mammals. In humans, coronaviruses often cause mild upper respiratory tract infections, and together with rhinoviruses are the two main underlying aetiologies for the normal cold, with severe disease secondary to these viruses usually restricted to immunocompromised individuals[1]. In 2002, however, and as a result of a coronavirus-associated outbreak of severe acute respiratory syndrome (SARS), a pathogenic role was established[2]. This first SARS-coronavirus (SARS-CoV) outbreak appeared in south-eastern China and Hong Kong and quickly spread to various parts of the world, highlighting its pandemic potential and leading to significant economic losses[3,4]. A decade later, in 2012, a second highly pathogenic coronavirus, the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), emerged in countries in the Middle East[5]. The virus was first isolated in June 2012[5]. By the end of 2016, more than 1850 cases of laboratory-confirmed MERS-CoV had been documented, with a case fatality rate of 35%[6].

The first cases of the new coronavirus 2019 disease (COVID-19) were reported in December 2019, when a group of patients was admitted to hospitals in Wuhan, the capital of the Hubei province in Central China, with an initial diagnosis of pneumonia of unknown etiology[7]. Initially the outbreak with the new SARS-CoV-2 coronavirus (coronavirus disease 2019; formerly 2019-nCoV), was confined to the Hubei province, but it rapidly spread to many other countries[8,9], compelling WHO to officially declare a global pandemic on March 11, 2020. The origin of the virus has yet to be fully elucidated, but genomic analysis suggests that it is closely related to viruses previously identified in bats[10].

SARS-CoV-2 infection appears to cause a wide range of symptoms, encompassing asymptomatic infection, mild infections of the upper respiratory tract, severe viral pneumonia, respiratory failure, multiple organ failure and more deaths than previously expected[11]. Some studies have shown detailed clinical features of patients with SARS-CoV-2-associated viral pneumonia (SARS-CoV-2 pneumonia)[12]. Of laboratory confirmed patients in China, 5% had critical illnesses and almost 50% of the critical patients died, with an overall rate of fatal cases (2.3%) estimated to be about ten-fold higher than that observed for seasonal influenza[13]. Most deaths involved older adults, many of whom had underlying chronic diseases[14,15].

Currently, there is no specific antiviral therapy recommended for coronavirus infections. Few treatment studies have been carried out because most strains of human coronavirus cause self-limiting disease, and routine supportive care is usually effective. For past severe strains of coronavirus, outbreaks were scattered, thus not allowing timely clinical trials. Since the 2002 SARS outbreak, new therapeutic agents targeting viral entry pathways, proteins, proteases, polymerases and methyltransferases have been tested in randomized clinical trials, with little success. Recent publications have drawn attention to the possible benefit of chloroquine sulphate and phosphate salts (chloroquine diphosphate-CQ) and hydroxychloroquine (HCQ) for the treatment of SARS-CoV-2 infected patients[16–21]. Both drugs historically have been used for the treatment of acute malaria, as well as in some chronic rheumatic conditions. HCQ, a derivative of CQ first synthesized in 1946, proved to be less (~40%) toxic when used for longer periods of time than the three-day course recommended for malaria. HCQ is therefore one of the drugs recommended for the treatment of systemic lupus erythematosus and rheumatoid arthritis[22]. Although both drugs have a bitter taste, they are generally very well tolerated, and after millions of doses used, their accumulated safety database is massive. In prolonged use (months or even years), which is not the targeted scenario in COVID-19, CQ may deposit in many tissues, especially the eye, causing retinal toxicity[23,24]. Myopathy has also been associated with the use of CQ[25]. The major complication, even in short regimens, is the potential for QTc prolongation, favoring fatal arrhythmias such as ventricular tachycardia and *torsades de pointes*[26].

The *in vitro* antiviral activity of QC was first identified in the late 1960s[27,28]. Two studies have shown anti-SARS-CoV activity[17,19]. Several studies suggest that CQ and HCQ have potential broad-spectrum antiviral activity, result in an increase in the endosomal pH required for virus/cell fusion, interfere with the glycosylation of SARS-CoV cell receptors and have anti-viral, anti-inflammatory and immunomodulating effects that together may provide effective treatment of patients with COVID-19 pneumonia[19,29,30].

In 100 COVID-19 affected patients, the effect of CQ was superior to the control treatment in inhibiting the exacerbation of pneumonia, improving pulmonary imaging findings and promoting a negative conversion of the virus and reducing the disease course[20]. Gautret et al.[21] evaluated 20 COVID-19 patients treated with 200 mg HCQ three times per day for ten days. Six patients also received azithromycin. The proportion of patients who tested negative in nasopharyngeal samples differed significantly between treated patients and controls on

days 3-4-5 and 6 after inclusion. On day 6 after inclusion, 100% of patients treated with a combination of HCQ and azithromycin were considered 'virologically cured' compared with only 57.1% in patients treated with HCQ alone and 12.5% in the control group. These results, albeit highly preliminary and probably not sufficiently powered to be conclusive, supported an effort to evaluate more thoroughly the effect of CQ in the evolution and prognosis of COVID-19.

Health Commission of Guangdong Province[18] recommended the use of CQ tablets at a dose of 500 mg twice daily for 10 days (total dose 10g), for the treatment of patients aged 18-65 years with mild, moderate or severe pneumonia secondary to COVID-19, as long as there were no specific contraindications. However, to guarantee an adequate patient follow-up, a strict monitoring and evaluation plan for the safety and efficacy is recommended. As opposed to the 10-day treatment recommended and evaluated in different studies, CDC[31] initially recommended for adults a loading dose consisting of 600 mg of CQ base (6 tablets of 100 mg), followed by 300 mg after 12 h on day 1, then 300 mg bid, given orally on days 2 to 5. This shorter treatment regimen (5 versus 10 days) would potentially reduce the side effects and assumes a drug half-life of about 30 hours.

The fact that in many countries the 'compassionate use' of CQ or HCQ has already been formally indicated for severe patients, made it unethical to test proper efficacy due to the lack of a placebo arm as a comparator. Our study aimed to comprehensively evaluate primarily the safety, and secondarily the efficacy of CQ in two different dosages, as compared to historical data reported in the literature for similar severe patients not receiving CQ for the treatment of severe respiratory syndrome caused by COVID-19. Here, we report the data of the first 81 randomized patients.

Methods

Ethical aspects

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization.

The protocol was timely approved by the *Brazilian Committee of Ethics in Human Research* (CONEP approval 3.929.646/2020). All patients and/or legal representatives in case of unconsciousness, were informed about objectives and risks of participation. They were given time to carefully read and then sign an informed consent form (ICF). After recovery, the patient also signed the ICF. Random online clinical monitoring and quality control was performed. A virtual independent *Data Safety and Monitoring Board* (DSMB), with epidemiologists, clinicians and experts in infectious diseases, was timely implemented to review the protocol and with daily meetings to follow-up the activities of the study. The trial was reported according to *Consolidated Standards of Reporting Trials* (Consort) statement.[32]

Study design and site

CloroCovid-19 was a parallel, double-blind, randomized, phase IIb clinical trial, which started on March 23rd, 2020, aiming to assess safety and efficacy of CQ in the treatment of hospitalized patients with severe respiratory syndrome secondary to SARS-CoV-2 infection (ClinicalTrials.gov, number NCT04323527).

This trial is being conducted at *Hospital e Pronto-Socorro Delphina Rinaldi Abdel Aziz*, in Manaus, Western Brazilian Amazon (currently the biggest public reference unit dedicated exclusively to the treatment of severe COVID-19 cases in Brazil, with capacity to hospitalize 350 patients in Intensive Care Units - ICU). The hospital has all source documents registered on-line in an electronic medical recording system (*Medview*). Clinical analyses laboratory and routine CT scanning are also available locally. Other participating sites were not able to enroll timely.

Manaus is the capital of the Amazonas State, the biggest Brazilian State, and has ~2.5 million inhabitants scattered in the ninth largest country subdivision of the world (>1.5M/km^2). It is a major industrial, academic and tourist centre in the Amazon region, with several transportation hubs and thousands of annual foreign visitors. It is mostly served by the socialized and free *Unified Health System* (SUS) in an organized health assistance network, but also counts with many private hospitals. The city also counts with various universities, graduate programs and traditional clinical research groups dedicated to the study of infectious diseases. At the beginning of the study, autochthonous SARS-CoV-2 transmission had already been recorded at the study site.

Participants

Hospitalized patients aged 18 years or older at the time of inclusion, with respiratory rate higher than 24 rpm AND/OR heart rate higher than 125 bpm (in the absence of fever) AND/OR peripheral oxygen saturation lower than 90% in ambient air AND/OR shock (defined as mean arterial pressure lower than 65 mmHg, with the need for vasopressors medicines or oliguria or a lower level of consciousness) were included. Children under 18 years of age were not included due to the known lower morbidity/mortality from COVID-19[33]. Patients were enrolled before laboratorial confirmation of COVID-19, considering that such procedure could delay randomization. For the analyses at this point, all patients were included regardless of the confirmed etiology which for safety issues (the focus of this manuscript) should not be an issue. For now, the flowchart of the study presents clinical-epidemiological suspected cases and cases already confirmed by RT-PCR.

Sample size calculation

The sample for the primary outcome (reduction in lethality) was calculated assuming a 20% lethality incidence in critically ill patients not using CQ (historical control)[15,34] and that both arms of CQ would be equally able to reduce lethality by at least 50%. Thus, considering a test of differences in proportions between 2 groups of the same size, 80% power and 5% alpha, 394 participants were needed (197 per group). Adding 10% of losses, the final sample of 440 participants was obtained. All statistical analyses were performed in the R statistical package (v3.6.1), with the functions implemented in the TrialSize and gsDesign packages.

Procedures

The interventions tested in this study were based on different regimens using CQ 150mg tablets (*Farmanguinhos*, Fiocruz, Brazil). Eligible participants were allocated at a 1:1 ratio to receive orally (or via nasogastric tube in case of orotracheal intubation) either: a) high dose CQ (600mg CQ (4x150mg tablets, twice daily for 10 days, total dose 12g); or b) low dose CQ (450mg CQ (3x150mg tablets + 1 placebo) twice daily on Day 0, 3x150mg tablets +1 placebo tablet followed by 4 placebo tablets from D1 to D4, and then 4 placebo tablets twice daily

from D5-D9, total dose 2.7g). Placebo tablets also produced by *Farmanguinhos* were used in the latter in order to standardize treatment and blinding of research team and participants.

As per hospital protocol, all patients meeting the same criteria of the study (ARDS) used intravenous ceftriaxone (1g 2x for 7 days) plus azithromycin (500mg 1x for 5 days), systematically, starting on day 0. Oseltamivir (75mg 2x for 5 days) was also prescribed when influenza infection was suspected (in the Amazon, the ongoing flu season is from January-April).

Clinical parameters were measured daily by the routine clinical staff from day 0 to discharge or death, and then at days 14 and 28 for discharged patients, to assess efficacy and safety outcomes. Laboratorial parameters and ECG were performed whenever needed at clinical discretion. Data were recorded on *Medview* and then transferred into an electronic database (REDCap), in tablet computers, at bedside in the wards, further validated by external trial monitoring staff.

Randomization and masking

An electronically generated randomization list was prepared by an independent statistician, with four blocks of 110 participants per block. This randomization list associated each patient's study number with an opaque surface hiding the treatment group designation. The list was accessible only to non-blinded pharmacists in the study, in an attempt to minimize observation bias. Participants were randomized by the study pharmacist to their designated treatment regimen at the time of inclusion and were subsequently identified throughout the study only by their allocated study number, always assigned following chronological order. Unmasking was available to DSMB members in case of severe adverse events.

Laboratory

Hematology and biochemistry analyses were performed in automatized machines. Samples (from two nasopharyngeal or one oropharyngeal swabs) were submitted to viral RNA extraction using QIAamp Viral RNA Mini Kit Viral RNA mini kit, according to the manufacturer's recommendations. Subsequently, all specimens for SARS-CoV-2 were tested using the protocol developed by the *US Centers for Disease Control and Prevention*

(CDC/USA), updated on March 15, 2020 (https://www.fda.gov/media/134922/download), targeting the virus nucleocapsid (N) gene and the human RNase P gene, as an internal control. For all assays, specimens were considered positive if both viral targets, N1 and N2, showed Ct lower than 40.00. No quantitative RT-PCR data were presented here. Swab specimens were collected on D0 and D4.

Outcomes

Safety outcomes included adverse events (AE) that occurred during treatment, serious adverse events (SAE), and premature or temporary discontinuation of treatment. Adverse events were classified according to the *National Cancer Institute Common Terminology Criteria for Adverse Events*. The working hypothesis around which this trial was designed was the halving of mortality in both groups by day 28. Thus, the primary endpoint was mortality by D28. Secondary endpoints included mortality on days 6 and 14, participant's clinical status on days 14 and 28, daily clinical status during hospitalization, duration of mechanical ventilation (if applicable) and supplementary oxygen (if applicable), total duration of hospitalization, and the time (in days) from treatment initiation to death or discharge. Here we present only analyses until day 6. Virologic measures included viral RNA detection on days 0 and 4.

Statistical analysis

An intention-to-treat analysis was conducted as part of the primary safety and efficacy analysis. Untaken or mistaken tablets, and dosage correction pending on renal and liver failure were not systematically registered daily, not allowing therefore per protocol analysis. Descriptive statistics were used for demographic, laboratory and clinical data. To assess the safety of the high and the low doses of CQ the proportion (95% CI) of deaths in each group was compared with the historical proportion (95% CI) of deaths in patients who did not use chloroquine in other countries. To assess whether the use of CQ reduced mortality by 50% in the study population, the chi-square test was performed to compare the proportions of deaths in both groups. For qualitative variables, Chi-square tests and Fisher's exact test were performed. An accumulated proportion of detection was assessed by survival models, using Kaplan-Meier estimate curves.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Population characteristics

At the study site, 81 patients were randomized as per protocol (41 in the high dosage CQ arm and 40 in the low dosage CQ arm; Figure 1 flowchart). As the analysis presented here was performed at Day 6, higher dose patients did not complete the full regimen (10 days). the Almost half of these patients were confirmed COVID-19 by RT-PCR *a posteriori* (40/81, 49.4%). The non-confirmed patients presented compatible clinical and epidemiological COVID-19 presentation, and were analysed together.

Older patients (aged over 75) were only enrolled in the high dosage CQ arm (n=5; Table 1). All the other characteristics were similar between age groups, allowing proper comparison. History of heart disease was more frequent among patients receiving the higher CQ dosage (p=0.05). Occurrence of myocarditis (defined as CKMB higher than 2x the upper normal limit), which may be a final complication of severe sepsis or a lesion triggered by the virus itself, was seen in 2/24 (8.3%) patients (1 patient/arm). No echocardiogram was performed.

Safety outcomes

One patient developed severe rhabdomyolysis, and causality could be attributed to the virus or to CQ, which is already known to cause myolysis (Table 2). Regarding cardiotoxicity and QTc over time, the variation in the QTc as compared to the baseline ECG increased more on days 2 and 3 in the high dose CQ arm, with both arms (low and high CQ) showing more similar QTc variations in the last three days of follow-up (Figure 2). Two patients in the high dose CQ arm evolved with ventricular tachycardia before death. This severe type of arrythmia is usually facilitated when QTc is prolonged.

No differences in hematological or renal toxicity was seen between the groups.

Efficacy until Day 6 outcomes

Major presented outcomes were not different between the arms (Table 3). Of 14 patients with paired samples (in both arms), respiratory secretion at day 4 was negative in only one patient.

The fatality rate in our sample was 13.5% (95%CI=6.9–23.0%), therefore still overlapping with the CI of the meta-analysis based on two major studies, which used similar patients without CQ (95%CI=14.5-19.2%). A Kaplan-Meier method was used to evaluate survival in which historical collation of available data from two other similar lethality studies with patients not receiving CQ was used (Figure 3). Both arms were very similar to these data showing no clear differences, despite the trend of more deaths in the higher dosage CQ arm. Only two out of 11 deaths were in older than 75 years-old. Eight out of 11 deaths had virological confirmation *antemortem.*

Based on the findings, DSMB recommended the immediate interruption of the high dose arm and that all patients in it were unmasked and reverted to the low dose arm.

Per protocol analysis was not performed due to the impossibility to monitor drug administration twice a day at the hospital. Radiological findings were presented in this manuscript only in the baseline due to the inability to perform careful analyses of the available CT scans over time. Radiological and complete efficacy data will be presented later.

Discussion

In a unique pandemic situation, health professionals have to choose between offering medical assistance and generating and reporting reliable data, a dichotomy that compromises the generation of good quality evidence for clinical management. Global recommendations for COVID-19 are being made based on unpowered studies, however, and due to the chaotic urgency, such drugs are being prescribed in a compassionate manner given the severity of this disease. However, CQ, despite being a safe drug used for more than 70 years for malaria, might be toxic in the dosages recommended by Chinese authorities (high dosage 10g, for 10 days). Our study raises enough red flags to stop the use of such dosage (12g of CQ in total,

for 10 days, due to the presentation of CQ tablets, 150mg, from *Farmanguinhos*) worldwide in order to avoid more unnecessary deaths. We were not able to independently assess the toxic role of azithromycin because all patients were already using this antibiotic as per hospital protocol. Oseltamivir, which also increases QTc, could potentiate cardiac side effects, because most of the patients (89.6%) were also in use of this drug for suspected influenza infection.

With the ethical impossibility of using a placebo arm, we were compelled to use historical data, based on very similar patients not using CQ. Fatality rates observed here were not lower, however one cannot reliably conclude that CQ is of no benefit. Placebo-controlled studies could still be performed in countries not routinely using the drug. Several ongoing trials have been addressing the early use of CQ, in which the anti-inflammatory properties could be more helpful. That information is urgently needed.

In addition to helping patients improve, CQ could be used to decrease the viral load in respiratory secretions, allowing less nosocomial and post-discharge transmission. However, our limited data provided no evidence of such an effect. Patients using CQ (irrespective of dosage) failed to present evidence of viral clearance by the fifth day (Day 4) of positive RT-PCR, even with the concomitant use of azithromycin. Therefore, we do not envision such use as an antiviral drug. Viremia dynamics in response to the drug will be further studied in our samples.

CQ is recommended for the treatment of malaria in particular due to its low cost; few doses resulting in safe concentrations are needed to treat the disease[25]. CQ can deposit in tissues, especially the eye, causing retinal toxicity, which is associated only with prolonged use[23,24]. QTc prolongation >500ms was seen in 17.9% of patients, which is not too dissimilar from what has been reported in patients with COVID-19 using HCQ (11.0%)[36]. Myopathy has also been associated with CQ use[25]. In our study, one patient developed rhabdomyolysis, which was attributed to CQ, and the drug was withdrawn. In two patients, myocarditis was suspected based on the CKMB elevation since the first day of hospitalization, suggesting myocarditis related to SARS-CoV-2 itself. In such cases, drugs prolonging QTc could lead to severe arrhythmias. Unfortunately, this study's randomization, probably due to the low sample size, assigned older patients with heart disease to the high dosage arm. Therefore, one limitation

for the conclusions of the study on lethality per arm is that high CQ dosage arm presented more patients prone to cardiac complications, with or without CQ.

The occurrence of myocarditis in our sample together with the confirmed QTc prolongation, warrants caution in relation to this drug's safety, particularly considering the eventual increase in fatal arrythmias.

This study had some strengths, as it was: (1) double-blinded; (2) performed in a public hospital, which will represent most of the cases in countries like Brazil; (3) compliant with good clinical practices, with a vigilant and highly involved DSMB; (4) an assessment of two dosing schemes of CQ for the first time in COVID-19 patients.

Major limitations however included: (1) one single center so far; (2) not using a placebo control group as the use of placebo in Brazil in severe cases of COVID-19 infections is not considered ethically acceptable by national regulatory health agencies, especially due to the compassionate use of CQ[37] – and because early reports seem to indicate its effectiveness *in vitro* and *in vivo*; (3) not all cases were COVID-19 confirmed by RT-PCR.

In conclusion, the high CQ dose scheme (12g), given for 10 days, was not sufficiently safe to warrant continuation of that particular study arm. We therefore strongly recommend that this dosage is no longer used anywhere for the treatment of severe COVID-19, especially because in the real world older patients using cardiotoxic drugs should be the rule. No apparent benefit of CQ was seen regarding lethality in our patients so far, but we will still enroll patients in the low CQ dose group to complete the originally planned sample size.

In order to better understand the role of CQ or HCQ in COVID-19[38], we recommend the following next steps: (1) trials evaluating its role as a prophylactic drug; (2) trials evaluating its efficacy against progression to severity when administered to patients with mild/moderate disease. Even if we fail to generate good evidence in time to control the current pandemic, the information will highly impact the way we deal with next coronavirus outbreaks in the future.

Contributors

FFAV, GCM, LAH, WMM, MVFG and MVGL conceived the study and developed the protocol with input from MGSB, VSS, RCP, DCBS, MPGM and QB. MGSB, MAAA, AMS, MPGM and MVGL supervised clinical work. GCM and FGN supervised laboratory work. MGSB supervised pharmacy work. VSS, LAH, DCBC, MSX, AS, JHRC, MLN, GASR, CJF, BCA, CTDR and AASB performed data management and analysis. VSS, JDBS, DCBS, AMS, QB, WMM, and MVGL wrote the manuscript with input from all other authors. CloroCovid-19 Team collected all the data. All authors critically read the manuscript and approved the final submitted version.

Declaration of interests

The study included a *Data and Safety Monitoring Board* (DSMB) composed by GASR, QB, BCA, CTDR and CJF. Given the involvement on the day to day review of activities of the trial, the close monitoring of safety events, and their role in the decision to halt the study on account of safety issues, the study PI decided to invite them on an individual basis to co-author the manuscript. All members of the DSMB agreed to be included.

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36 Chorin E, Dai M, Shulman E, *et al.* The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. *medRxiv* 2020; : 2020.04.02.20047050.

37 COVID-19 in Brazil: advantages of a socialized unified health system and preparation to contain cases. .

38 Monteiro WM, Brito-Sousa JD, Baía-da-Silva D, *et al.* Driving forces for COVID-19 clinical trials using chloroquine: the need to choose the right research questions and outcomes. *Rev Soc Bras Med Trop* 2020; **53**. DOI:10.1590/0037-8682-0155-2020.

Table 1. Demographic, clinical, laboratory, and radiographic findings of patients at baseline.

Variable	Total	CQ low dosage¶	CQ high dosage§	*p*-value
Age, years, mean (SD)	51.1 (13.9)	47.4 (13.3)	54.7 (13.7)	**0.02**
Age group (years)				
18-50 (%)	41/81 (50.6)	24/40 (60)	17/41 (41.5)	**0.04**
>50-75 (%)	35/81 (43.2)	16/40 (40)	19/41 (46.3)	
>75 (%)	5/81 (6.2)	0/40 (0)	5/41 (12.2)	
Female (%)	20/81 (24.7)	10/40 (25)	10/41 (24.4)	0.95
Race				
White (%)	17/81 (21)	10/40 (25)	7/41 (17.1)	0.53
Black (%)	6/81 (7.4)	2/40 (5)	4/41 (9.8)	
Admixed (%)	58/81 (71.6)	28/40 (70)	30/41 (73.2)	
Health professional (%)	5/81 (6.2)	1/40 (2.5)	4/41 (9.8)	0.36
Pregnancy (%)	2/20 (10)	1/9 (10)	1/9 (10)	1.00
History of smoking				
Never smoked (%)	32/47 (68.1)	16/22 (72.7)	16/25 (64)	0.25
Former smoker (%)	11/47 (23.4)	3/22 (13.6)	8/25 (32)	
Current smoker (%)	4/47 (8.5)	3/22 (13.6)	1/25 (4)	
Comorbidities				
Any comorbidity (%)	54/81 (67.5)	26/40 (66.7)	28/41 (68.3)	0.87
Hypertension (%)	25/54 (46.3)	10/26 (37)	15/28 (53.6)	0.28
Diabetes (%)	14/54 (25.9)	5/26 (19.2)	9/28 (32.1)	0.50
Alcoholism (%)	13/50 (26)	7/24 (29.2)	6/26 (23.1)	0.91
Heart disease (%)	5/54 (9.3)	0/26 (0)	5/28 (17.9)	0.05
Asthma (%)	3/48 (6.2)	1/24 (4.2)	2/24 (8.3)	1.00
Chronic kidney disease (%)	4/53 (7.5)	1/25 (4)	3/28 (10.7)	0.75
Rheumatic diseases (%)	3/54 (5.6)	3/26 (11.5)	0/28 (0)	0.16
Liver diseases (%)	2/54 (3.7)	2/26 (7.7)	0/28 (0)	0.43
Tuberculosis (%)	2/54 (3.7)	2/26 (7.7)	0/28 (0)	0.43
HIV/Aids (%)	1/54 (1.9)	0/26 (0)	1/28 (3.6)	1.00
Influenza vaccine in the last two years (%)	16/80 (20)	8/39 (20.5)	8/41 (19.5)	0.90
Medicines on admission				
Corticoid anti-inflammatories (%)	3/56 (5.4)	2/30 (6.7)	1/26 (3.8)	1.00
ACE inhibitors (%)	6/58 (10.3)	2/31 (6.5)	4/27 (14.8)	0.40
Bronchodilators (%)	3/81 (3.9)	1/40 (2.7)	2/41 (5)	1.00
Oseltamivir, %	69/77 (89.6)	37/40 (92.5)	32/37 (86.5)	0.39
Oxygen therapy (%)	72/81 (88.9)	36/40 (90)	36/41 (87.8)	1.00
ICU hospitalization, %	35/81 (43.2)	22/41 (53.6)	13/40 (32.5)	0.05
Days from illness onset to hospital admission, median (IQR)	7 (4,9)	6.5 (4,9)	7 (5,10)	0.74
Temperature distribution				

<37.5°C (%)	56/76 (73.7)	29/38 (76.3)	27/38 (71.1)	0.35
37.5–38.0°C (%)	10/76 (13.2)	6/38 (15.8)	4/38 (10.5)	
38.1–39.0°C (%)	10/76 (13.2)	3/38 (7.9)	7/38 (18.4)	
Heart rate, bpm, mean (SD)	91 (17.6)	91.7 (19)	90.4 (16.4)	0.75
Respiratory rate, rpm, median (IQR)	26.5 (21,30)	26 (22,30)	28 (20,31)	0.58
Mean blood pressure, mmHg	93.9 (16.7)	95.2 (18.2)	92.7 (15.4)	0.51
Body mass index, kg/m^2, median (IQR)	28 (26,31.6)	28.9 (26.1,32.7)	27.1 (25.7,31.1)	0.25
Capillary refill time, seconds	13/69 (18.8)	6/34 (17.6)	7/35 (20)	0.80
Oxygen saturation (SpO_2), %, median (IQR)	96 (93.5,98)	96 (92,98)	95 (94,98)	0.88
White blood cell count, ×10□/L, mean (SD)	9.7 (4.4)	9.3 (4.7)	10 (4.2)	0.63
Hemoglobin, g/L, mean (SD)	13.1 (2.3)	13.6 (2.7)	12.8 (2)	0.30
Platelet count, ×10□/L, median (IQR)	211 (178.5,260)	220 (171,251)	210 (179,260)	0.82
Alanine aminotransferase, U/L, mean (SD)	86.4 (42.2)	66.3 (49.3)	106.4 (25.5)	0.20
Creatinine, μmol/L, mean (SD)	1.3 (1,2.7)	1.3 (1,2.3)	1.3 (1,2.7)	0.53
Lactate dehydrogenase, U/L, mean (SD)	890.7 (414.6)	704.4 (333.7)	1123.5 (424)	0.14
Creatine kinase, U/L, median (IQR)	112.2 (66.8,261.2)	110.5 (55.8,234.7)	112.2 (81.8,470)	0.32
Creatine kinase MB, U/L, median (IQR)	21.7 (16.5, 28.0)	21.6 (16.1,24.7)	21.8 (18.5,28.3)	0.51
International Normalized Ratio, median (IQR)	1.1 (1.1,1.2)	1.1 (1.1,1.1)	1.2 (1.1,1.2)	0.86
C-reactive protein, mg/L, median (IQR)	82.3 (63.2,92)	82.1 (62.5,91.7)	88.3 (70.5,92.2)	0.48
QTc, ms, median (IQR)	421.5 (407.5,440)	417 (407,432.5)	433 (409,449)	0.28
Radiological findings	48/80 (60)	25/39 (64.1)	23/41 (56.1)	0.46
Unilateral ground-glass (%) opacity infiltration (%)	40/81 (49.4)	19/40 (47.5)	21/41 (51.2)	0.74
Bilateral ground-glass opacity infiltration (%)	8/81 (9.9)	6/40 (15)	2/41 (4.9)	0.15
Unilateral consolidation (%)	25/81 (30.9)	15/40 (37.5)	10/41 (24.4)	0.20
Bilateral consolidation (%)	14/81 (17.3)	6/40 (15)	8/41 (19.5)	0.59
Pleural effusion (%)	5/81 (6.2)	3/40 (7.5)	2/41 (4.9)	0.67
qSOFA score <2 (%)	54/81 (66.7)	30/40 (75)	24/41 (58.5)	0.11

§ High dose CQ (600g CQ twice daily for 10 days);
¶ Low dose CQ for 5 days (450mg CQ twice daily on the first day and 450mg once a day for the remaining 4 days).

Table 2. Safety outcomes in the intention-to-treat population until Day 6*.

Variable	**Total**	**CQ low dosage¶**	**CQ high dosage§**	***p*-value**
Hemoglobin decreased¥ (%)	7/20 (35)	4/8 (50)	3/12 (25)	0.36
Creatinine increased† (%)	13/18 (72.2)	5/7 (71.43)	8/11 (72.72)	0.99
QTcF >500ms‡ (%)	10/56 (17.9)	3/28 (10.71)	7/28 (25)	0.29
Ventricular tachycardia* (%)	2/56 (3.5)	0/28 (0.0)	2/28 (7.1)	0.51

* Not all patients have completed Day 6 visit until this publication was finalized
¶ Low dose CQ for 5 days (450mg CQ twice daily on the first day and 450mg once a day for the remaining 4 days);
§ High dose CQ (600g CQ twice daily for 10 days).
Adverse events were classified according to the Medical Dictionary for Regulatory Activities, version 19.1.
¥ Shown are decreases in hemoglobin level of more than 3 g per deciliter or 30% or more from baseline.
¶ Shown are increases in serum levels of 30% or more from baseline.
‡ Severe adverse events related to the trial regimen were prolongation of the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

Table 3. Efficacy outcomes after enrollment, in the intention-to-treat population until Day 6*.

Variable	**Total**	**CQ low dosage**	**CQ high dosage**	***p*-value**
Oxygen support need (%)	4/28 (14.3)	1/13 (7.7)	3/15 (20.0)	0.35
Invasive mechanical ventilation need (%)	6/39 (15.4)	2/19 (10.5)	4/20 (20.0)	0.41
ICU need, %	2/13 (15.4)	1/11 (9.1)	1/2 (50.0)	0.14
Need for inotropics (%)	1/34 (2.9)	1/19 (5.3)	0/15 (0.0)	0.37
Death (%)	11/81 (13.6)	7/40 (17.5)	4/41 (9.7)	0.35
Naso/oropharyngeal swab viral clearance (%)	1/26 (3.9)	1/12 (8.3)	0/14 (0.0)	0.27

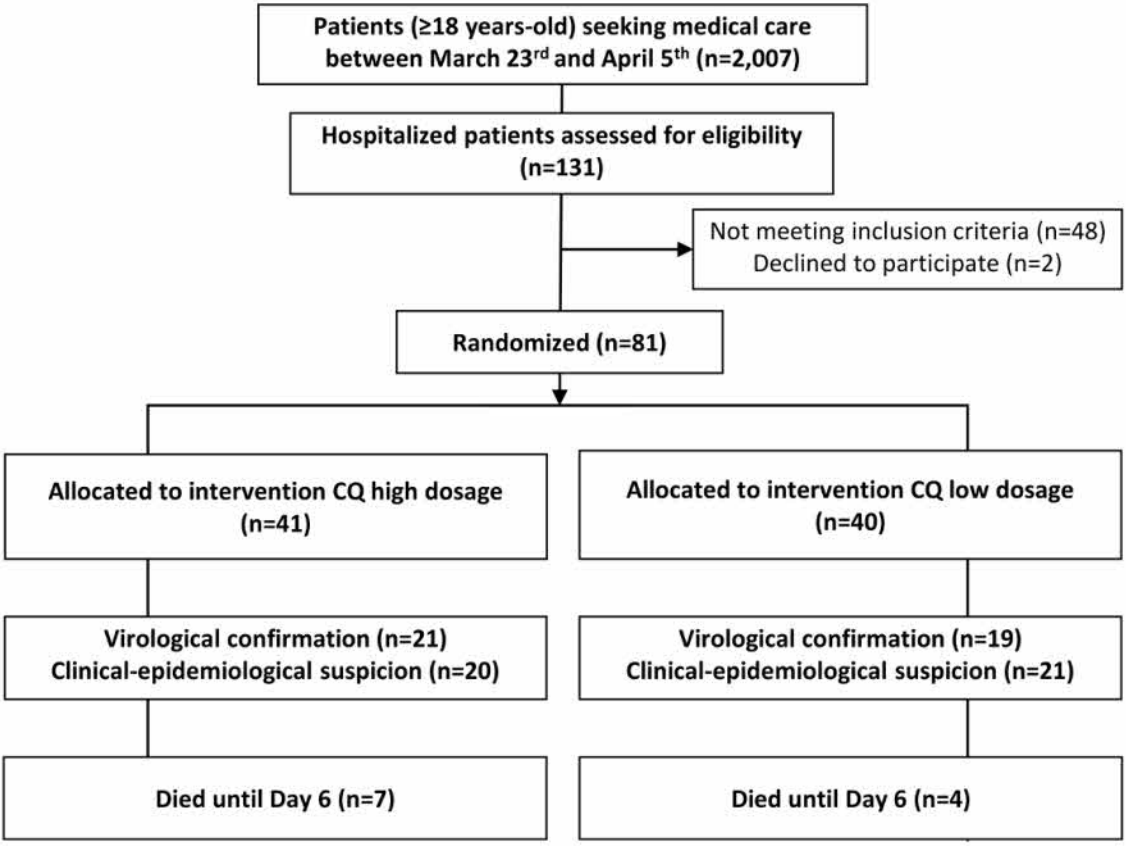
*Except viral clearance, which was performed on Day 4.

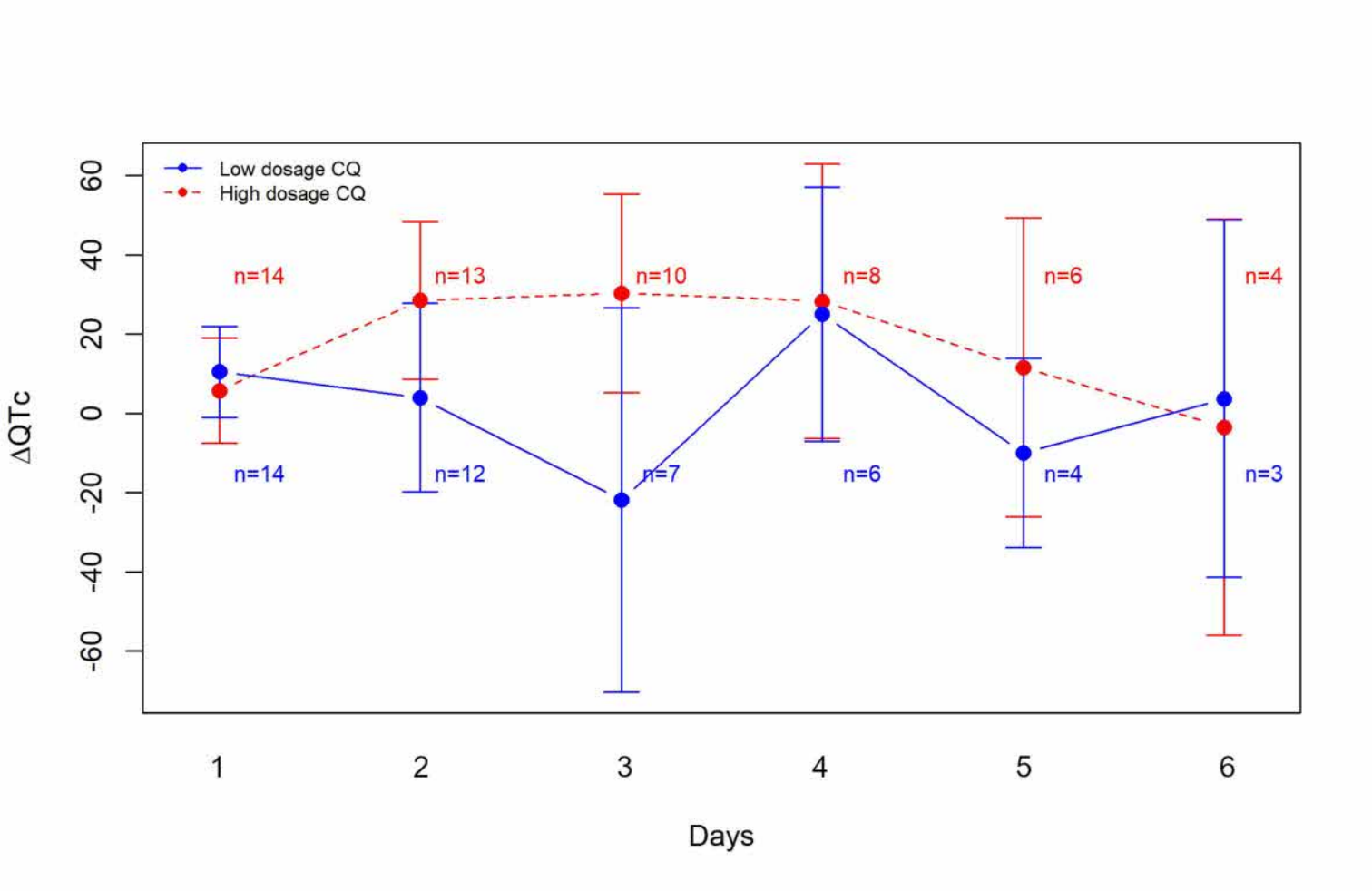
Figure legends

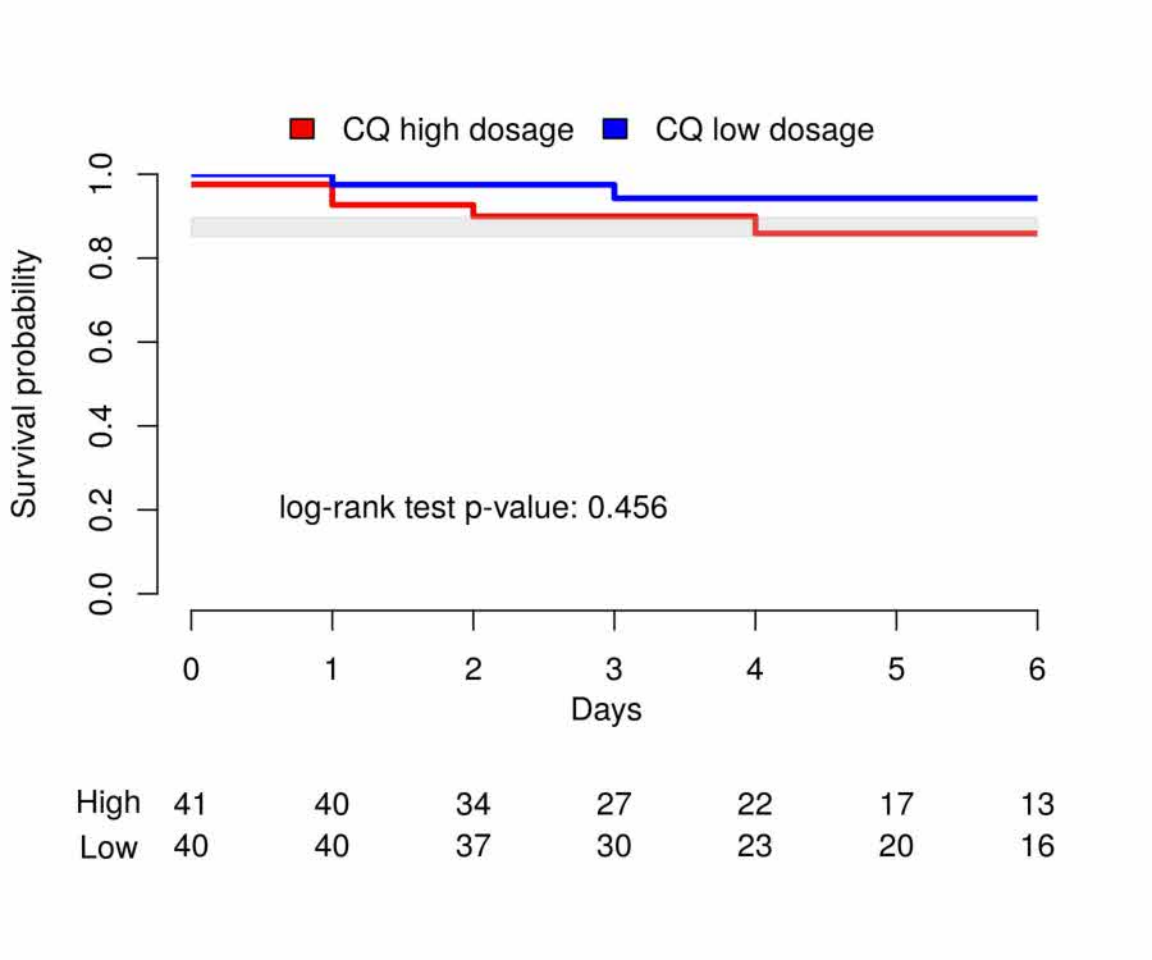
Figure 1. Study flowchart. Eligible participants were allocated at a 1:1 ratio to receive CQ to two arms at either high dose (600g CQ twice daily for 10 days) or low dose CQ (450mg CQ twice daily on the first day and 450mg once a day for the remaining 4 days, for a total of 5 days).

Figure 2. Daily variation (delta) of QTc values (in milliseconds) as compared to baseline, before CQ was prescribed, per group.

Figure 3. Time (in days) from randomization to death, in patients treated with each chloroquine dosage. The gray band represents the upper and lower limits of the confidence interval for lethality in hospitalized patients not receiving CQ obtained by the meta-analysis of the studies by Zhou et al. (Lancet, 2020) and Chen et al. (BMJ, 2020) (167/990 = 16.9%; 95% CI 14.5-19.2).


Patients (≥18 years-old) seeking medical care between March 23rd and April 5th (n=2,007)
Hospitalized patients assessed for eligibility (n=131)
Not meeting inclusion criteria (n=48)
Declined to participate (n=2)
Randomized (n=81)
Allocated to intervention CQ high dosage (n=41)
Allocated to intervention CQ low dosage (n=40)
Virological confirmation (n=21)
Clinical-epidemiological suspicion (n=20)
Virological confirmation (n=19)
Clinical-epidemiological suspicion (n=21)
Died until Day 6 (n=7)
Died until Day 6 (n=4)


Low dosage CQ
High dosage CQ
n=14
n=13
n=10
n=8
n=6
n=4
n=14
n=12
n=7
n=6
n=4
n=3
ΔQTc
60
40
20
0
-20
-40
-60
1
2
3
4
5
6
Days


CQ high dosage
CQ low dosage
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
log-rank test p-value: 0.456
0
1
2
3
4
5
6
Days
High 41 40 34 27 22 17 13
Low 40 40 37 30 23 20 16

From: CDC IMS 2019 NCOV Response Chief Medical Officer
Sent: Fri, 18 Sep 2020 20:42:20 +0000
To: CDC IMS 2019 NCOV Response Chief Medical Officer; CDC IMS Response Coordinator -2; CDC IMS Response Coordinator; EOC Report (CDC)
Cc: Ackers, Marta (CDC/DDPHSIS/CGH/DGHT); Ao, Trong (CDC/DDPHSIS/CGH/DGHT); Beavers, Suzanne (CDC/DDPHSS/CSELS/DSEPD); Brooks, John T. (CDC/DDID/NCHHSTP/DHP); Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHP); Dowell, Deborah (Debbie) (CDC/DDNID/NCIPC/DOP); Dunne, Eileen F. (CDC/DDID/NCHHSTP/DHP); Eisenberg, Judith (CDC/NIOSH/DFSE/HETAB); Ende, Zachary (CDC/DDID/NCIRD/ID); Hutchinson, Angela (CDC/DDID/NCHHSTP/DHP); Iqbal, Kashif (CDC/DDID/NCHHSTP/DHP); Lowe, David (CDC/DDID/NCEZID/DHCPP); Martin, Diana (CDC/DDPHSIS/CGH/DPDM); Montesanti Porter, Angela (CDC/DDPHSIS/CGH/GID); Mpofu, Jonetta J. (CDC/DDID/NCHHSTP/DASH); Peterson, Amy (CDC/DDID/NCEZID/DVBD); Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE); Schieber, Richard A. (CDC/DDPHSS/CSELS/OD); Welsh, Clement (ATSDR/OAD/OIA); White, Jianglan Z. (CDC/DDID/NCHHSTP/DVH); Wiese, Nicholas (CDC/DDID/NCEZID/DHCPP)
Subject: COVID-19 - Science Update - 2020-09-18 Edition (FRIDAY)
Attachments: 2020 09 18 Science Update_Final_Public.pdf

Good afternoon EOC report,

Could you please send out this email announcement, along with the attached document, to distribute the Science Update for Friday September 18, 2020?:

**********START EMAIL ANNOUNCEMENT**********

Please find attached the September 18, 2020 COVID-19 Science Update from the Office of the Chief Medical Officer, CDC COVID-19 Response.

****As of September 1, 2020 the COVID-19 Science Update series is publicly available****

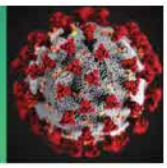
NEW LINK: ***https://www.cdc.gov/library/covid19***

All previously released Science Updates will remain archived on the CDC Intranet until they are migrated to the public site.
Intranet Link: (b)(5)

We welcome your feedback. Please send any comments/suggestions to CDC IMS 2019 NCOV Response Chief Medical Officer eocevent385@cdc.gov .

**********END EMAIL ANNOUNCEMENT**********

COVID-19 Science Update



From the Office of the Chief Medical Officer, CDC COVID-19 Response, and the CDC Library, Atlanta, GA.
Intended for use by public health professionals responding to the COVID-19 pandemic.

***** Available on-line at https://www.cdc.gov/library/covid19 *****

Healthcare Setting Associated COVID-19

Below we present three studies that investigate the risks for infection with SARS-CoV-2 in healthcare settings. These studies look at occupational as well as nosocomial risks for patients and healthcare workers (HCWs). Across all three studies, higher levels of infection control and prevention protect both patients and HCWs.

PEER-REVIEWED

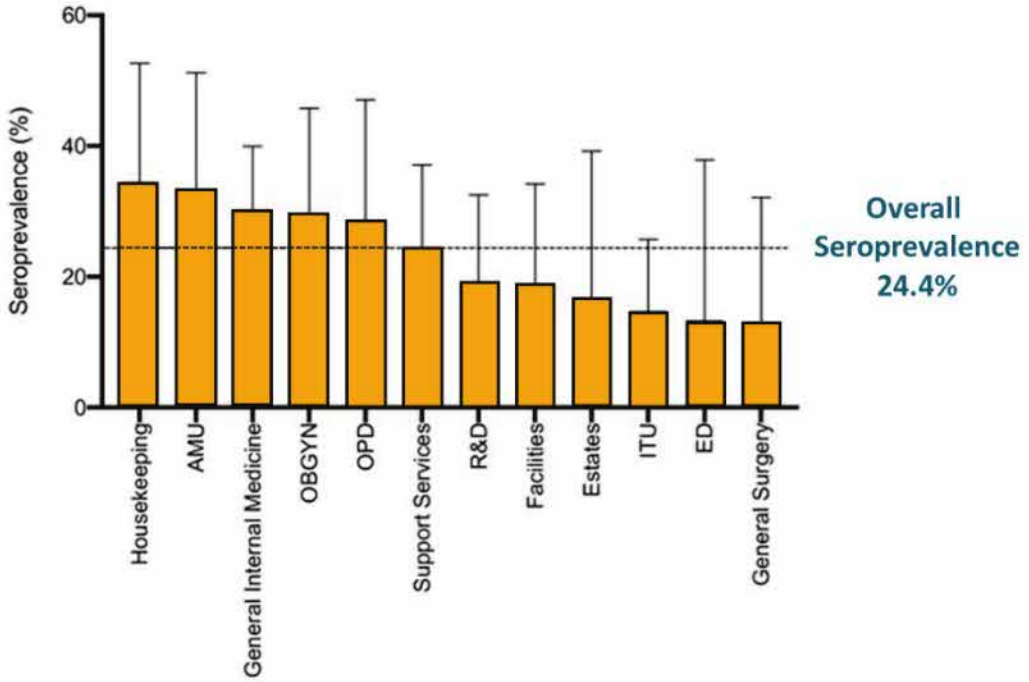
SARS-CoV-2 seroprevalence and asymptomatic viral carriage in healthcare workers: A cross-sectional study. Shields *et al.* Thorax (September 11, 2020).

Key findings:

- Over a 24-hour period, 2.4% (n = 13/545) of asymptomatic HCWs tested RT-PCR positive.
- The seroprevalence among HCWs was 4 times higher than reported regionally (24% vs 6%).
    - Black, Asian, and minority ethnicity HCWs were at increased risk for seropositivity (adjusted OR: 1.92, 95% CI 1.14 to 3.23, p = 0.01), even after controlling for external risk factors.
    - Seropositivity was highest among housekeeping, acute medicine, and general internal medicine staff and lowest among intensive care, emergency department, and general surgery staff (Figure).

Methods: Cross-sectional convenience sample of 545 asymptomatic HCWs recruited at work in Birmingham, UK, on April 24 and April 25, 2020. Anyone with symptoms of COVID-19 on that day, who was home due to self-isolation, or had symptomatic illness was excluded. Participants were tested using RT-PCR and serology.
Limitations: The study did not look at how representative the study respondents were of the worker cohort at the time of the study; single cross-sectional sampling may underestimate the seroprevalence.

Figure:



Note: Adapted from Shields *et al*. Seroprevalence of SARS-CoV-2 antibody by department. AMU-acute medical unit; ED-emergency department; ITU-intensive care unit; OBGYN-obstetrics and gynecology; OPD-outpatient department; R&D-research and development. Licensed under CC-BY-NC 4.0.

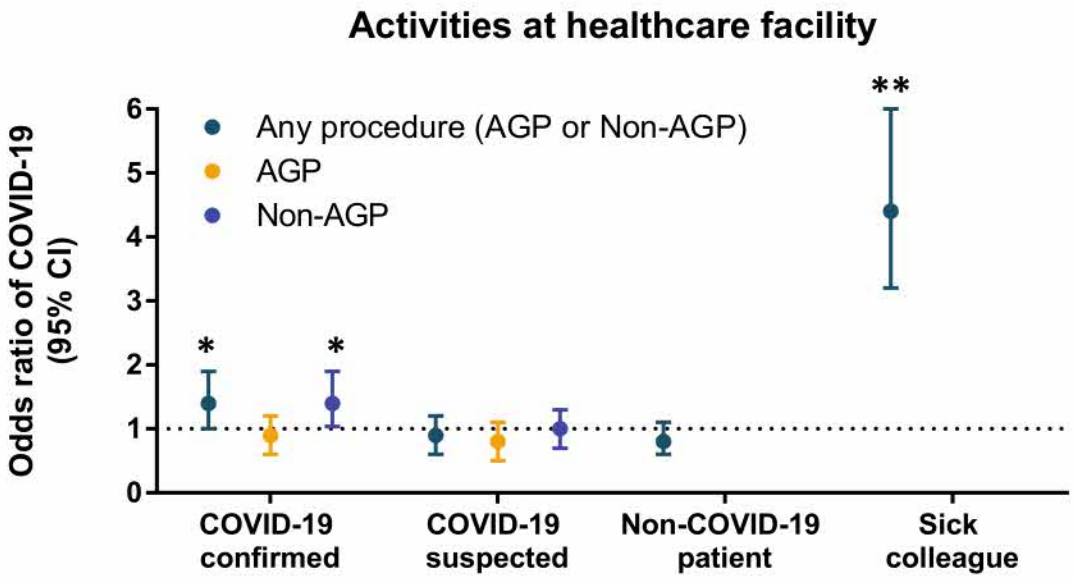
Assessing COVID-19 Transmission to Healthcare Personnel: The Global ACT-HCP Case-Control Study. Lentz *et al.* Infection Control and Hospital Epidemiology (September 9, 2020).

Key findings:

- The proportion of COVID-19 cases was greater among nurses (41%) than either physicians and nurse practitioners (20%) or respiratory therapists (6%).
- At work, contact with a sick colleague, contact with patients with laboratory-confirmed COVID-19, and performing non-aerosol-generating procedures (AGP) on patients with laboratory-confirmed or suspect COVID-19 were significantly associated with testing positive for SARS-CoV-2 (Figure 1).
- Outside of work, attending gatherings of >10 people, going to a restaurant or bar, using public transportation, or being exposed to a household member with COVID-19 were significantly associated with testing positive for SARS-CoV-2 (Figure 2).

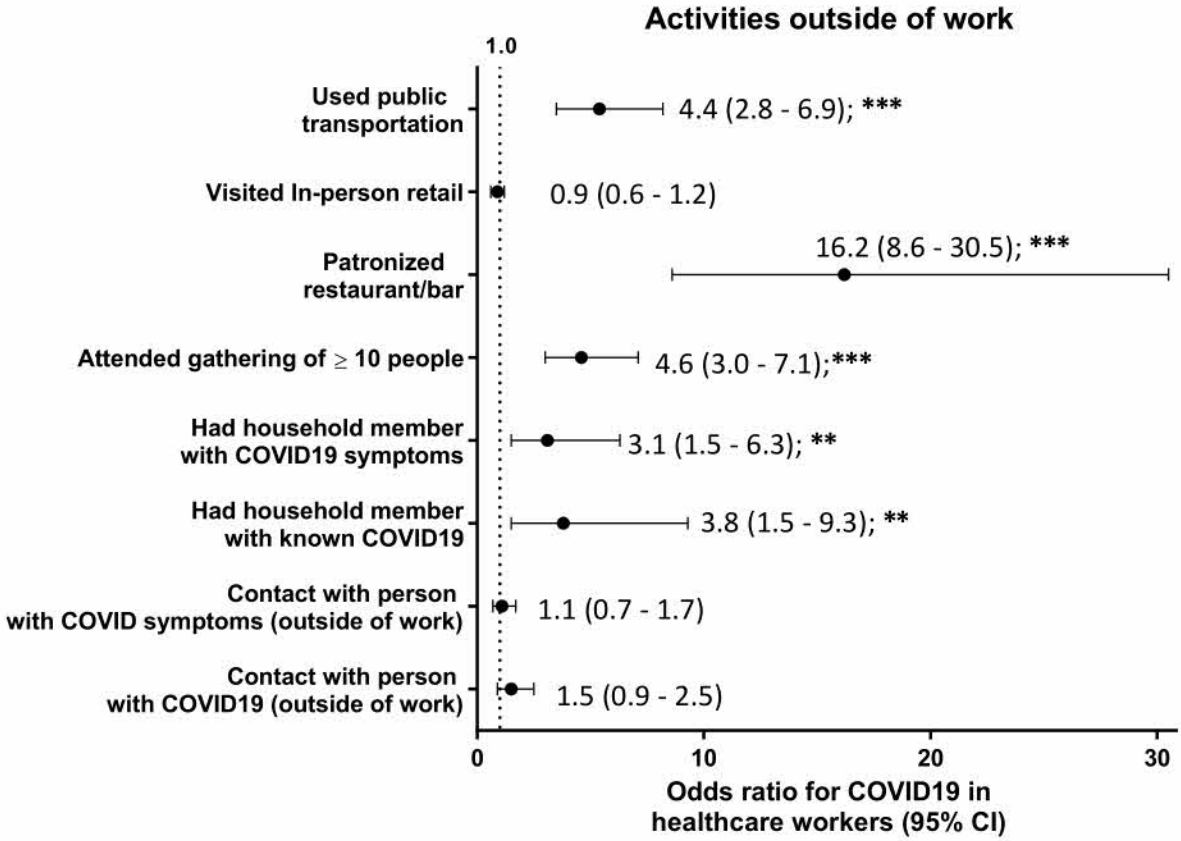
Methods: Case-control study among 1,678 healthcare personnel from 67 countries using an online survey tool, between April 20 and May 5, 2020. Inclusion criteria included working in a healthcare setting between January 1, 2020 and survey completion. Cases (n = 244) were those reporting a laboratory-confirmed COVID-19 diagnosis and controls (n = 886) were those who remained healthy. Possible cases who experienced COVID-19 symptoms without laboratory confirmation were excluded. *Limitations*: Mid-level providers and physicians were overrepresented; confirmation of case or control status was not possible; asymptomatic cases may have been present in the control group.

Figure 1



Note: Adapted from Lentz, *et al.* OR of COVID-19 in healthcare workers based on type of contact with patients and colleagues for **Any procedure** data, **AGP** and **Non-AGP**. Bars represent the 95% CI and the dashed line is OR of 1, PUI-person under investigation, *p-value <0.05, **p-values <0.01. Reproduced with permission of Cambridge University Press.

Figure 2



Note: Adapted from Lentz *et al.* ORs for COVID-19 in healthcare workers based on activities outside of work. Dots represent the ORs, while bars represent 95% CI. **p-value <0.01, ***p-value <0.001. Reproduced with permission of Cambridge University Press.

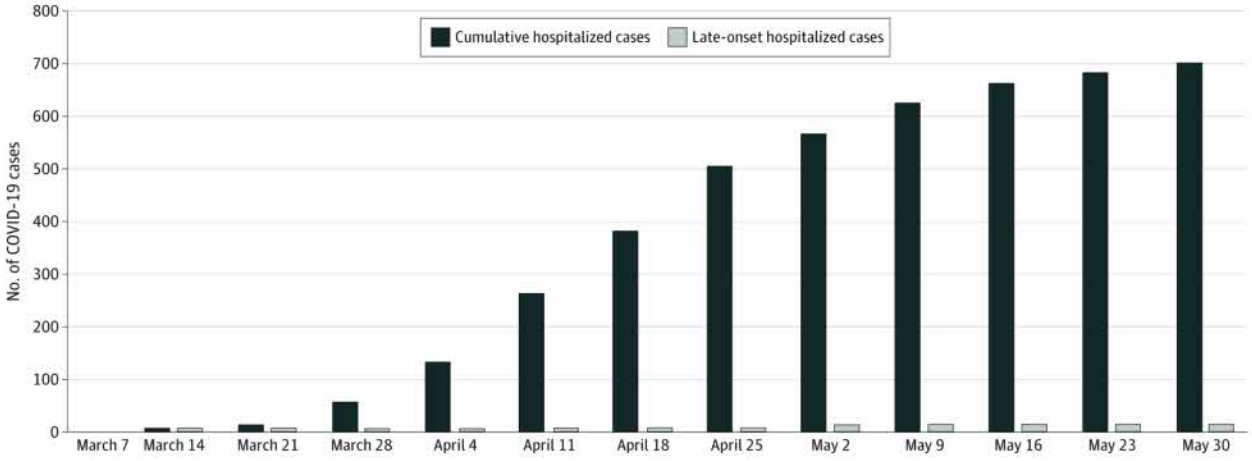
Incidence of nosocomial COVID-19 in patients hospitalized at a large US academic medical center. Rhee *et al.* JAMA (September 9, 2020).

Key findings:

- 12/697 (1.7%) hospitalized patients tested positive for SARS-CoV-2 infection after admission.
  - Only 1 patient acquired SARS-CoV-2 infection while hospitalized through exposure to a visiting asymptomatically infected spouse.
- 11/8,370 (0.1%) patients tested positive for SARS-CoV-2 infection within 14 days of discharge.
  - In one person, infection was likely hospital-acquired.

Methods: Cohort study among all 9,149 patients admitted to Brigham and Women's Hospital in Boston, MA, between March 7 and May 30, 2020. SARS-CoV-2 infection was determined by positive RT-PCR. Test timing, clinical course, and exposure history were used to classify cases as having community- or hospital-acquired SARS-CoV-2 infection. *Limitations*: Testing practices changed during the study period; asymptomatic cases might not have sought testing after discharge; those who may have sought testing more than 14 days after discharge and cases diagnosed outside the hospital catchment area were not captured; the hospital did not exceed surge capacity during the study period.

Figure:



Note: Adapted from Rhee *et al*. Cumulative number of **Total** and **Late-Onset** hospitalized coronavirus disease 2019 (COVID-19) cases by week. Licensed under CC-BY.

Implications for 3 studies (Shields *et al*., Lentz *et al.* & Rhee *et al.*): Healthcare settings present risks for SARS-CoV-2 infection to both healthcare personnel and patients. Healthcare personnel face different risks based on occupation and afterwork activities. With comprehensive infection control programs, risk of nosocomial and healthcare-associated SARS-CoV-2 infection among patients and staff, respectively, can be minimized even in the context of high-risk procedures and settings.

Racial Disparities in COVID-19 Morbidity and Mortality

PEER-REVIEWED

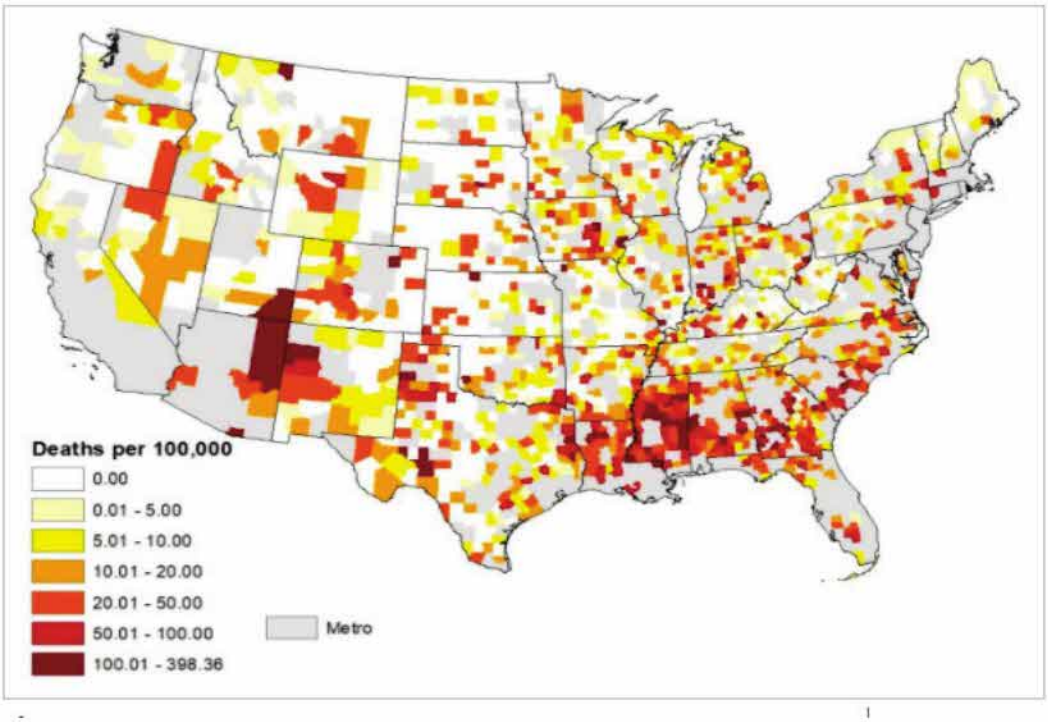
COVID-19 death rates are higher in rural counties with larger shares of Blacks and Hispanics. Cheng *et al*. Journal of Rural Health (September 7, 2020).

Key findings:

- The average daily increase in COVID-19 mortality has been significantly greater in rural counties with the largest percentages of Black and Hispanic residents (Figure).
- In this study, when the 20 rural counties with the highest mortality rates were stratified in quartiles by percentage of racial/ethnic minority residents:
    - By Black race, the average daily increase in COVID-19 deaths was 70% higher in the top quartile compared with the bottom quartile (incidence rate ratio (IRR) 1.70, CI 1.48-1.95, p <0.001).
    - By Hispanic ethnicity, the average daily increase in COVID-19 deaths was 50% higher in the top quartile compared with the bottom quartile (IRR 1.50, CI 1.33-1.69, p <0.001).

Methods: Regression analysis was used to measure differences in the increase in the COVID-19 mortality rate based on the proportion of the Black or Hispanic population during the first 5 months of the pandemic from 1,976 US non-metropolitan US counties. *Limitations*: This study did not assess individual mortality risk; because race/ethnicity-specific COVID-19 mortality data were lacking, it's possible that White persons also had higher mortality rates in rural areas.

Figure:



Note: From Cheng *et al.* COVID-19 mortality rates (per 100,000 persons) in non-metro counties. Gray counties are metro counties. Permission request in process.

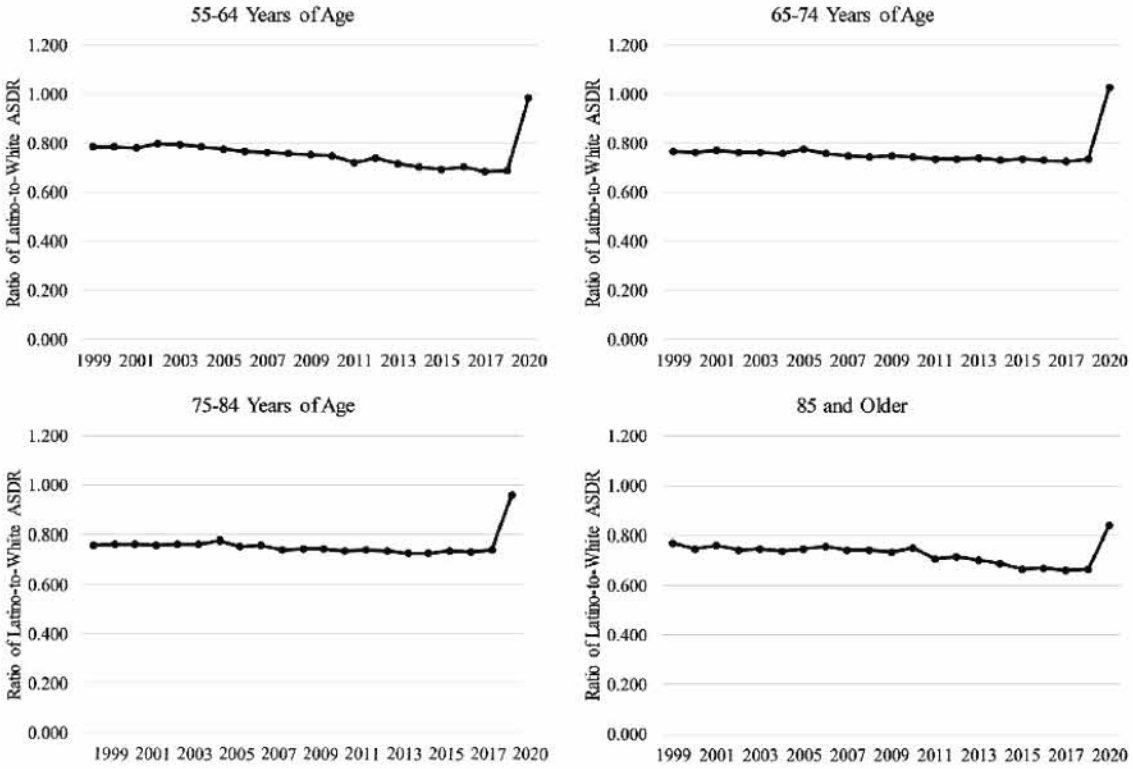
The disproportionate impact of COVID-19 on older Latino mortality: The rapidly diminishing Latino paradox. Saenz *et al*. Journal of Gerontology (September 8, 2020).

Key findings:

- Historically, age-specific death rates (ASDR) for Hispanic persons have been lower than for Whites. However, in 2020 the death rates for Hispanics increased in all age groups (Figure).
- Older Hispanic persons experienced a higher COVID-19 age-adjusted mortality than White persons across all age groups; however, Hispanic persons had lower *non*-COVID-19 age-adjusted mortality than White and Black persons.
    - The difference in COVID-19 age-adjusted mortality decreased in older age groups (i.e., 6.1 times higher in Hispanic persons compared with White persons in the 55-64 years age group vs 1.6 times higher than Whites persons in the ≥85 years age group).

Methods: Investigators estimated age-adjusted mortality rates from February to August, 2020 and the age-adjusted mortality ratio of Hispanic persons to White persons across four age groups (55-64 yrs., 65-74 yrs., 75-84 yrs., and 85+). Mortality rates from 1999 to 2018 were used for historical comparisons. *Limitations:* Mortality data were provisional and subject to revision.

Figure:



Note: From Saenz *et al*. Age-specific death ratios in Hispanic persons compared with White persons, 1999-2020. Values lower than 1 indicate a lower death rate for Hispanic persons relative to White persons. Permission request in process.

Implications of both studies (Cheng *et al*. & Saenz *et al*.): Communities of color bear a disproportionate share of the mortality risk of COVID-19 and this extends to rural areas of the US, highlighting the need to address structural inequities that contribute these mortality differences. Greater COVID-19 age-adjusted mortality in Hispanic persons relative to White persons has diminished the "Latino paradox" in which Latino persons have historically had greater longevity than non-Hispanic persons.

Epidemiology

PEER-REVIEWED

Asthma in COVID-19 hospitalizations: An overestimated risk factor? Broadhurst *et al.* Annals of the American Thoracic Society (August 31, 2020).

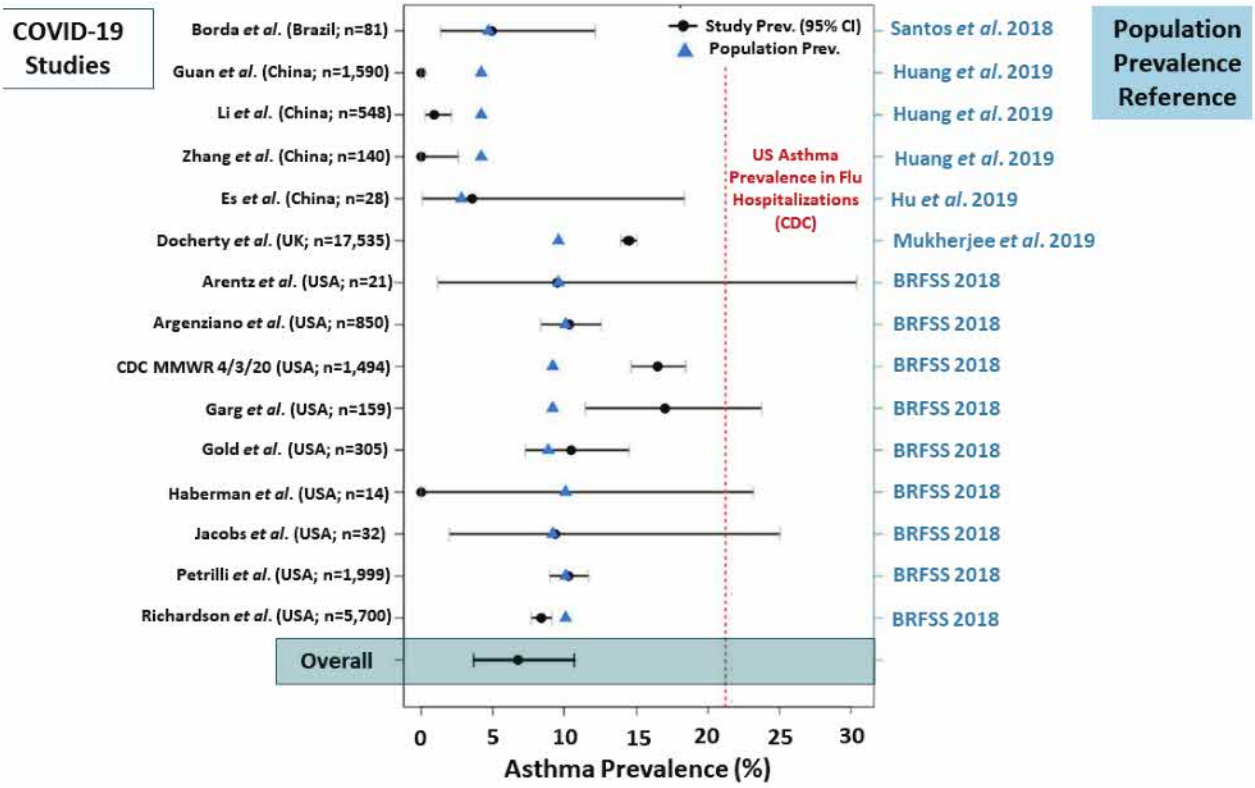
Key findings:

- Asthma prevalence among hospitalized COVID-19 patients is not greater than that of the local population and lower than US hospitalized influenza patients (6.8% pooled estimate vs 21%) (Figure).
- Hospitalized COVID-19 patients with asthma were not more likely to be intubated than COVID-19 patients without asthma (OR 0.69, 95% CI 0.33-1.45, adjusting for age, sex, and body mass index).

Methods: Meta-analysis conducted among 15 studies comparing asthma prevalence among COVID-19 hospitalized patients to local population prevalence and asthma prevalence among US influenza hospitalizations. Additionally, the likelihood of intubation among asthmatics was evaluated among 436 hospitalized COVID-19 patients in one hospital in Colorado. *Limitations*: Possible difference in comorbidity reporting and four studies added after initial review for meta-analysis; small sample size and limited generalizability for cross-sectional study.

Implications: Asthma does not appear to be a significant risk factor for hospitalization or intubation from COVID-19.

Figure:



Notes: Adapted from Broadhurst *et al.* Asthma prevalence in various COVID-19 studies. **Dots** are asthma prevalence among COVID-19 hospitalized patients with 95% CI in 15 studies and triangles are the corresponding population asthma prevalence. The vertical dotted line is the 4-year average US asthma prevalence among influenza hospitalizations. Licensed under CC-BY-NC-ND 4.0.

Clinical Treatment & Management

PEER-REVIEWED

Comparison of clinical features of COVID-19 vs seasonal influenza A and B in US children. Song *et al.* JAMA Network Open (September 8, 2020).

Key findings:

- There was no significant difference in clinical outcomes between children with COVID-19 versus seasonal influenza with regard to hospitalization (17% vs 21%), ICU admission (6% vs 7%) and mechanical ventilation (3% vs 2%) (Table).
- More COVID-19 patients had fever, diarrhea or vomiting, myalgia and chest pain than patients with seasonal influenza.
- 65% of patients hospitalized for COVID-19 had at least one comorbidity compared with 42% of patients hospitalized for seasonal influenza (p = 0.002).

Methods: Retrospective cohort study comparing 315 children diagnosed with COVID-19 between March 25 and May 15, 2020 and 1,402 children diagnosed with seasonal influenza between October 1, 2019 and June 6, 2020 at Children's National Hospital in Washington D.C. Diagnosis of either COVID-19 or influenza was confirmed by RT-PCR. Clinical outcomes and symptoms were compared. *Limitations*: Retrospective study with potential recall bias and missing information; single hospital; some patients were over the age 20 years.

Implications: Clinical outcomes appeared similar comparing children with COVID-19 with those who had seasonal influenza. Diagnosis and clinical management of children with acute respiratory infections may be challenging without diagnostic testing for influenza and SARS-CoV-2.

Table:

		Seasonal influenza		
Outcome	COVID-19	A and B	A	B
Patients tested positive, No.	315	1402	674	728
Patients hospitalized, No. (%)	54 (17.1)	291 (20.8)	143 (21.2)	148 (20.3)
Patients requiring ICU stay, No. (%)	18 (5.7)	98 (7.0)	59 (8.8)	39 (5.4)
Patients requiring mechanical ventilator support, No. (%)	10 (3.1)	27 (1.9)	16 (2.4)	11 (1.5)
Hospital length of stay, mean (range), d	8.4 (1-45)	5.7 (1-100)	6.3 (1-100)	5.1 (1-58)
Mechanical ventilator support, median (range), d	10.1 (2-41)	7.0 (1-38)	8.1 (1-38)	5.4 (1-16)
Deaths, No. (%)	0	2 (0.1)	2 (0.3)	0

Note: Adapted from Song *et al*. Outcomes in pediatric patients with COVID-19 or seasonal influenza. Numbers in parentheses represent either the percentage or range (in days). Licensed under CC-BY.

Clinical outcomes in young US adults hospitalized with COVID-19. Cunningham *et al.* JAMA Internal Medicine (August 14, 2020).

Key findings:

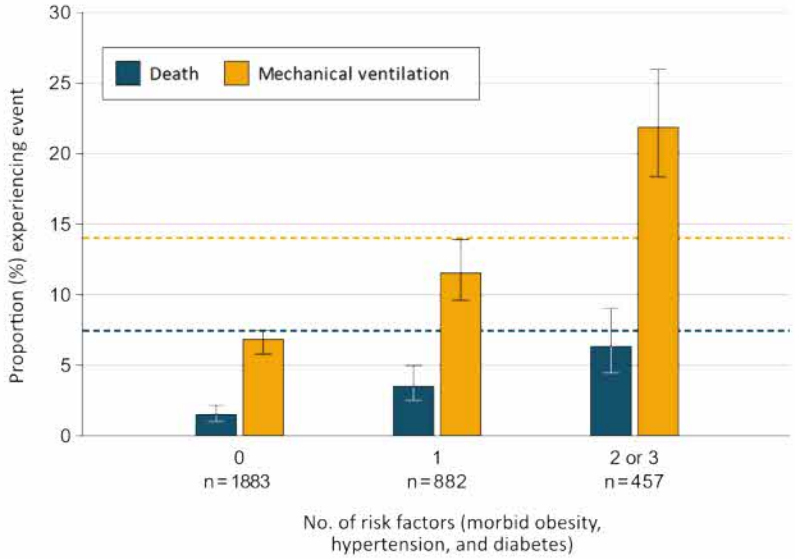
- Of 3,222 adults age 18-34 years, 684 patients (21%) required intensive care; 331 (10%) required mechanical ventilation and 88 (2.7%) died.

- A higher proportion of young adults with 2 or 3 comorbid conditions (either morbid obesity, hypertension, or diabetes) required mechanical ventilation or died compared with young adults with no comorbidities.
- The proportion of young adults with 2 or 3 comorbidities requiring mechanical ventilation was greater than the proportion of older adults with no comorbidities (Figure).
    - Proportions of deaths were similar between these two groups.

Methods: Evaluation of adults with COVID-19 hospitalized between April 1 and June 30, 2020. Outcomes of 3,222 adults aged 18-34 years were compared with 8,862 adults age 35-64 years. *Limitation:* ICD-10 coding might have resulted in misclassification; no confirmation of laboratory diagnosis of SARS-CoV-2 infection.

Implications: Young adults are at risk for severe COVID-19 and death. The increased risk for mechanical ventilation and death conferred by multiple comorbidities common among young persons is comparable to that of otherwise healthy older adults.

Figure:



Note: Adapted from Cunningham *et al.* Number of risk factors (morbid obesity, hypertension, diabetes) and proportion of **death** and **mechanical ventilation** in persons 18-34 years. Dashed lines are proportion of persons age 35-64 years with COVID-19 and no comorbidities who required **mechanical ventilation** or **died**. Reproduced with permission from JAMA Intern Med. doi:10.1001/jamainternmed.2020.5313. Copyright©2020 American Medical Association. All rights reserved.

Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated with COVID-19 in the United States. Matsubara *et al.* Journal of American College of Cardiology. (September. 2020).

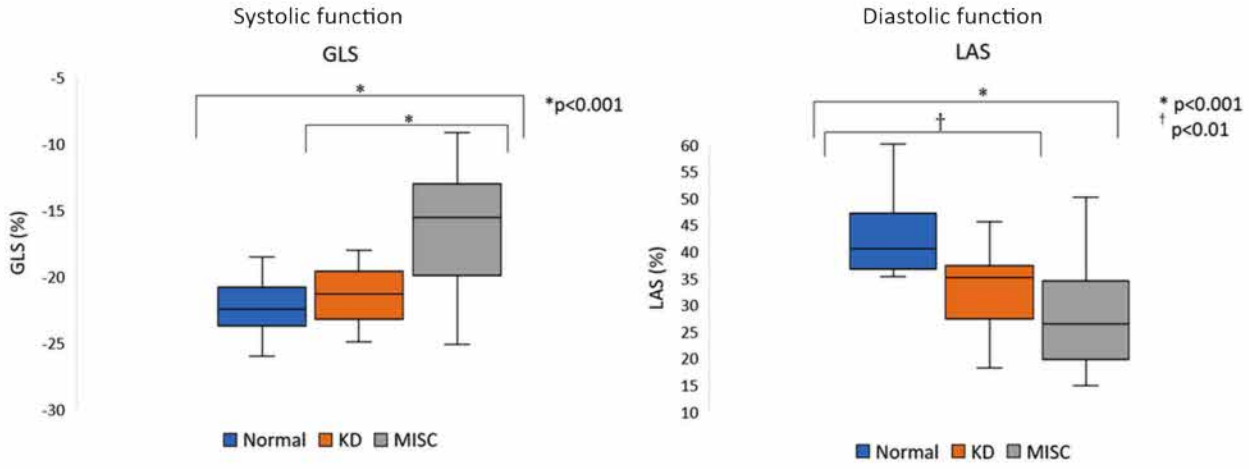
Key findings:

- One (4%) of 28 patients with pediatric multisystem inflammatory syndrome associated with COVID-19 (MIS-C) had coronary artery abnormalities that resolved on follow up; in the Kawasaki disease (KD) group, 4 (20%) of 20 patients had coronary artery abnormalities.
- Compared with healthy children and children with KD, 61% of children with MIS-C had weaker heart function (left ventricular systolic and diastolic function) (Figure 1).
    - This impaired function was associated with myocardial injury (myocarditis).
- During the early follow-up period (the period after the acute period), there was good recovery of systolic (pumping) function but diastolic (relaxation) dysfunction persisted compared with the acute phase (Figure 2).

Methods: Retrospective single-center study at the Children's Hospital of Philadelphia, of 28 pediatric patients with MIS-C caused by SARS-CoV-2 infection, compared with 20 KD patients, and 20 age-matched healthy controls. Echocardiographic imaging and laboratory data were reviewed in acute phase of MIS-C and KD groups, and during early follow-up period in MIS-C group (interval: 5.2 ± 3 days). *Limitations*: Small sample of MIS-C; short follow up period; MIS-C patients were significantly older and had larger statures than the KD group; no endomyocardial biopsy or cardiac magnetic resonance imaging performed.

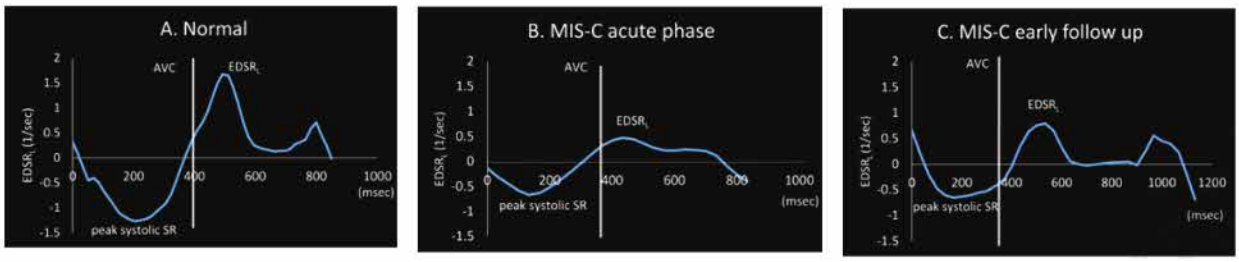
Implications: The study found MIS-C caused by SARS-CoV-2 infection was accompanied by changes in myocardial function that differs from what is seen in KD. Early recognition and diagnosis of MIS-C to more accurately assess cardiac function will aid prompt treatment and better outcomes. Long term effects of MIS-C are currently unknown.

Figure 1



Note: Adapted from Matsubara *et al*. Decreases in systolic and diastolic function in patients with MIS-C. Increased global longitudinal strain (GLS) indicates decrease in systolic function in patients with **KD** and **MIS-C**. Decreased peak left atrial strain (LAS) shows decreased diastolic function in patients with **KD** and MIS-C. Available via Elsevier COVID-19 Resource Centre through PubMed Central.

Figure 2



Note: Adapted from Matsubara *et al*. Early diastolic strain rate curves in a normal (**A**), MIS-C patient during acute phase (**B**), and MIS-C patient during early follow up period (**C**). Reduced EDSR in acute phase resolves during the follow up but remains lower compared with normal. AVC-aortic valve closure; EDSR-early diastolic strain rate; SR-strain rate. Available via Elsevier COVID-19 Resource Centre through PubMed Central.

Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study. Lund *et al.* PLOS Medicine (September 8, 2020).

Key findings:

- Use of non-steroidal anti-inflammatory drugs (NSAID)s for treatment of symptoms related to COVID-19 infection was *not* associated with an increased risk of 30-day mortality.
    - The NSAID user group had a mortality of 6.3%, (95% CI: 3.1% to 9.4%) while non-users had a mortality of 6.1% (95% CI 4.4% to 7.8%).
- The NSAID user group did not have an increased risk of hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy compared with the non-users group.

Methods: Population-based cohort study of all individuals who tested positive for SARS-CoV-2 by RT-PCR between February 27 and April 29, 2020 in Denmark. Infected individuals were grouped according to those who did (n = 248) or did not (n = 8,988) have a prescription filled for NSAIDs up to 30 days prior to diagnosis. *Limitations*: Potential misclassification of non-users and users as it is not known if NSAIDs were taken.

Implications: It is reassuring that NSAIDs do not appear to lead to a more severe course of COVID-19 as this class of drugs offers benefit in the treatment of constitutional symptoms associated with SARS-CoV-2 infection.

Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): A randomised clinical trial. Furtado *et al.* Lancet (September 11, 2020).

Key findings:

- There was no significant difference in clinical status at hospital day 15 between the persons treated with azithromycin plus standard care and those treated with standard care only (OR 1.36, 95% CI 0.94 –1.9, p = 0.11).
- There was no significant difference in 29-day mortality between the azithromycin and the standard care-only groups: 90 deaths (42%) vs 73 deaths (40%), respectively (hazard ratio 1.08, 95% CI 0.79-1.47, p = 0.63).

Methods: Randomized, open-label, multi-center trial at 57 centers in Brazil. Patients with severe COVID-19 received azithromycin (500 mg once daily for 10 days) with standard care (n = 214) or standard care only (n = 183). Standard care included hydroxychloroquine for 10 days. The primary endpoint was clinical status at day 15 and a secondary outcome was mortality at day 29. *Limitations*: The protocol was revised four times during the trial regarding entry criteria and analysis; only severe COVID-19 cases included, precluding any effects in milder cases; study did not examine azithromycin as a standalone therapy.

Implications: This study does not support the routine use of azithromycin in patients with severe COVID-19.

Laboratory Science

PEER-REVIEWED

Broad and strong memory CD4⁺ and CD8⁺ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Peng *et al.* Nature Immunology (September 4, 2020).

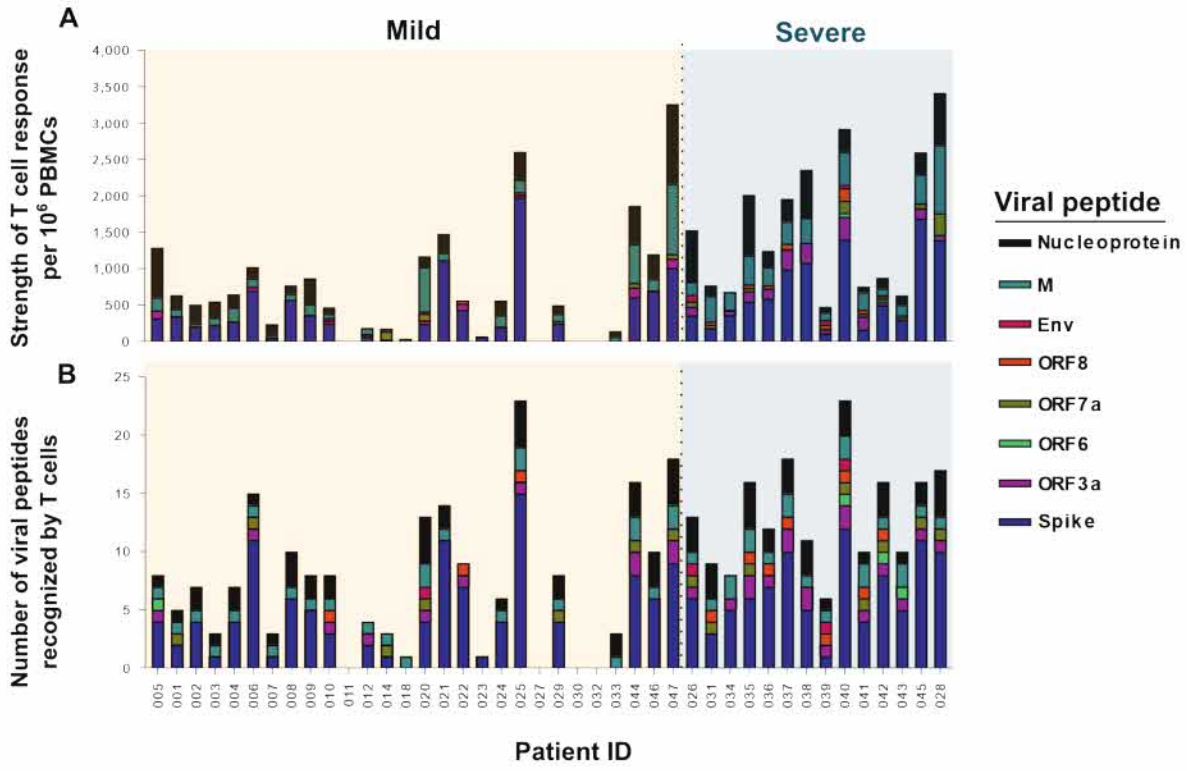
Key findings:

- T cell responses were significantly higher in persons with severe COVID-19 as compared with persons with mild COVID-19 (Figure).
- T cells from persons with severe COVID-19 recognized more viral epitopes than those from persons with mild disease.

Methods: A total of 42 persons recovered from COVID-19 were enrolled between March and May 2020 and classified as either mild (n = 28) or severe cases (n = 14). Specimens from 16 individuals collected between 2017 and 2019 were used as controls. Peripheral blood mononuclear cells (PBMCs) were exposed to pools of peptides spanning the SARS-CoV-2 genome. *Limitations*: Excluded analysis of peptides from ORF 1ab of SARS-CoV-2, which is more than 2/3 of the genome.

Implications: Persons recovered from COVID-19 possess strong and broad T cell responses potentially indicative of long-lasting protective immunity. The broad response to several different epitopes suggests vaccine-escape viruses would need several mutations.

Figure:



Note: Modified from Peng *et al*. **A:** PBMC responses in severe and mild cases when stimulated with viral peptides. **B**: Number of viral peptides recognized in severe and mild cases. Colored stacked bars represent different viral peptides. Permission request in process.

In Brief

- Consiglio *et al.* **The immunology of multisystem inflammatory syndrome in children with COVID-19.** Cell. Description and comparison of the immune response for MIS-C versus Kawasaki disease, including differences for biomarkers to aid in diagnosis.
- Lee *et al*. **Clinical significance of timing of intubation in critically ill patients with COVID-19: A multi-center retrospective study**. Journal of Clinical Medicine. A multicenter retrospective study of intubation timing in 47 patients with COVID-19 showed early intubation was not associated with improving survival.
- Kirenga *et al.* **Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda.** BMJ Open Respiratory Research. Describes COVID-19 in 56 patients at two hospitals in Uganda. COVID-19 cases were young and there was a high proportion of persons who were asymptomatic and had mild disease.
- Shuren *et al.* **COVID-19 molecular diagnostic testing — Lessons learned.** NEJM. Perspective from two senior FDA officials that describes the Emergency Use Authorization (EUA) changes for SARS-CoV-2 testing and provides recommendations for future EUAs during pandemics.
- Wadman, M. **Why COVID-19 Is More Deadly in People with Obesity—Even if they're young.** Science. Reviews the increased risks of COVID-19 to individuals with obesity. The review describes potential causes for the increased risk of hospitalization.
- Guderian *et al.* **In vitro comparison of surgical techniques in times of the SARS-CoV-2 pandemic: electrocautery generates more droplets and aerosol than laser surgery or drilling.** European Archives of Oto-Rhino-Laryngology. Aerosol analysis of ENT procedures found that certain activities, such as drilling, laser ablation, and electrocauterization generated aerosols.
- Lachapelle, F. **COVID-19 preprints and their publishing rate: An improved method (preprint).** medRxiv. Only ~15% of COVID-19-related preprints went on to be peer-reviewed manuscripts between January and August 2020.

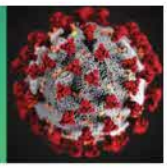
cdc.gov/coronavirus

From: McLean, Catherine (CDC/DDPHSIS/CGH/DGHT)
Sent: Wed, 16 Sep 2020 19:19:54 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Subject: 2020 09 15 Science Update_Final Public.pdf
Attachments: 2020 09 15 Science Update_Final Public.pdf

John,
Thanks for your team's continued production of these updates – invaluable. I'm knee deep in our quarterly data reviews for every country in our CDC portfolio, progress on HIV and now also COVID testing and mitigation. Continuing to balance PHS COVID (and hurricane) deployment requests/requirements with primary assignment here, as you are doing. Keep me posted, or call if you'd like to consult, on the evolving landscape and if you have a recommendation for where to head next for return Covid deployment.

(b)(6) Keep that up! C

COVID-19 Science Update



From the Office of the Chief Medical Officer, CDC COVID-19 Response, and the CDC Library, Atlanta, GA.
Intended for use by public health professionals responding to the COVID-19 pandemic.

***** Available on-line at https://www.cdc.gov/library/covid19 *****

Vaccine Development

PEER-REVIEWED

Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Logunov *et al.* Lancet (September 4, 2020).

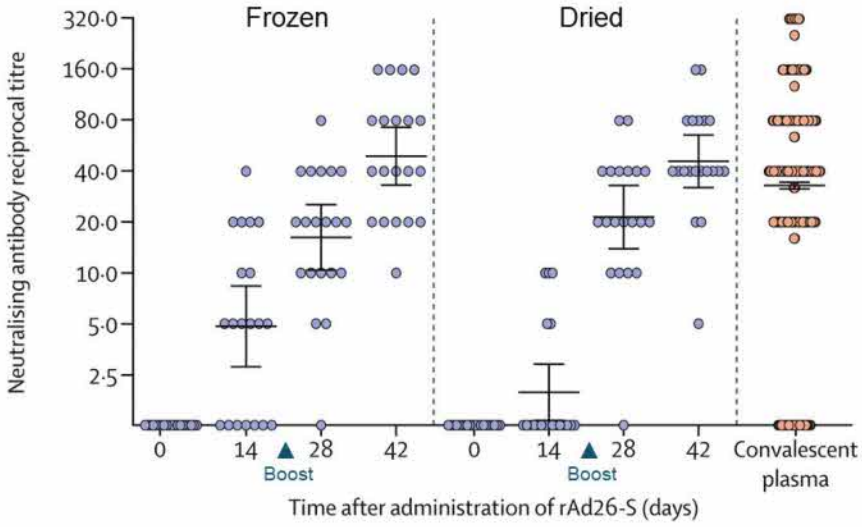
Key findings:

- After vaccination, no serious adverse events occurred, though mild adverse events were common, including: pain at injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), muscle and joint pain (24%).
- All participants produced neutralizing antibodies to SARS-CoV-2 (Figure).
    - Neutralizing antibody titers in the vaccine participants were not significantly different from convalescent plasma donors who experienced mild and moderate disease.
    - The frozen and dried vaccine formulations performed similarly.
    - Cell-mediated responses were detected in all participants.

Methods: Open-label, non-randomized phase 1 (n = 36) and 2 (n = 40) vaccination studies in adults between June 18 and August 3, 2020, Russia. Frozen or lyophilized (dried) vaccine formulations utilized two recombinant adenovirus vectors, rAd26 and rAd5. Both vectors express the SARS-CoV-2 spike (S) protein and were administered intramuscularly. Phase 1 assessed one dose of rAd26-S or rAd5-S with assessment on days 0, 2, 14, 21, and 28. Phase 2 assessed one dose of rAd26-S, followed 21 days later by one dose of rAd5-S with assessment on days 0, 14, 21, 28, and 42. Safety, antiviral antibodies, and T cell responses were examined. Post-vaccination immunity was compared to antibody levels in convalescent plasma among 4,817 people with mild (fever ≤39°C without pneumonia) and moderate (fever >39°C with pneumonia) prior SARS-CoV-2 infection. *Limitations*: Small sample size; short follow-up period; no placebo or control vaccine; no participants >60 years of age; limited information on how the dose was chosen; phase 2 started 5 days after phase 1 began; detailed analysis of cell-mediated responses were not reported.

Implications: A phase 1/2 vaccine trial in Russia demonstrated immunogenicity with no serious adverse events reported. Although a phase 3 trial is planned, Russia is moving forward with approval of this vaccine. In an accompanying editorial, Burki points out that immune response may not corelate with protection. Further investigation including large scale trials is needed to determine long-term immunity, vaccine safety, effectiveness, and correlates of protection.

Figure:



Note: Adapted from Logunov *et al*. **Neutralizing antibody levels** at 0, 14, 21, 28, and 42 days after the first dose of rAd26 with heterologous **boost of rAd5-S** at day 21 and in **convalescent plasma** from individuals recovered from mild-to-moderate severity COVID-19. Frozen (left) and dried (right) vaccine formulations are shown. Permission request in process.

SARS-CoV-2 Wastewater Surveillance

PEER-REVIEWED

Temporal detection and phylogenetic assessment of SARS-CoV-2 in municipal wastewater. Nemudryi *et al*. Cell Reports Medicine. (August 31, 2020).

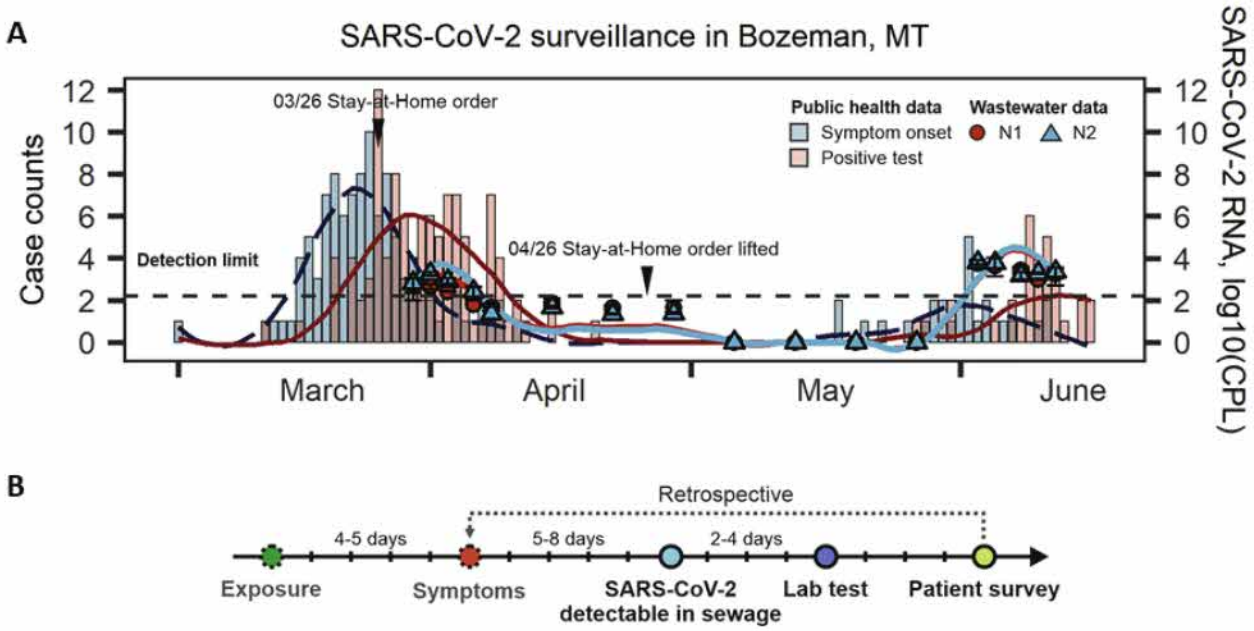
Key findings:

- During two outbreaks of SARS-CoV-2 in Bozeman, MT, detection of SARS-CoV-2 RNA in sewage *followed* symptom onset in persons within the wastewater catchment community by 5–8 days and *preceded* clinical PCR diagnosis of patients by 2–4 days (Figure).
- The quantity of SARS-CoV-2 RNA detected in wastewater catchment community tended to mirror the burden of infection in the community.

Methods: Environmental surveillance study used RT-PCR to monitor wastewater in Montana for SARS-CoV-2 RNA. Genome sequencing and phylogenetic analyses were used to identify circulating strains and mutations. A survey of patients in the wastewater catchment community who had been diagnosed with SARS-CoV-2 infection was used to determine timing of wastewater detection with patients' symptom onset and clinical diagnosis by PCR testing. *Limitations*: Localized study and results are not generalizable.

Implications: SARS-CoV-2 RNA concentrations in wastewater correlate with COVID-19 epidemiology. Testing of untreated wastewater may help public health officials identify communities that warrant focused COVID-19 testing and implementation of more stringent infection control policies, as well as monitor community disease burden.

Figure:



Note: Adapted from Nemudryi *et al.* **A**: Temporal dynamics of SARS-CoV-2 RNA in the municipal wastewater superimposed on the epidemiological data with dates of Symptom onset data (collected by retrospective interviews of COVID-19 patients with positive tests) and positive SARS-CoV-2 RT-PCR tests. The **red circles** and **blue triangles** are SARS-CoV-2 RNA concentration in municipal wastewater measured with RT-PCR using N1 and N2 primers (shown on the y-axis). The lines show curves fitted to RT-PCR and epidemiological data using local polynomial regression. **B**: Timeline of symptoms, detection of SARS-CoV-2 in wastewater and clinical PCR test results.

Epidemiology

PEER-REVIEWED

Social distancing for COVID-19 and diagnoses of other infectious diseases in children. Hatoun *et al.* Pediatrics (September 1, 2020).

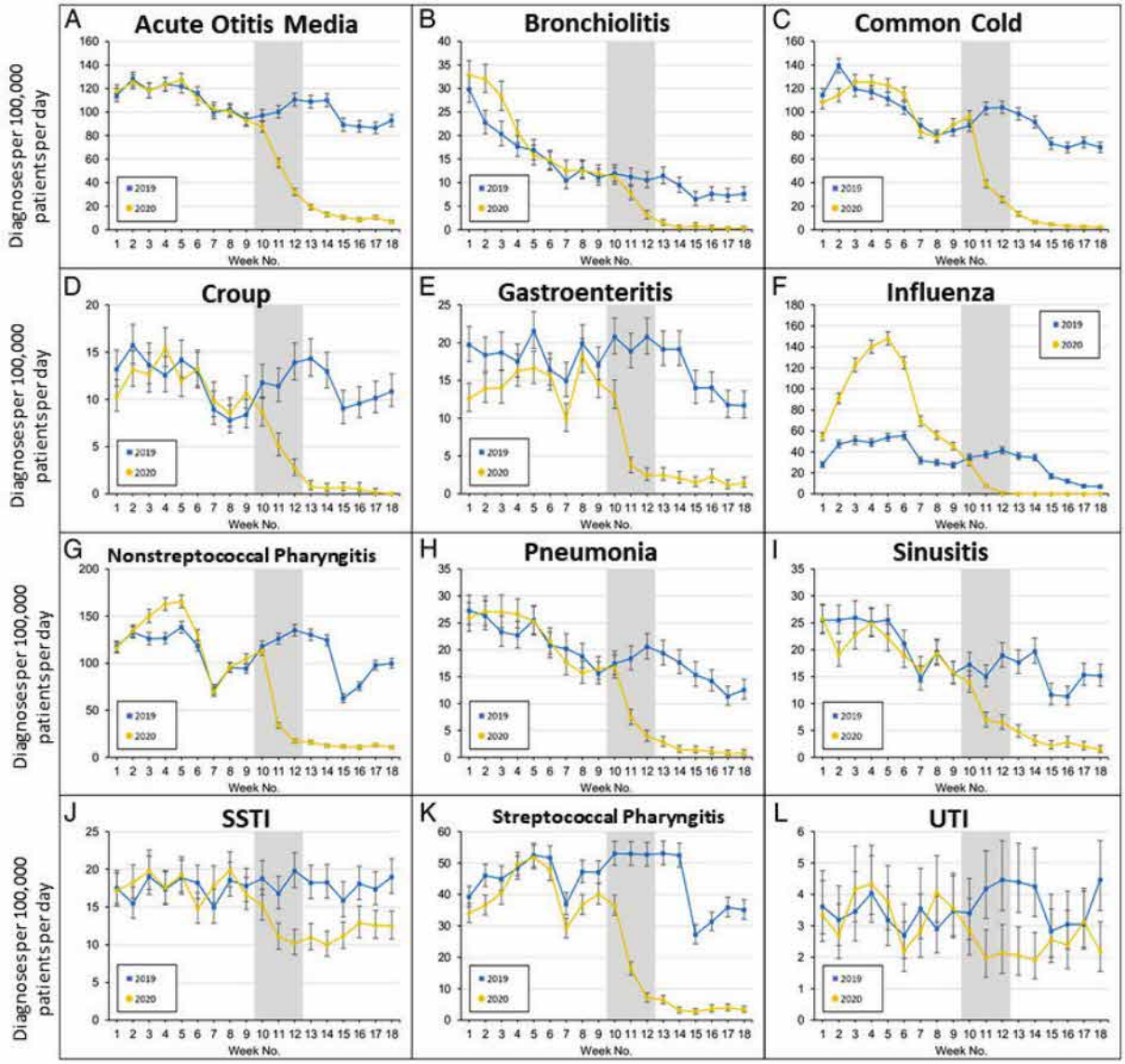
Key findings:

- The prevalence of 12 common pediatric infectious syndromes was significantly lower in the 2020 post-social distancing (SD) period than the equivalent 2019 period ($p < 0.001$), (Figure).

Methods: Retrospective analysis from a pediatric primary care network in Massachusetts covering approximately 375,000 children. Weekly incidence of 12 common pediatric infectious diseases (e.g., acute otitis media [AOM], upper respiratory infections, gastroenteritis, skin and soft tissue infections [SSTI], urinary tract infections [UTI]) were analyzed for the first 18 weeks of 2019 and 2020. For 2020, pre-SD period was the first 9 weeks of the year, the SD implementation period was weeks 10-12 and post-SD period was weeks 13-18. *Limitations*: No information on demographics or other covariates; results may not be generalizable to other locations.

Implications: The SD policies implemented to slow the spread of SARS-CoV-2 appear to have decreased the spread of common communicable pediatric infections. UTI are not communicable and should not be impacted by SD; decreases may have reflected reluctance of parents to seek care. Kimberlin *et al.* caution that missed scheduled vaccinations during the pandemic may result in outbreaks of measles and other infectious agents that had previously been kept under control via immunization programs.

Figure:



Note: Adapted from Hatoun *et al.* Weekly diagnosis rates per 100,000 patients per day with 95% CIs of common pediatric infectious diseases, week 1 to week 18, 2019 and 2020. The grey shaded area represents period of SD implementation in 2020. Permission request in process.

Healthcare worker perception of a global outbreak of novel coronavirus (COVID-19) and personal protective equipment: Survey of a pediatric tertiary-care hospital. Piche-Renaud *et al*. Infection Control & Hospital Epidemiology (August 12, 2020).

Key findings:

- In a survey of hospital-based healthcare workers (HCW):
  - Only 50% identified the correct donning order and 35% identified the correct doffing order of personal protective equipment (PPE).
  - Respondents were more concerned about COVID-19 exposure at work than outside of work.
    - Emergency department staff scored highest for concern about workplace exposure.
    - Administration staff scored highest for concern about exposure outside of work.

Methods: Self-administered questionnaire completed by 175 HCWs at a large children's hospital in Canada between March 6 and 10, 2020. HCW knowledge and concerns regarding exposure and infection at and outside work were assessed and scored. *Limitations*: Convenience sample; results not generalizable; 18.4% response rate; HCW knowledge and perceptions during a limited period.

Implications: Routine training for all HCWs on appropriate PPE procedures in combination with updates on current COVID-19 knowledge may increase adherence with PPE recommendations.

Clinical Treatment & Management

PEER-REVIEWED

A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. White *et al.* Clinical Infectious Diseases (August 29, 2020).

Key findings:

- Fifty-one of 135 COVID-19 ICU patients (37.8%; 95% CI 30.0-46.2) had ≥1 positive test for invasive fungal disease (IFD).
    - 17 tests were positive for yeast (mainly *Candida*), 30 were positive for *Aspergillus*, 4 were unspecified fungal infections.
- The prognosis of patients with IFD was overall poorer than those without; however, when treated with anti-fungal therapy (AFT), mortality rates returned to levels seen among COVID-19 patients without IFD.

Methods: Multi-center, prospective cohort evaluation of IFD among 135 COVID-19 ICU patients. Diagnostic testing included culture, β-D-Glucan, *Aspergillus* antigen assay or *Aspergillus* PCR and chest imaging. Some patients received antifungal treatment. *Limitations*: Only select ICU patients were screened for IFD; AFT was administered at physician discretion, potentially biasing outcomes.

Implications: In the context of ICU care for COVID-19 patients, IFD may occur. Diagnosing and treating may lead to improved outcomes. According to an editorial by Hoenigl, these results point to a need for trials to evaluate antifungal prophylaxis in COVID-19 patients.

Cardiovascular Disease Among Athletes Recovered from COVID-19

As competitive sports start to resume in the US, recent studies showing myocardial inflammation after SARS-CoV-2 infection among some athletes have raised concerns because this condition can lead to life-threatening arrythmias (abnormal heart rates). Cardiac magnetic resonance (CMR) imaging is an important tool used to detect myocardial inflammation. The following studies used CMR to identify cardiac inflammation among athletes who recently recovered from COVID-19.

PEER-REVIEWED

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. Rajpal *et al.* JAMA Cardiology (September 13, 2020).

Key findings:

- Four athletes (15%) had contrast (gadolinium)-enhanced CMR findings consistent with myocarditis.
    - Of these, two had mild symptoms (shortness of breath) and 2 were asymptomatic.
- Eight additional athletes (30.8%) had indication of prior myocardial injury.

Methods: CMR was performed on 26 previously SARS-CoV-2 PCR-positive competitive college athletes between June and August 2020. Electrocardiogram, serum troponin I, and transthoracic echocardiogram were performed on day of CMR imaging *Limitations*: Lack of baseline CMR imaging and variable timing of CMR imaging from a positive COVID-19 test result.

PREPRINTS (NOT PEER-REVIEWED)

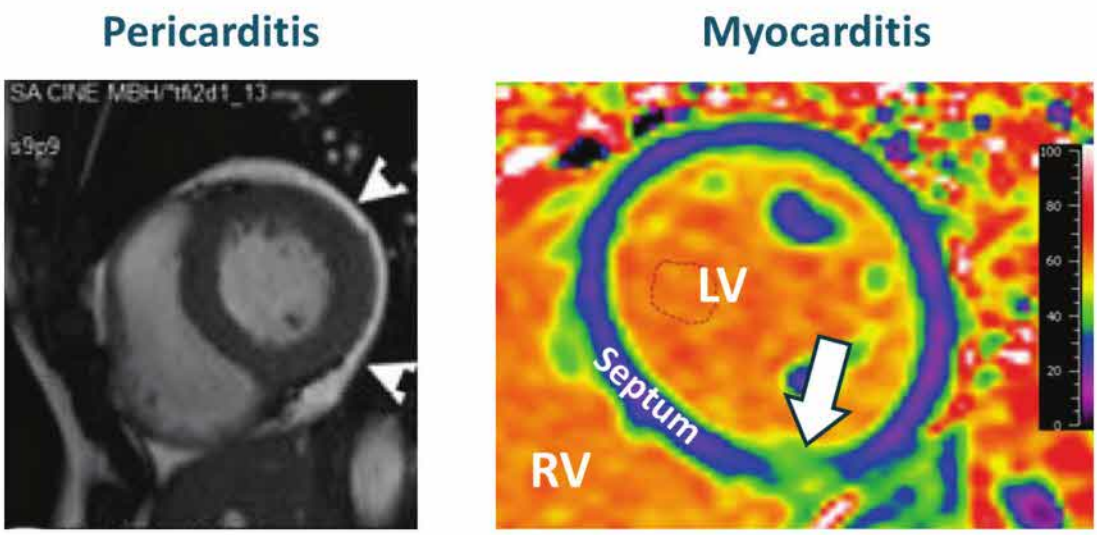
COVID-19 myocardial pathology evaluated through screening cardiac magnetic resonance (COMPETE CMR). Clark *et al*. medRxiv (September 2, 2020).

Key findings:

- Contrast-enhanced cardiac magnetic resonance (CMR) of 22 collegiate athletes recovered from mild or asymptomatic COVID-19 was abnormal in 2 (9%) cases athletes.
    - One had pericarditis with effusion (inflammation of the sac surrounding the heart) and the other had acute myocarditis (inflammation of the heart muscle) (Figure).
- All other cardiac assessments were normal.

Methods: Retrospective study of collegiate athletes with prior SARS-CoV-2 infection at a single Division 1 university in August 2020. Electrocardiogram, troponin I, echocardiogram with strain imaging, and contrasted CMR were performed. *Limitations*: Small sample; single university.

Figure:



Note: Adapted from Clark *et al*. **Left panel:** White arrows show pericardial effusion in athlete with pericarditis and pericardial effusion. **Right panel:** Inflammation (white arrow) of the bottom of the wall (septum) dividing the right (RV) and left (LV) cardiac ventricles in athlete with myocarditis. Licensed under CC-BY-NC-ND 4.0.

Implications for 2 studies (Rajpal *et al*. & Clark *et al*.): Myocarditis and pericarditis both can increase the risk of life-threatening abnormal cardiac rhythms, especially during strenuous exertion. These preliminary data suggest CMR may be useful to screen for such heart abnormalities following COVID-19 and guide return-to-play decisions. A further review of the cardiovascular effects of COVID-19 is detailed by Capotosto *et al*.

Neutralizing Antibodies

PEER-REVIEWED

Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19. Chen *et al.* Signal Transduction and Targeted Therapy (September 2, 2020).

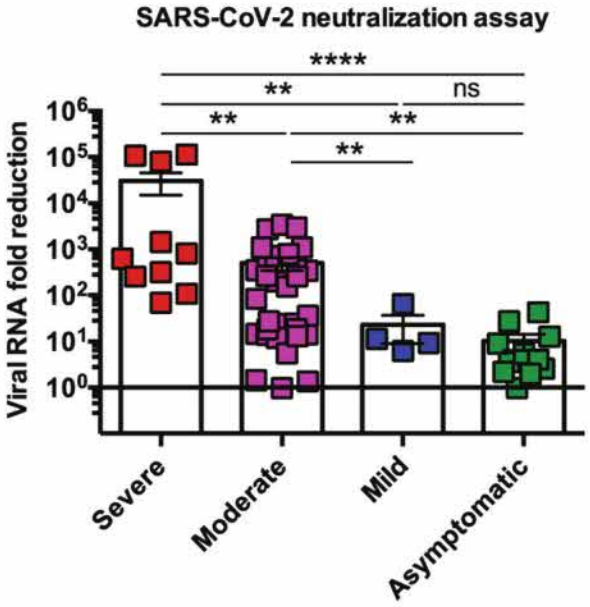
Key findings:

- Neutralizing antibody (NAb) levels were higher among persons who experienced severe or moderate COVID-19 illness compared with persons whose illness was asymptomatic or mild (Figure).

Methods: Cross-sectional analysis of 59 adults recovered from COVID-19 between January and April 2020. Asymptomatic (n = 11) patients were identified from screening close contacts of COVID-19 patients. Data from these persons were compared with persons who experienced mild (n = 4), moderate (n = 34) and severe (n = 10) COVID-19. NAbs were examined for binding and receptor blocking of SARS-CoV-2 spike (S) protein and were assessed functionally using neutralization assays against both pseudovirus and SARS-CoV-2. *Limitations*: Low numbers of asymptomatic, mild and severe patients.

Implications: This small study suggests increasing severity of COVID-19 illness correlated positively with subsequent development of greater concentrations of NAbs.

Figure:



Note: Adapted from Chen *et al*. Level of reduction of viral RNA by neutralizing antibodies by disease severity. **p <0.01, and ****p <0.0001. ns-not significant. Licensed under CC-BY 4.0.

In Brief

- Sanchez *et al*. **Violence against women during the COVID-19 pandemic: An integrative review**. International Journal of Gynaecology & Obstetrics. This meta-analysis of 38 articles reviews many factors that could be responsible for the increase in cases of violence against women reported during this pandemic. Prolonged

quarantine/lockdown with potential abuser is only one of many factors. Healthcare providers need to be aware of this issue and increase their screening for domestic violence when seeing patients.

- Gostin *et al*. **Universal masking in the United States: The role of mandates, health education, and the CDC.** JAMA. Explores whether a national mandate on masking would be a lawful and effective COVID-19 prevention strategy. It discusses the various state pandemic responses and if CDC should have enhanced funding and powers to forge a nationally coordinated response to COVID-19 and to future health emergencies.
- Hsu *et al*. **One benefit of COVID-19 measures in Taiwan: The reduction of influenza infections and severe complications**. Influenza and other respiratory viruses. This letter notes that during the period after Taiwan's first COVID-19 case, the number of people with influenza per week and the number of people with severe complications from influenza were significantly lower relative to the same period in 2019.
- Ledford H. **Coronavirus reinfections: Three questions scientists are asking.** Nature. Explanation of key questions about reinfection including: (1) How common is reinfection? (2) Are reinfections more or less severe than the first? (3) What implications do reinfections have for vaccine prospects?
- Abbasi J. **COVID-19 and mRNA vaccines – First large test for a new approach**. JAMA. Perspective on mRNA vaccine being developed and its effectiveness. If mRNA vaccines work then it's a huge breakthrough, not just for COVID-19, but for the future of vaccinations generally.
- Provenzi *et al.* **The little professor and the virus: Scaffolding children's meaning making during the COVID-19 emergency**. Frontiers in Psychiatry. Children's explanations and interpretations of events are heavily influenced by those around them. It may be useful for parents and teachers to give children the tools they need to create good explanations to minimize risk of stress and anxiety during and after the pandemic.
- Miglis *et al*. **A case report of postural tachycardia syndrome after COVID-19**. Clinical Autonomic Research. A case report of a 26-year-old nurse who developed postural tachycardia syndrome several months after confirmed SARS-CoV-2 infection.

Erratum

In the 2020 09 08 COVID-19 Science Update, the entry for Hu *et al*. (**Antibody profiles according to mild or severe SARS-CoV-2 infection, Atlanta, Georgia, USA, 2020**), had the y-axis in Figure B labeled incorrectly. This error has been corrected in the online version of the Science Update.

cdc.gov/coronavirus

From: Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE)
Sent: Thu, 4 Jun 2020 16:43:46 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Cc: Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHP)
Subject: Fwd: Did we put this one in a prior update?
Attachments: jama_casadevall_2020_ed_A Randomized Trial of Convalescent Plasma for COVID-19.pdf, Nahum 2020 - DVTs in 34 French patients - JAMA Network Open.pdf, Li 2020 - convalescent plasma for COVID-19 Wuhan no effect possily under powered - JAMA.pdf, Tu 2020 - self-collection midturbinate nasal tongue vs. NP swab SUPP - N Engl J Med.pdf, Tu 2020 - self-collection midturbinate nasal tongue vs. NP swab - N Engl J Med.pdf, Toubiana 2020 - MIS-C in French children in Paris - BMJ.pdf, Boulware 2020 -HCQ did not work as COVID-19 prophylaxis - N Engl J Med.pdf

I will bring it up on the call---I was just saving some of those same articles, also added the ed to the conv. plasma article

I think that between John and me, we do come across many articles and we will talk about good ways of communicating this to the team…

Begin forwarded message:

From: "Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)" <zud4@cdc.gov>
Subject: RE: Did we put this one in a prior update?
Date: June 4, 2020 at 12:28:22 PM EDT
To: "Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE)" <rzr3@cdc.gov>

Agreed! What Brian and Bob and Kate Buchacz and I did at the beginning was subscribe to all those journals' automatic notification services and I realized I'm the only one left!

That's where I find a lot of the papers I forward.

Agreed we should have a way to make sure they're covered each week. Yesterday's and day before's NEJM, JAMAs, and Lancets had a number of things to consider (attached).

John T. Brooks, MD
Chief Medical Officer, CDC COVID-19 Response

Email: zud4@cdc.gov
Apologies for errors in my messages that may be due to my need to dictate.

http://intranet.cdc.gov/library/covid19/index.html

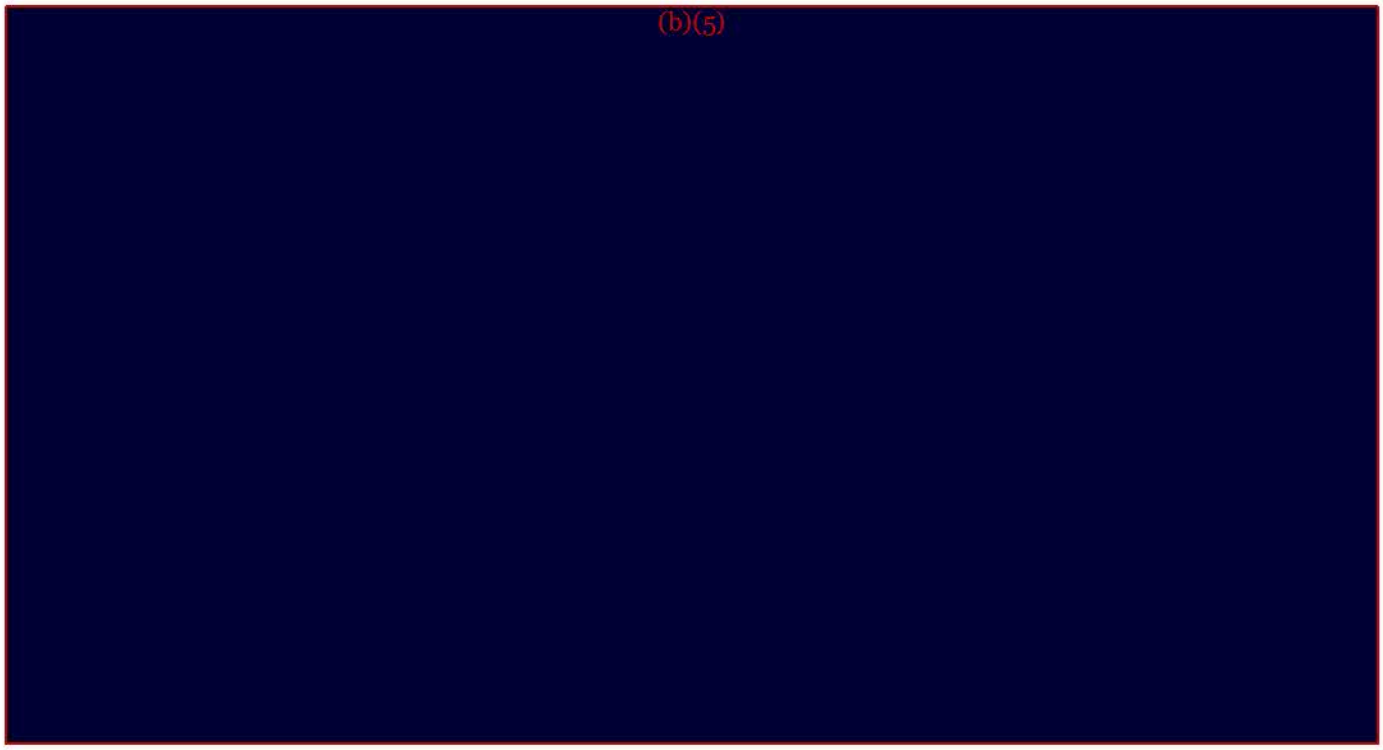
From: Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE) <rzr3@cdc.gov>
Sent: Thursday, June 4, 2020 12:13 PM
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Subject: Fwd: Did we put this one in a prior update?

Want to run something by you… noticed this on the call today, interesting and had not see it before. Seems like something that we may have had in the update. I asked PC about it. (b)(5) (b)(5) (b)(5) took a quick look and I think it is (b)(5) (b)(5) I was thinking about maybe (b)(5) (b)(5) What do you think?

Begin forwarded message:

From: Renee Ridzon <rzr3@cdc.gov>
Subject: Did we put this one in a prior update?
Date: June 4, 2020 at 10:22:41 AM EDT
To: "Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHPSE)" <geo5@cdc.gov>

(b)(5)



EDITORIAL

A Randomized Trial of Convalescent Plasma for COVID-19—Potentially Hopeful Signals

Arturo Casadevall, MD, PhD; Michael J. Joyner, MD; Liise-Anne Pirofski, MD

Convalescent plasma for the treatment of infectious diseases has been used since the early 20th century and was associated with reduced mortality during the 1918 influenza,[1] 2003 SARS,[2] and 2009 influenza H1N1[3] pandemics. However, most published studies of these diseases were case series and retrospective comparisons of treated and nontreated individuals. Consistent with this, several uncontrolled case series of convalescent plasma use in patients with coronavirus disease (2019) COVID-19 have suggested a possible benefit.[4-6] Given encouraging historical precedents and the absence of proven SARS-CoV-2 (severe acute respiratory disease coronavirus 2) antiviral therapies, convalescent plasma therapy has been proposed as a treatment option for COVID-19.[7] The availability of clinical information generated from randomized clinical trials is therefore of substantial importance given that the world remains in the grip of the COVID-19 epidemic and convalescent plasma is currently in use in many countries, including the US.

Related article

In their article in *JAMA*, Li et al[8] present findings from the first randomized clinical trial of convalescent plasma therapy for patients with COVID-19 conducted in China. In contrast to most other reports of convalescent plasma use in past epidemics, this study is noteworthy in that it used a randomized trial design and well-characterized plasma units with a high titer of antibody to SARS-CoV-2. It was an important accomplishment to conduct a carefully controlled trial during a pandemic with an entirely new highly contagious disease that stressed health systems in an unprecedented way.

However, the authors report that because the COVID-19 outbreak in China was being contained while the trial was ongoing and new cases were unavailable for enrollment, the trial was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (for whom randomization was stratified by disease severity). Consequently, the study was underpowered and many comparisons between the convalescent plasma group and the control group were not statistically significant.

In the primary analysis, based on 52 patients who were randomized to receive convalescent plasma in addition to standard treatment and 51 patients who were randomized to receive standard treatment alone (control), the primary outcome of time to clinical improvement within 28 days (defined as being discharged alive or having a reduction of 2 points on a 6-point disease severity scale) was 2.15 days shorter (95% CI, −5.28 to 0.99 days) in the intervention group compared with the control group, and clinical improvement at 28 days occurred in 27 patients (51.9%) in the intervention group vs 22 patients (43.1%) in the control group (difference, 8.8%; 95% CI, −10.4% to 28%; hazard ratio, 1.40 [95% CI, 0.79-2.49]; $P = .26$).

In analyses stratified by disease severity, among patients with severe disease (23 in the convalescent plasma group and 22 in the control group), time to clinical improvement within 28 days was 4.94 days shorter (95% CI, −9.33 to −0.54 days) in the intervention group compared with the control group, and clinical improvement at 28 days occurred in 21 patients (91.3%) in the intervention group vs 15 patients (68.2%) in the control group (hazard ratio, 2.15 [95% CI, 1.07-4.32]; $P = .03$). Among the subgroup of patients with life-threatening disease (29 in the convalescent plasma group and 29 in the control group), there were no significant differences in the primary outcome or rates of clinical improvement at 28 days: 6 patients (20.7%) in the convalescent plasma group vs 7 patients (24.1%) in the control group (HR, 0.88 [95% CI, 0.30-2.63]; $P = .83$) (P for interaction = .17).

In the entire study population, the findings for several of the secondary end points appeared to signal a more favorable outcome for patients who received convalescent plasma, although there were no statistically significant differences between the convalescent plasma group vs the control group in any of the major secondary outcomes, including 28-day mortality (15.7% vs 24.0%, respectively; $P = .30$) or rate of discharge at 28 days (51% vs 36%; $P = .13$).

Convalescent plasma use in the study by Li et al[8] was associated with some clinical improvement in severely ill patients, but not in critically ill patients. Greater efficacy in less ill individuals is expected because antibody therapies generally work best when administered earlier in disease.[9] Historically, antibody therapy was effective in reducing the mortality of pneumococcal pneumonia when instituted in the first 3 days of symptom onset.[10] Consequently, it is not surprising that patients with COVID-19 who had tachypnea and hypoxia might benefit more from convalescent plasma than those who required mechanical ventilation. However, any indication of possible benefit in the severely ill group is noteworthy because these individuals had advanced disease, which is not considered optimal for antibody therapy. Lack of efficacy among patients who were receiving mechanical ventilation, some with multiorgan failure, highlights that the pathologic process in these individuals is likely irreversible.

The convalescent plasma used in the study by Li et al had high titers of IgG to SARS-CoV-2, which correlated with neutralizing activity. While neutralizing activity is considered to be the main determinant of convalescent plasma efficacy,

other antibody functions may also mediate protection. Correlates of antibody efficacy should be investigated in future studies. As reported in case series from Wuhan,[4,5] plasma-treated patients had large reductions in their serum viral loads and most were virus negative 3 days after infusion. This observation establishes that convalescent plasma has antiviral activity, which is important because it indicates that antibody administration mediates a clear biological effect. The precedent of antiviral drug use against HIV and hepatitis C shows that reductions in viral load translate into clinical improvement, and earlier therapy is more effective than later therapy when organ damage is already present. In this regard, antibody-mediated viral elimination removes damaging antigens, which may translate into reduced tissue damage and inflammation. Hence, the antiviral effect of COVID-19 convalescent plasma suggests that its use earlier in the course of disease could have potentially important therapeutic activity, especially in less severely ill individuals.

Significant concerns have been raised about the use of convalescent plasma in COVID-19.[11] These include transfusion-related lung injury and transfusion-related circulatory overload. In addition, there have been theoretical concerns that the administration of antibodies might aggravate disease through antibody-mediated enhancement of proinflammatory effects.[11] The study by Li et al[8] reported only 2 adverse events among the 52 individuals who received convalescent plasma, each of whom responded to corticosteroid administration. The occurrence of one episode within 2 hours of plasma administration characterized by chills and rash suggests a transfusion reaction. However, the second episode occurred within 6 hours and its association with plasma infusion is less certain. Overall, the paucity of adverse effects is reassuring and reduces concerns about adverse effects from antibody administration.

Although the observed differences in mortality rates and hospital discharge rates between the convalescent plasma group and the control group did not reach statistical significance, these data provide valuable information for the magnitude of effects that may be expected in convalescent plasma studies. For example, the observed overall mortality difference of 24% vs 15.7% provides actionable information for the design of future trials to help ensure they are adequately powered. This difference in mortality is smaller than mortality reductions associated with convalescent plasma reported in prior studies involving 1918 influenza,[1] SARS,[2] and 2009 influenza H1N1,[3] which ranged from 50% to 70%. Hence, assuming the results of the study by Li et al[8] are generalizable, the findings may be helpful in estimating effect sizes for future studies of convalescent plasma use in hospitalized patients with COVID-19.

In the study by Li et al, the median age of the patients with severe disease was 70 years, and the median time between symptom onset and randomization was 30 days. Promising results with convalescent plasma treatment in patients with SARS[2] and influenza H1N1[3] were obtained among younger patients, and in the case of SARS, earlier in the disease. The importance of a possible treatment benefit in older persons, in whom mortality from COVID-19 is markedly higher than in younger persons,[12] cannot be overstated. In addition, the apparent improvement in the clinical status of the subgroup of less severely ill patients a month after the onset of symptoms suggests that the beneficial effects of antibodies in COVID-19 may be measurable as an improvement in inflammatory markers and viral elimination before clinical improvement is observed. The prolonged course of COVID-19 in patients who recover also should be considered in the design of future studies.

However, the study by Li et al has several important limitations, which are acknowledged by the investigators. The early termination of the trial most likely resulted in an underpowered study, thereby precluding any definitive conclusions about the role and potential efficacy of convalescent plasma for patients with COVID-19. In addition, the open-label design, the possibility of an element of subjectivity for the primary outcome, lack of a protocolized approach to standard therapy, and variability among study centers also must be considered when interpreting the study findings. Despite these limitations, by virtue of its randomized design, this study takes prior case studies[5,6] one step further by helping to separate the effects of convalescent plasma from concurrently administered agents, such as corticosteroids and antiviral agents.[13]

The signal of potential benefit of convalescent plasma in the subgroup of patients with severe COVID-19 disease (ie, those without life-threatening COVID-19 disease) is similar to findings from a recent preliminary report of a clinical trial of remdesivir for COVID-19.[14] Like remdesivir, convalescent plasma administration was associated with clinical improvement without a statistically significant effect on mortality, with the important caveat that remdesivir was evaluated in a larger study (n = 1063 randomized patients), whereas the study by Li et al[8] was terminated prematurely and underpowered. For both studies, the importance of clinical improvement as a primary end point became apparent as the trials progressed.[14]

The availability of both convalescent plasma and remdesivir means that physicians now have at least 2 therapeutic options for COVID-19, which raises the question of combination therapy. Despite only a few studies of the efficacy of combination therapy with antiviral drugs and specific antibodies, there is evidence that these agents may work well in combination.[9] Given that the mechanisms of action of antiviral drugs and neutralizing antibodies are distinct, they could be synergistic. Future trials should consider the efficacy of combination antiviral and antibody therapies.

In summary, the first randomized clinical trial of convalescent plasma in COVID-19, reported by Li et al in *JAMA*, showed no statistically significant benefit in clinical improvement at 28 days or mortality among all randomized patients, but does provide an important signal of possible benefit in the subgroup of severely ill patients and suggests that high titer antibody against SARS-CoV-2 may have antiviral efficacy. These results, while preliminary and subject to important study limitations, should stimulate more clinical trials to establish the optimal conditions for antibody therapies against COVID-19 and suggest that future studies

should focus on determining efficacy in less severely ill patients. If the efficacy of convalescent plasma is established by future studies, the ratio of donor to patients is favorable because individuals who recover from COVID-19 can donate 2 or 3 units of plasma, which could be used to treat more than 1 person with COVID-19 disease. Therapeutic success against such a complex and challenging disease as COVID-19 is likely to require more than 1 modality, and the results from Li et al[8] provide optimism for the future of antibody therapy in this disease.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Casadevall serves on the scientific advisory board of SAB Therapeutics, which is working to develop cow-derived human antibodies for the therapy of COVID-19. No other disclosures were reported.

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JAMA Network Open

Research Letter | Critical Care Medicine

Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19)

Julien Nahum, MD; Tristan Morichau-Beauchant, MD; Fabrice Daviaud, MD; Perrine Echegut, MD; Jérôme Fichet, MD; Jean-Michel Maillet, MD; Stéphane Thierry, MD

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) was identified as a new coronavirus causing pneumonia and acute respiratory distress syndrome. It has become a pandemic, spreading particularly quickly across Europe and the US. Most deaths are related to severe acute respiratory distress syndrome, but other organ failures, such as acute kidney failure and acute cardiac injury, seem also related to the disease.[1] Inflammatory response is highly increased in coronavirus disease 2019 (COVID-19) infection, and inflammation is known to favor thrombosis. High dimerized plasmin fragment D (D-dimer) levels and procoagulant changes in coagulation pathways were reported among patients with severe COVID-19.[2,3] An elevated rate of venous and arterial thrombotic events associated with COVID-19 infection has also been reported.[4,5] This case series reports a systematic assessment of deep vein thrombosis among patients in an intensive care unit (ICU) in France with severe COVID-19.

Author affiliations and article information are listed at the end of this article.

Methods

This case series was approved by the ethical committee of the Centre Cardiologique du Nord, which granted a waiver of consent because the research presented no risk of harm and required no procedures for which consent is normally required outside a research context. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Patients with severe COVID-19 pneumonia were admitted to our ICU located in the suburban Paris area from mid-March 2020 to the beginning of April 2020. All patients had acute respiratory distress syndrome according to the Berlin definition and required mechanical ventilation.

We prospectively performed a venous ultrasonogram of the inferior limbs for all patients at admission to our ICU, considering previous data that showed increased levels of inflammatory markers, preliminary reports from the intensive care community signaling frequent events of deep vein thrombosis in ICU patients with COVID-19 at the time we received our first patients, and the high rate of deep vein thrombosis found among the first patients with COVID-19 admitted to our unit. Considering the high prevalence of venous thrombosis at admission, we systematically repeated venous ultrasonography after 48 hours if the first examination returned normal results. As recommended, all patients received anticoagulant prophylaxis at hospital admission. Statistical analyses were conducted in Prism version 5.0 (GraphPad) and Excel 365 (Microsoft Corp). Statistical significance was set at $P < .05$, and all tests were 2-tailed.

Results

A total of 34 consecutive patients were included in this study. COVID-19 diagnosis was confirmed with polymerase chain reaction on nasopharyngeal swabs of 26 patients (76%); 8 patients (24%) had a negative result on polymerase chain reaction but had a typical pattern of COVID-19 pneumonia on chest computed tomography scan. Mean (SD) age was 62.2 (8.6) years, and 25 patients (78%) were men. Major comorbidities were diabetes (15 [44%]), hypertension (13 [38%]), and obesity (mean [SD] body mass index [calculated as weight in kilograms divided by height in meters squared], 31.4

[9.0]). Overall, 26 patients (76%) required norepinephrine at admission, 16 (47%) required prone positioning, and 4 (12%) required venovenous extracorporeal membrane oxygenation (**Table 1**). Only 1 patient (3%) received anticoagulant therapy before hospitalization.

Deep vein thrombosis was found in 22 patients (65%) at admission and in 27 patients (79%) when the venous ultrasonograms performed 48 hours after ICU admission were included (**Table 2**). Eighteen patients (53%) had bilateral thrombosis, and 9 patients (26%) had proximal thrombosis. Comparable with previously published data,[2,3] our population had high levels of D-dimer (mean [SD], 5.1 µg/mL [to convert to nanomoles per liter, multiply by 5.476]), fibrinogen (mean [SD], 760 [170] mg/dL [to convert to grams per liter, multiply by 0.01]) and C-reactive protein (mean [SD], 22.8 [12.9]

Table 1. Clinical Characteristics and Laboratory Findings Among 34 Patients at Admission

Characteristic	Total	Patients without deep vein thrombosis	Patients with deep vein thrombosis
No. (%)	34 (100)	7 (21)	27 (79)
Age mean (SD), y	62.2 (8.6)	59.9 (11.2)	62.9 (7.9)
Men, No. (%)	25 (78)	5 (71)	20 (74)
BMI, mean (SD)	31.4 (9.0)	27.8 (4.8)	32.2 (9.6)
Comorbidities, No. (%)			
Cancer	1 (3)	0	1 (4)
Chronic obstructive pulmonary disease	2 (6)	1 (14)	1 (4)
Diabetes mellitus	15 (44)	3 (43)	12 (44)
Ischemic cardiopathy	3 (9)	2 (29)	1 (4)
ACE or ARB treatment	7 (21)	2 (29)	5 (19)
Hypertension	13 (38)	4 (57)	9 (33)
Time from hospital admission to ICU admission, mean (SD), d	1.6 (2.6)	2.7 (4.5)	1.3 (1.8)
Receipt of norepinephrine, No. (%)	26 (76)	5 (71)	21 (78)
Ventilation therapy, No. (%)			
Mechanical ventilation	34 (100)	7 (100)	27 (100)
Prone positioning	16 (47)	6 (86)	10 (37)
Nitric oxide inhalation	5 (15)	1 (14)	4 (15)
Venovenous ECMO	4 (12)	2 (29)	2 (7)
Laboratory findings, mean (SD)			
White blood cell count, /µL	9305 (3912)	7510 (3553)	9770 (3926)
Lymphocytes, /µL	1109 (566)	918 (731)	1158 (521)
Platelets, $\times 10^3$/µL	256 (107)	198 (106)	271 (104)
Serum creatinine, mg/dL	1 (0.5)	1.44 (0.99)	0.93 (0.25)
Prothrombin, % of activity	85 (11.4)	79.7 (16.1)	86.3 (9.7)
Activated clotting time, ratio	1.2 (0.1)	1.3 (0.1)	1.1 (0.1)
Fibrinogen, mg/dL	760 (170)	790 (150)	750 (180)
D-dimer level, mg/l	5.1 (5.4)	3.3 (2.6)	5.4 (5.8)
Troponin level, pg/ml	42.2 (57.2)	45.7 (56.5)	41.3 (58.4)
C-reactive protein, mg/dL	22.8 (12.9)	24.6 (16.0)	22.4 (12.3)
N-terminal pro-brain natriuretic peptide, pg/ml	518 (946)	251 (203)	602 (1072)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); D-dimer, dimerized plasmin fragment D; ECMO, extracorporeal membrane oxygenation.

SI conversion factors: To convert C-creative protein to milligrams per liter, multiply by 10.0; creatinine to micromoles per liter, multiply by 88.4; D-dimer to nanomoles per liter, multiply by 5.476; fibrinogen to grams per liter, multiply by 0.01; lymphocytes and white blood cell count to $\times 10^9$ per liter, multiply by 0.001; n-terminal pro–brain natriuretic peptide to nanograms per liter, multiply by 1.0; platelets to $\times 10^9$ per liter, multiply by 1.0; and troponin to micrograms per liter, multiply by 1.0.

Table 2. Rate of Deep Vein Thrombosis at Admission and at 48 Hours

	Patients, No. (%) (N = 34)		
Deep vein thrombosis	At admission	48 h after admission	Total
Total	22 (65)	5 (15)	27 (79)
Proximal	8 (24)	1 (3)	9 (26)
Distal	19 (56)	4 (12)	23 (68)
Bilateral	15 (44)	3 (9)	18 (53)

mg/dL [to convert to milligrams per liter, multiply by 10]). Prothrombin activity (mean [SD], 85% [11.4%]) and platelet count (mean [SD], 256 [107] × 10^3/μL) were normal (Table 1).

Discussion

Mortality of patients with COVID-19 admitted to ICUs has been reported to be high, at 50%.[6] Frequent venous and arterial thrombotic events have been reported, with rates from 27% to 69% of peripheral venous thromboembolism and up to 23% of pulmonary embolism.[4,5] The occurrence of pulmonary embolism might be favored by deep vein thrombosis. The main limitations of this study were its monocentric nature and the relatively small size of our cohort. In view of the high rate (ie, 79%) of deep vein thrombosis reported in this study, prognosis might be improved with early detection and a prompt start of anticoagulant therapy. Despite anticoagulant prophylaxis, 15% of our patients developed deep vein thrombosis only 2 days after ICU admission. Systematic anticoagulant therapy for all ICU patients with COVID-19 should be assessed.

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JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

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IMPORTANCE Convalescent plasma is a potential therapeutic option for patients with coronavirus disease 2019 (COVID-19), but further data from randomized clinical trials are needed.

OBJECTIVE To evaluate the efficacy and adverse effects of convalescent plasma therapy for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, randomized clinical trial performed in 7 medical centers in Wuhan, China, from February 14, 2020, to April 1, 2020, with final follow-up April 28, 2020. The trial included 103 participants with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation). The trial was terminated early after 103 of a planned 200 patients were enrolled.

INTERVENTION Convalescent plasma in addition to standard treatment (n = 52) vs standard treatment alone (control) (n = 51), stratified by disease severity.

MAIN OUTCOMES AND MEASURES Primary outcome was time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale (ranging from 1 [discharge] to 6 [death]). Secondary outcomes included 28-day mortality, time to discharge, and the rate of viral polymerase chain reaction (PCR) results turned from positive at baseline to negative at up to 72 hours.

RESULTS Of 103 patients who were randomized (median age, 70 years; 60 [58.3%] male), 101 (98.1%) completed the trial. Clinical improvement occurred within 28 days in 51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; $P = .26$). Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; $P = .03$); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the convalescent plasma group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; $P = .83$) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; $P = .30$) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; $P = .12$). Convalescent plasma treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; $P < .001$). Two patients in the convalescent plasma group experienced adverse events within hours after transfusion that improved with supportive care.

CONCLUSION AND RELEVANCE Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.

TRIAL REGISTRATION Chinese Clinical Trial Registry: ChiCTR2000029757

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Editorial
Supplemental content

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Since December 2019, coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has spread rapidly around the world, with high rates of transmission and substantial mortality. COVID-19 symptoms can range from mild, self-limited respiratory disease to severe progressive pneumonia, multiple organ failure, and even death.[1,2] To date, there is no effective treatment or vaccine to contain the disease.

Convalescent plasma therapy has been used to treat patients with infections using plasma collected from recovered patients.[3] This approach has been evaluated in the treatment of SARS,[4,5] Middle East respiratory syndrome (MERS),[6] and Ebola,[7] but not well studied and with no definitive results. Recently, case series from China reported improved outcomes after COVID-19 convalescent plasma transfusion.[8,9] The US Food and Drug Administration (FDA) recently approved the emergency use of convalescent plasma for patients with severe or life-threatening COVID-19.[10] Although the use of convalescent plasma shows promise, the evidence supporting its use in the treatment of COVID-19 remains limited, and thus its use remains investigational.

In addition, due to the limited understanding of the mechanism and precise therapeutic components of convalescent plasma, there is no standardization or evidence-based rationale for donor selection, quality control of convalescent plasma, or recipient transfusion indications for convalescent plasma. This may help to explain the varied therapeutic effects of convalescent plasma seen in a variety of infectious diseases. To address these issues, the World Health Organization issued a guideline on the use of convalescent plasma in a pandemic, advocating for standardization in donor selection and convalescent plasma quality control to maximize therapeutic potency.[11]

The objective of this randomized clinical trial was to evaluate the efficacy and adverse effects of convalescent plasma added to standard treatment, compared with standard treatment alone, for patients with severe or life-threatening COVID-19 using a standardized approach in donor selection and convalescent plasma quality control.

Key Points

Question What is the effect of convalescent plasma therapy added to standard treatment, compared with standard treatment alone, on clinical outcomes in patients with severe or life-threatening coronavirus disease 2019 (COVID-19)?

Finding In this randomized clinical trial that included 103 patients and was terminated early, the hazard ratio for time to clinical improvement within 28 days in the convalescent plasma group vs the standard treatment group was 1.40 and was not statistically significant.

Meaning Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment did not significantly improve the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a clinically important difference.

Methods

This study was a collaborative effort by the Institute of Blood Transfusion of the Chinese Academy of Medical Sciences; Union Hospital of Tongji Medical College of Huazhong University of Science and Technology; the Guanggu District Maternal and Child Health Hospital of Hubei Province; Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology; General Hospital of the Central Theater Command of the People's Liberation Army; Wuhan Red Cross Hospital; Wuhan Asia Heart Hospital; and Wuhan Pulmonary Hospital.

This study was approved by the ethics committee of the Institute of Blood Transfusion of the Chinese Academy of Medical Sciences and the ethics committees of the participating hospitals. Written informed consent was obtained from all study participants or their legal representatives. The trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2.

Participants

Patients were recruited from 7 medical centers. The study recruitment was from February 14, 2020, to April 1, 2020. Follow-up was completed on April 28, 2020.

Inclusion Criteria

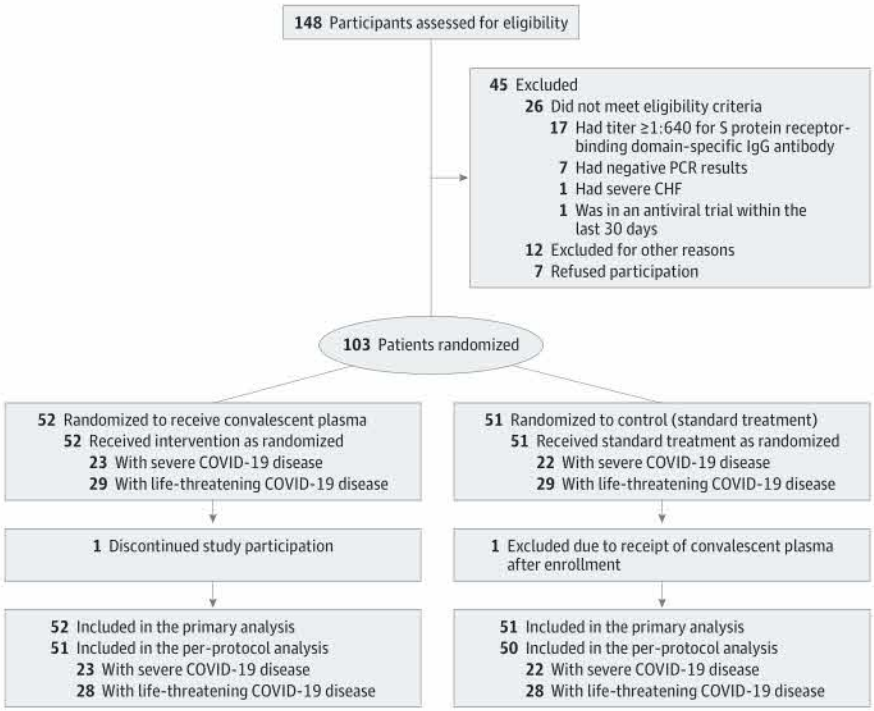
Inclusion criteria were the following: (1) signed informed consent; (2) aged at least 18 years; (3) COVID-19 diagnosis based on polymerase chain reaction (PCR) testing; (4) positive PCR result within 72 hours prior to randomization; (5) pneumonia confirmed by chest imaging; (6) clinical symptoms meeting the definitions of severe or life-threatening COVID-19; (7) acceptance of random group assignment; (8) hospital admission; (9) willingness to participate in all necessary research studies and be able to complete the study follow-up; and (10) no participation in other clinical trials, such as antiviral trials, during the study period.

Severe COVID-19 was defined as respiratory distress (≥30 breaths/min; in resting state, oxygen saturation of 93% or less on room air; or arterial partial pressure of oxygen (Pa_{O_2})/fraction of inspired oxygen (F_{IO_2}) of 300 or less. Life-threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring.

Exclusion Criteria

Exclusion criteria were the following: (1) pregnancy or lactation; (2) immunoglobulin allergy; (3) IgA deficiency; (4) preexisting comorbidity that could increase the risk of thrombosis; (5) life expectancy less than 24 hours; (6) disseminated intravascular coagulation; (7) severe septic shock; (8) Pa_{O_2}/FIO2 of less than 100; (9) severe congestive heart failure; (10) detection of high titer of S protein-RBD-specific (receptor binding domain) IgG antibody (≥1:640); (11) other contraindications as determined by the patient's physicians; and (12) participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrollment.

Figure 1. Patient Enrollment and Treatment Assignment



PCR indicates polymerase chain reaction; CHF, congestive heart failure; COVID-19, coronavirus disease 2019.

Randomization

Potential study participants were screened for eligibility 72 hours prior to study randomization. Patients were randomly assigned via computer-generated random numbering (1:1) to receive standard treatment coupled with convalescent plasma transfusion or standard treatment alone (control group) (**Figure 1**). The randomization was stratified based on the severity of COVID-19 (severe or life-threatening) and a randomization schedule was generated using block randomization with block size of 4 for each type of COVID-19 by SAS software. Patients and clinicians were not masked to treatment assignment.

Procurement of Convalescent Plasma

In brief, patients with a laboratory-confirmed COVID-19 diagnosis, who had fully recovered and been discharged from the hospital for more than 2 weeks, were recruited. Convalescent plasma-specific donor screening and selection were based on the following criteria: age of 18 through 55 years, suitable for blood donation, initially diagnosed with COVID-19 but with 2 negative PCR test results from nasopharyngeal swabs (at least 24 hours apart) prior to hospital discharge, discharged for more than 2 weeks from the hospital, and no persisting COVID-19 symptoms. Convalescent plasma collection was performed based on routine plasma collection procedures via plasmapheresis. The plasma products were prepared as fresh-frozen plasma. COVID-19 convalescent plasma was collected and processed at the Wuhan Blood Center.

S-RBD-specific IgG antibody titer was measured for convalescent plasma products and reported as the following: less than 1:160, 1:160, 1:320, 1:640, 1: 1280, or greater than 1:1280. There was a positive correlation between the SARS-CoV-2 viral neutralization titer and the S-RBD-specific IgG titer (r = 0.622, P = .03). A serum neutralization titer of 1:80 is approximately equivalent to a titer of 1:1280 for S-RBD-specific IgG. To ensure the therapeutic potency of the convalescent plasma, only the plasma units with an S-RBD-specific IgG titer of at least 1:640 were used for this study.

Additional details regarding plasma preparation standards can be found in the eMethods in Supplement 3, and the preparation requirements of convalescent plasma used were similar to the recently updated FDA recommendations.[10]

Convalescent Plasma Transfusion

The transfusion dose of COVID-19 convalescent plasma was approximately 4 to 13 mL/kg of recipient body weight. ABO type of the convalescent plasma transfused was compatible with the patient's ABO type. In addition, the convalescent plasma was crossmatched with the patient's red blood cells to ensure compatibility. Convalescent plasma transfusion was administered at approximately 10 mL for the first 15 minutes, which was then increased to approximately 100 mL per hour with close monitoring. Adjustments in the infusion rates were allowed based on the patient's risk for volume overload and tolerance, at the discretion of the treating physicians. No premedication was given before convalescent plasma transfusion.

Standard Treatment

Standard treatment consisted of symptomatic control and supportive care for COVID-19, mostly based on the evolving Chinese national COVID-19 treatment guidelines and hospital

practice.[12] Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications.

Outcome Measures

The primary end point was time to clinical improvement within a 28-day period. Clinical improvement was defined as patient discharge or a reduction of 2 points on a 6-point disease severity scale.[13] The scale was defined as follows: 6 points, death; 5 points, hospitalization plus extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; 4 points, hospitalization plus noninvasive ventilation or high-flow supplemental oxygen; 3 points, hospitalization plus supplemental oxygen (not high-flow or noninvasive ventilation); 2 points, hospitalization with no supplemental oxygen; 1 point, hospital discharge.

Patient discharge criteria included body temperature returned to normal for longer than 3 days, respiratory symptoms significantly improved without the need for oxygen support, and 2 consecutive negative PCR test results from nasopharyngeal swabs at least 24 hours apart.

Secondary clinical outcomes were as follows: (1) 28-day mortality, including analysis of time from randomization to death; (2) duration of hospitalization, including analyses of time from randomization to discharge, time from admission to discharge, and 28-day discharge rates; and (3) conversion of nasopharyngeal swab viral PCR results from positive at baseline to negative at follow-up assessed at 24, 48, and 72 hours. Once nasopharyngeal swab viral PCR testing yielded negative results 2 times consecutively, no further testing was performed.

A post hoc analysis was added to compare rates of improvement at days 7, 14, and 28.

This clinical trial was an open-label, randomized clinical study. To avoid assessment bias, the evaluation of clinical outcomes was performed by an investigator who was blind to the study group allocation.

Statistical Analysis

The original sample size was determined to be 100 for each group, which would provide 80% power, with a 2-sided significance level of $\alpha = .05$, to detect an 8-day change for the convalescent plasma group in time to clinical improvement, assuming that this would be 20 days in the control group and 60% of the patients would reach clinical improvement.

Unless otherwise stated, analyses were performed based on the full analysis set, which is defined as the set of all randomized patients who received at least one treatment specified in the trial. Statistical analysis was performed on randomly assigned treatment groups. Continuous variables were summarized by presenting the median and interquartile range (IQR) for the total number of patients who contributed values. Categorical variables were summarized by presenting the frequency and proportion of patients in each category. Time-to-event data were analyzed using the Kaplan-Meier method, and the median time to event and corresponding 95% CI were calculated. For the cases in which more than 50% of patients were censored and therefore the median time to event was indeterminate, the restricted mean survival time would be used for post hoc analysis.

For the primary end point of time to clinical improvement, death, withdrawal, and crossover between groups before day 28 were considered to be right-censored at day 28, and otherwise would be considered to be right-censored at the last observation date. Hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazards models. Three Cox proportional hazards models were fitted in this study. We referred to the model that included only the treatment group as the unadjusted model. The model that included disease severity (severe or life-threatening) and treatment group is referred to as model 1, and the model that further considered the interaction between disease severity and treatment group is referred to as model 2. Study sites were considered as a random effect in these models. Proportionality hazard assumption was assessed for treatment group and disease severity by extending the Cox models to include the corresponding time-dependent covariates.[14] If the coefficient of the time-dependent covariate was statistically significant, the proportionality hazard assumption would be considered to be violated.

A per-protocol analysis was performed for the primary end point as a sensitivity analysis. The per-protocol set was defined as the set of all randomized patients who received at least one treatment specified in the trial and who had no significant protocol violations that affected the efficacy evaluation.

Treatment effects for secondary end points were assessed using odds ratios and HRs with 95% CIs for the discrete variables and time-to-event data, respectively. For the analyses of time from randomization to discharge, time from randomization to death, and length of stay, the definition of censoring was consistent with the primary end point. Missing data for secondary outcomes and adverse events were not imputed. Only observed values were used for data analysis and presentation.

Subgroup analyses of efficacy were performed according to disease severity. Interactions between treatment group and disease severity group were tested using model 2.

Statistical analyses were performed with SAS software, version 9.4. Statistical significance was defined using a 2-sided significance level of $\alpha = .05$. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Early Study Termination

Due to the containment of the COVID-19 epidemic in Wuhan, China, the numbers of patients with COVID-19 decreased in late March 2020. No new cases were reported in Wuhan for 7 consecutive days after March 24 (data from the National Health Commission of the People's Republic of China).[15] The last patient enrolled in this study was on March 27, 2020, and for the next 3 days, we were not able to recruit more patients and did not have any recruitment targets. After discussion with the expert committee of the Institute of Blood Transfusion, the study was terminated by the sponsor (Chinese Academy of Medical Sciences) and the leading primary investigator on April 1, 2020, with a total of 103 patients enrolled.

Table 1. Baseline Demographics and Clinical Characteristics of All Patients With COVID-19[a]

	Convalescent plasma group (n = 52)	Control group (n = 51)
Demographic and clinical characteristics		
Age, median (IQR), y	70 (62-80)	69 (63-76)
Sex, No. (%)		
Male	27 (51.9)	33 (64.7)
Female	25 (48.1)	18 (35.3)
Allergy history, No. (%)[b]	6 (11.5)	5 (9.8)
Coexisting diseases, No. (%)[c]		
Hypertension	29 (55.8)	27 (52.9)
Cardiovascular disease	14 (26.9)	12 (23.5)
Cerebrovascular disease	11 (21.2)	7 (13.7)
Diabetes	9 (17.3)	12 (23.5)
Liver disease	5 (9.6)	5 (9.8)
Cancer	3 (5.8)	0
Kidney disease	2 (3.9)	4 (7.8)
Laboratory values[d]		
Body temperature, median (IQR), °C	36.5 (36.2-36.7) [n = 52]	36.4 (36.2-36.8) [n = 50]
≥37.3 °C, No. (%)	4/52 (7.7)	7/50 (14.0)
Respiratory rate >24/min, No. (%)	11/52 (21.2)	7/49 (14.3)
Heart rate >100/min, No. (%)	13/52 (25.0)	8/50 (16.0)
Systolic blood pressure >140 mm Hg, No. (%)	10/52 (19.2)	15/50 (30.0)
White blood cell count, median (IQR), cells/μL	7590 (6300-11 460)	7160 (6130-11 200)
White blood cell count categories, No. (%)		
<4000/μL	5 (9.6)	4 (7.8)
4000-10 000/μL	31 (59.6)	29 (56.9)
>10 000/μL	16 (30.8)	18 (35.3)
Neutrophil count, median (IQR), cells/μL	7030 (4890-10 350)	5800 (4420-10 150)
Neutrophil count categories, No. (%)		
<1800/μL	0	2 (3.9)
1800-6300/μL	23 (44.2)	25 (49.0)
>6300/μL	29 (55.8)	24 (47.1)
Lymphocyte count, median (IQR), cells/μL	830 (570-1420)	800 (500-1370)
Lymphocyte count categories, No. (%)		
<1000/μL	32 (61.5)	32 (62.8)
≥1000/μL	20 (38.5)	19 (37.3)
Platelet count, median (IQR), $\times 10^3$/μL	164.5 (99.0-248.0)	214.0 (138.0-274.0)
Platelet count categories, No. (%)		
<100 × 10^3/μL	13 (25.0)	7 (13.7)
≥100 × 10^3/μL	39 (75.0)	44 (86.3)
CRP, median (IQR), mg/L	20.40 (5.13-65.60) [n = 49]	8.87 (1.73-40.32) [n = 48]
>5 mg/L, No. (%)	37/49 (75.5)	29/48 (60.4)
IL-6, median (IQR), pg/mL	16.62 (5.76-73.68) [n = 44]	21.67 (5.10-64.00) [n = 35]
>7 pg/mL, No. (%)	32/44 (72.7)	25/35 (71.4)
Prothrombin time, median (IQR), s	13.50 (12.00-15.20) [n = 51]	13.30 (12.35-14.15) [n = 48]
APTT, median (IQR), s	33.10 (28.30-41.10) [n = 49]	33.85 (29.95-42.95) [n = 48]
Thrombin time, median (IQR), s	16.45 (14.60-18.90) [n = 46]	16.10 (15.10-18.55) [n = 48]
Fibrinogen, median (IQR), mg/dL	3.86 (2.93-4.71) [n = 50]	4.00 (3.29-5.12) [n = 48]
D-dimer, median (IQR), μg/mL	1.88 (0.91-4.78) [n = 47]	2.23 (0.79-5.21) [n = 46]
>0.2 μg/mL, No. (%)	45/47 (95.7)	43/46 (93.5)

(continued)

Table 1. Baseline Demographics and Clinical Characteristics of All Patients With COVID-19[a] (continued)

	Convalescent plasma group (n = 52)	Control group (n = 51)
ALT, median (IQR), U/L	35.05 (22.25-55.90) [n = 52]	28.50 (18.95-59.50) [n = 48]
ALT categories, No. (%)		
≤50 U/L	36/52 (69.2)	33/48 (68.8)
>50 U/L	16/52 (30.8)	15/48 (31.3)
AST, median (IQR), U/L	28.50 (20.95-42.00) [n = 52]	24.50 (19.10-33.50) [n = 48]
AST categories, No. (%)		
≤40 U/L	35/52 (67.3)	40/48 (83.3)
>40 U/L	17/52 (32.7)	8/48 (16.7)
Urea nitrogen, median (IQR), mg/dL	20.36 (14.34-28.07) [n = 50]	20.08 (16.22-32.97) [n = 49]
Urea nitrogen categories, No. (%)		
<5.0 mg/dL	0/50	0/49
5.0-19.9 mg/dL	23/50 (46.0)	24/49 (49.0)
>19.9 mg/dL	27/50 (54.0)	25/49 (51.0)
Serum creatinine, median (IQR), mg/dL	0.75 (0.60-0.89) [n = 50]	0.83 (0.62-1.04) [n = 49]
Serum creatinine categories, No. (%)		
≤1.5 mg/dL	46/50 (92.0)	47/49 (95.9)
>1.5 mg/dL	4/50 (8.0)	2/49 (4.1)

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IQR, interquartile range.

SI conversion factors: To convert D-dimer to nmol/L, multiply values by 5.476; to convert urea nitrogen to mmol/L, multiply values by 0.357; to convert creatinine to μmol/L, multiply values by 88.4.

[a] The values shown were based on total number of patients who contributed values.

[b] History of allergy to certain allergens, including food, medicine, etc.

[c] Details of coexisting diseases were collected from medical records.

[d] The vital signs and laboratory values are the last available values within 72 hours prior to randomization. The laboratory values selected were associated with the clinical status and factors that may affect convalescent plasma therapy. The values used for categorization of laboratory values are local divisions of low, normal, and high values.

There was no interim or preliminary data review prior to making this decision.

Results

Study Population

A total of 103 patients were enrolled in this randomized clinical trial. They were assigned to either the convalescent plasma group or the control group in a 1:1 ratio and were categorized as follows: 23 patients in the convalescent plasma group and 22 patients in the control group had severe COVID-19, and 29 patients in the convalescent plasma group and 29 patients in the control group had life-threatening COVID-19. Of these, 1 patient with life-threatening disease in the convalescent plasma treatment group withdrew from the study and 1 patient with life-threatening disease in the control group received convalescent plasma transfusion after randomization (protocol violation). Thus, 103 patients were included in the full analysis set and 101 patients were included in the per-protocol set (Figure 1).

The median age was 70 years (IQR, 62-78 years) among all patients, 71 years (IQR, 66-82 years) for patients with severe COVID-19, and 69 years (IQR, 61-76 years) for patients with life-threatening COVID-19. Of the patients included in the study, 60 (58.3%) were men, and the percentages of men with severe and life-threatening COVID-19 were 53.3% and 62.1%, respectively. A total of 89.2% of the patients had a normal body temperature at the time of participation, and the median body temperature was 36.5 °C (IQR, 36.2-36.7 °C) (**Table 1** and eTable 1 and eTable 2 in Supplement 3).

The median interval between the onset of symptoms and randomization was 30 days (IQR, 20-39 days) overall, 33 days (IQR, 22-43 days) for patients with severe disease, and 26 days (IQR, 20-36 days) for patients with life-threatening disease. There were 5 patients with severe disease and 3 patients with life-threatening disease who had an interval between the onset of symptoms and randomization that was fewer than 14 days (**Table 2**).

Overall and within disease severity strata, the convalescent plasma and control groups were similar in terms of demographic characteristics, baseline laboratory results, and distribution on the 6-point disease severity scale at baseline, with the exception of systolic blood pressure in the patients with severe COVID-19 and sex in the patients with life-threatening COVID-19 (eTable 1 and eTable 2 in Supplement 3). Additional details regarding patients' clinical status at the time of randomization and additional medications received are provided in Table 2 and eTable 3, eTable 4, and eTable 7 in Supplement 3. For patients in the convalescent plasma group, median plasma infusion volume was 200 mL (IQR, 200-300 mL), and 96% received a single dose of plasma infusion.

Primary Clinical Outcome

For all patients combined, there was no significant difference in the primary outcome of time to clinical improvement within 28 days: 51.9% (27/52) in the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; HR, 1.40 [95% CI, 0.79-2.49]; P = .26). Results for the per-protocol population were not materially different (eTable 5 in Supplement 3). Among those with severe disease, the primary outcome occurred in 91.3% (21/23) vs 68.2% (15/22) (HR, 2.15 [95% CI, 1.07-4.32]; P = .03). Among those with life-threatening disease, the primary outcome occurred in 20.7% (6/29) vs 24.1% (7/29) (HR, 0.88 [95% CI, 0.30-2.63]; P = .83) (P for interaction = .17) (**Table 3**, **Figure 2**, and eTable 6 in Supplement 3). For all proportional hazards models, the proportionality assumptions were met.

Secondary Clinical Outcomes

There was no significant difference in the secondary outcome of 28-day mortality (15.7% in the convalescent plasma group vs 24.0% in the control group; OR, 0.65 [95% CI, 0.29-1.46]; P = .30). There was also no significant difference in the time from randomization to death between the convalescent group and the control group (HR, 0.74 [95% CI, 0.30-1.82]; P = .52) (Table 3). Among patients with severe disease, no patients died in the convalescent plasma group, while 2 patients (9.1%) died in the control group. Among patients with life-threatening disease, 8 patients (28.6%) died in the convalescent plasma group, while 10 patients (35.7%) died in the control group.

There was also no significant difference in the secondary outcome of time from randomization to discharge (51.0% in the convalescent plasma group vs 36.0% in the control group were discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; P = .12). The 28-day discharge rate of the convalescent plasma group reached 51%, among which the discharge rate of those with severe disease in the convalescent plasma group reached 91.3%.

At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR in the convalescent plasma group were all significantly higher than that of the control group (44.7% vs 15.0%, P = .003 at 24 hours; 68.1% vs 32.5%, P = .001 at 48 hours; 87.2% vs 37.5%, P < .001 at 72 hours) (Table 3 and eFigure 1 in Supplement 3). Among patients with severe disease, the rate of negative viral PCR at 72 hours was significantly higher in the convalescent plasma group compared with the control group, but there was no significant difference at 24 hours and 48 hours. Among patients with life-threatening disease, there was a statistically significant difference in favor of the convalescent plasma group at 24, 48, and 72 hours.

Post hoc Analysis

The clinical improvement rates overall and by disease severity subgroups at various time points during the study are presented in Table 3.

Adverse Events

Two participants reported transfusion-related adverse events following convalescent plasma transfusion. One patient in the severe COVID-19 group developed chills and rashes within 2 hours of transfusion but recovered fully after treatment with dexamethasone and promethazine. This was determined to be a definite nonsevere allergic transfusion reaction and also a probable nonsevere febrile nonhemolytic transfusion reaction. The other patient, who was in the life-threatening COVID-19 group, presented with shortness of breath, cyanosis, and severe dyspnea within 6 hours of transfusion. The patient was given dexamethasone, aminophylline, and other supportive care immediately and gradually improved after 2 hours. This was determined to be possible severe transfusion-associated dyspnea.

Table 2. Patients' Clinical Status at Randomization and Medications Received[a]

All patients	Convalescent plasma group (n = 52)	Control group (n = 51)
Time between symptom onset and randomization, median (IQR), d	27 (22-39) [n = 49]	30 (19-38) [n = 48]
≤14 d, No. (%)	3/49 (6.1)	5/48 (10.4)
>14 d, No. (%)	46/49 (93.9)	43/48 (89.6)
Interval between symptom onset and admission, median (IQR), d	12 (5-20) [n = 49]	10 (6-16) [n = 48]
6-Point scale at study day 1, No. (%)		
2- Hospitalization, no supplemental oxygen	1/51 (2.0)	1/50 (2.0)
3- Hospitalization, requiring supplemental oxygen (not high-flow or noninvasive ventilation)	15/51 (29.4)	15/50 (30.0)
4- Hospitalization, requiring noninvasive ventilation and/or high-flow supplemental oxygen	21/51 (41.2)	23/50 (46.0)
5- Hospitalization, requiring extracorporeal membrane oxygenation and/or invasive mechanical ventilation	14/51 (27.5)	11/50 (22.0)
Medications used after randomization		
Antiviral	41/46 (89.1)	44/49 (89.8)
Antibacterial	38/46 (82.6)	39/49 (79.6)
Chinese herbal medicine	26/46 (56.5)	30/49 (61.2)
Steroids	21/46 (45.7)	16/49 (32.7)
Antifungal	15/46 (32.6)	13/49 (26.5)
Human immunoglobulin	13/46 (28.3)	11/49 (22.5)
Interferon	12/46 (26.1)	7/49 (14.3)

[a] The values shown were based on total number of patients who contributed values. Details of medications used were provided in eTable 7 in Supplement 3.

Discussion

In this randomized clinical trial of patients with severe or life-threatening COVID-19, there was no significant difference in the time to clinical improvement between patients who received convalescent plasma transfusion therapy combined with standard treatment vs those who received standard treatment alone. There was also no significant difference in secondary outcomes of 28-day mortality or time from randomization to discharge. Convalescent plasma treatment was

Table 3. Primary and Secondary Clinical Outcomes at Day 28[a]

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
All patients					
Primary clinical outcome					
Time to clinical improvement, median (IQR),d[d]	28.00 (13.00-Indeterminate)	Indeterminate (18.00-Indeterminate)	−2.15 (−5.28 to 0.99)	HR, 1.40 (0.79-2.49)	.26
Clinical improvement rate, No./total (%)[e]					
At day 7	5/52 (9.6)	5/51 (9.8)	−0.2% (−11.6% to 11.2%)	OR, 0.98 (0.30-3.19)	.97
At day 14	17/52 (32.7)	9/51 (17.6)	15.0% (−1.4% to 31.5%)	OR, 1.85 (0.91-3.77)	.08
At day 28	27/52 (51.9)	22/51 (43.1)	8.8% (−10.4% to 28.0%)	OR, 1.20 (0.80-1.81)	.37
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	26/51 (51.0)	18/50 (36.0)	15.0% (−4.1% to 34.1%)	OR, 1.42 (0.90-2.24)	.13
Time from randomization to discharge, median (IQR), d[d]	28.00 (13.00-Indeterminate)	Indeterminate (19.00-Indeterminate)	−2.43 (−5.56 to 0.69)	HR, 1.61 (0.88-2.93)	.12
Time from hospitalization to discharge, median (IQR),d[d]	41.00 (31.00-Indeterminate)	53.00 (35.00-Indeterminate)	−11.95 (−26.33 to 2.43)	HR, 1.68 (0.92-3.08)	.09
Mortality at 28 d, No./total (%)	8/51 (15.7)	12/50 (24.0)	−8.3% (−23.8% to 7.2%)	OR, 0.65 (0.29-1.46)	.30
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	0.52 (−2.10 to 3.14)	HR, 0.74 (0.30-1.82)	.52
Viral nucleic acid negative rate, No./total (%)					
At 24 h	21/47 (44.7)	6/40 (15.0)	29.7% (11.7% to 47.7%)	OR, 4.58 (1.62-12.96)	.003
At 48 h	32/47 (68.1)	13/40 (32.5)	35.6% (15.9% to 55.3%)	OR, 4.43 (1.80-10.92)	.001
At 72 h	41/47 (87.2)	15/40 (37.5)	49.7% (32.0% to 67.5%)	OR, 11.39 (3.91-33.18)	<.001
Patients with severe disease					
Primary clinical outcome					
Time to clinical improvement, median (IQR), d[d]	13.00 (9.00-21.00)	19.00 (15.00-Indeterminate)	−4.94 (−9.33 to −0.54)	HR, 2.15 (1.07-4.32)	.03
Clinical improvement rate, No./total (%)[e]					
At day 7	3/23 (13.0)	4/22 (18.2)	−5.1% (−26.3% to 16.1%)	OR, 0.72 (0.18-2.85)	.70
At day 14	14/23 (60.9)	6/22 (27.3)	33.6% (6.3% to 60.9%)	OR, 2.23 (1.05-4.76)	.02
At day 28	21/23 (91.3)	15/22 (68.2)	23.1% (−3.9% to 50.2%)	OR, 1.34 (0.98-1.83)	.07
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	21/23 (91.3)	15/22 (68.2)	23.1% (−3.9% to 50.2%)	OR, 1.34 (0.98-1.83)	.07
Time from randomization to discharge, median (IQR), d[d]	13.00 (10.00-16.00)	19.00 (11.00-Indeterminate)	−4.09 (−8.44 to 0.27)	HR, 1.97 (1.00-3.88)	.05
Time from hospitalization to discharge, median (IQR), d	32.00 (26.00-40.00)	41.00 (30.00-53.00)	−9.38(−23.63 to 4.88)	HR, 1.74 (0.89-3.41)	.11
Mortality at 28 d, No./total (%)	0/23	2/22 (9.1)	−9.1% (−25.6% to 7.4%)		.49
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	1.42 (−0.88 to 3.71)	HR, 0.00	>.99
Viral nucleic acid negative rate, No./total (%)					
At 24 h	7/21 (33.3)	2/17 (11.8)	21.6% (−9.1% to 52.2%)	OR, 3.75 (0.66-21.20)	.15
At 48 h	13/21 (61.9)	6/17 (35.3)	26.6% (−4.2% to 57.4%)	OR, 2.98 (0.79-11.25)	.10
At 72 h	19/21 (90.5)	7/17 (41.2)	49.3% (22.7% to 75.9%)	OR, 13.57(2.36-77.95)	<.001
Patients with life-threatening disease					
Primary clinical outcome					
Time to clinical improvement, median (IQR), d[d]	Indeterminate	Indeterminate	0.23 (−3.11 to 3.57)	HR, 0.88 (0.30-2.63)	.83
Clinical improvement rate, No./total (%)[e]					
At day 7	2/29 (6.9)	1/29 (3.4)	3.4% (−11.4% to 18.3%)	OR, 2.00 (0.19-20.86)	>.99
At day 14	3/29 (10.3)	3/29 (10.3)	0.0% (−19.1% to 19.1%)	OR, 1.00 (0.22-4.55)	>.99
At day 28	6/29 (20.7)	7/29 (24.1)	−3.4% (−24.9% to 18.0%)	OR, 0.86 (0.33-2.24)	.75

(continued)

Table 3. Primary and Secondary Clinical Outcomes at Day 28[a] (continued)

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	5/28 (17.9)	3/28 (10.7)	7.1% (−14.7% to 28.9%)	OR, 1.67 (0.44-6.32)	.71
Time from randomization to discharge, median (IQR), d[d]	Indeterminate	Indeterminate	−0.80 (−3.74 to 2.14)	HR, 1.77 (0.42-7.40)	.44
Time from hospitalization to discharge, median (IQR), d[d]	Indeterminate (46.00-Indeterminate)	Indeterminate	−4.61 (−15.07 to 5.85)	HR, 1.90 (0.45-8.04)	.38
Mortality at 28 d, No./total (%)	8/28 (28.6)	10/28 (35.7)	−7.1% (−31.5% to 17.2%)	OR, 0.80 (0.37-1.72)	.57
Time from randomization to death, median (IQR), d[d]	Indeterminate (22.00-Indeterminate)	Indeterminate (15.00-Indeterminate)	−0.04 (−3.86 to 3.77)	HR, 0.86 (0.34-2.17)	.74
Viral nucleic acid negative rate, No./total (%)					
At 24 h	14/26 (53.8)	4/23 (17.4)	36.5% (11.8% to 61.1%)	OR, 5.54 (1.47-20.86)	.01
At 48 h	19/26 (73.1)	7/23 (30.4)	42.6% (17.3% to 68.0%)	OR, 6.20 (1.79-21.46)	.003
At 72 h	22/26 (84.6)	8/23 (34.8)	49.8% (25.9% to 73.7%)	OR, 10.31(2.63-40.50)	<.001

Abbreviations: HR, hazard ratio; IQR, interquartile range; OR, odds ratio.

[a] The values shown were based on total number of patients who contributed values. The primary clinical outcome was analyzed by primary analysis set. Times to outcomes in the secondary clinical outcomes were analyzed by primary analysis set. Indeterminate events could not be calculated due to the low percentage of outcome events.

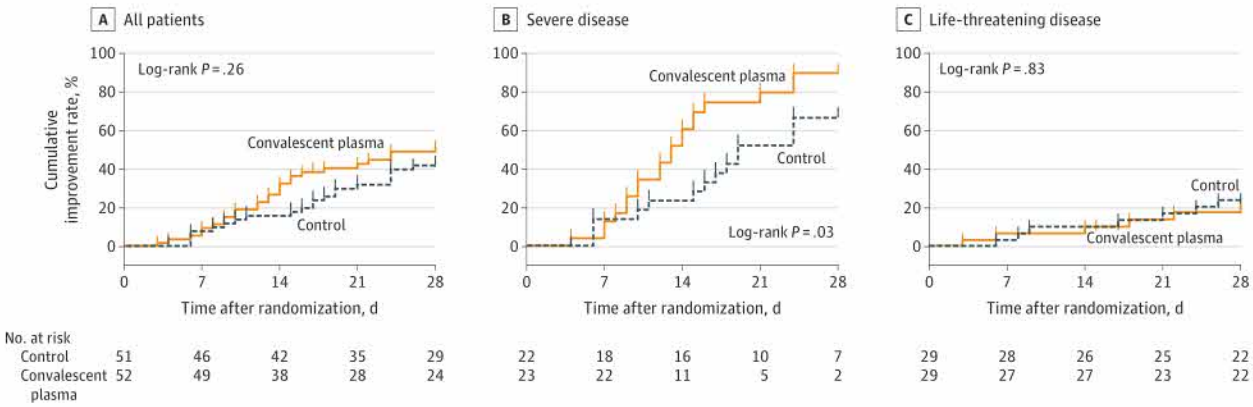
[b] The absolute differences of time to clinical improvement, times to discharge, and times from randomization to death were calculated based on restricted mean survival time.

[c] *P* value was calculated by Cox regression, χ^2 test, or Fisher exact test.

[d] Medians and quartiles of time to clinical improvement, times to discharge, and times from randomization to death could not be determined because too few patients had reached improvement or discharge by the end of the study. By the end of the study, for all, severe, and life-threatening patients, respectively, 27 (51.9%), 21 (91.3%), and 6 (20.7%) were clinically improved in the convalescent plasma group; 22 (43.1%), 15 (68.2%), and 7 (24.1%) were clinically improved in the control group; 26 (51.0%), 21 (91.3%), and 5 (17.9%) were discharged in the convalescent plasma group; 18 (36.0%), 15 (68.2%), and 3 (10.7%) were discharged in the control group; 8 (15.7%), 0, and 8 (28.6%) died in the convalescent plasma group; and 12 (24.0%), 2 (9.1%), and 10 (35.7%) died in the control group.

[e] These analyses were developed post hoc to better illustrate disease progression.

Figure 2. Time to Clinical Improvement in Patients With COVID-19



The cumulative improvement rate is the percentage of patients who experienced a 2-point improvement or were discharged alive from the hospital. Ticks on the curves indicate censored events. All patients who did not reach clinical improvement were observed for the full 28-day period or until death. COVID-19 indicates coronavirus disease 2019.

The median (IQR) follow-up times for the convalescent plasma group and control group, respectively, were 15 (10-28) days and 24 (13-28) days overall; 13 (10-16) and 18.5 (11-26) days among those with severe COVID-19; and 28 (12-28) and 26 (15-28) days among those with life-threatening COVID-19.

associated with higher rates of negative SARS-CoV-2 viral PCR results from nasopharyngeal swabs at 24, 48, and 72 hours, demonstrating that the convalescent plasma treatment was associated with antiviral activity in patients with COVID-19.

Plasma transfusions can result in transfusion-related adverse events including febrile and allergic transfusion reactions, transfusion-associated dyspnea, hypotensive transfusion reaction, to hemolytic transfusion reactions, septic transfusion reaction, transfusion-related acute lung injury, and transfusion-associated circulatory overload. In this study, most patients tolerated convalescent plasma transfusions well. There were 2 cases of reported transfusion-associated adverse events. One case was determined to be a definite nonsevere allergic transfusion reaction and also a probable nonsevere febrile

nonhemolytic transfusion reaction, and the other case was determined to be possible severe transfusion-associated dyspnea. The rate is somewhat higher than the general rate of reactions associated with plasma transfusion, possibly due to the small sample size and active surveillance.[16]

In the subgroup analysis by disease severity, there was a signal of possible clinical benefit for convalescent plasma among patients with severe COVID-19. However, because the test for interaction by disease severity was not statistically significant, the findings for the severe and life-threatening subgroups should not be interpreted as different. Given the early study termination, it is possible that the study was underpowered to detect a statistically significant interaction, and a larger trial of convalescent plasma focusing on patients with severe COVID-19 may be warranted.

Patients with COVID-19 who were recruited in this study were heterogeneous with regard to the duration and severity of the illness. The possible antiviral activity with convalescent plasma treatment in patients aged 60 to 80 years and after 14 days of disease onset is notable. To our knowledge, no other antiviral treatments have demonstrated therapeutic effects in this age group or this late in the course of the disease. However, the convalescent plasma treatment was given at least 14 days after the onset of symptoms in most cases, and it is not known whether earlier convalescent plasma treatment could have resulted in better clinical outcomes. Further studies are needed to optimize patient selection and timing of convalescent plasma treatment.

While the use of convalescent plasma has been investigated and used many times in the past,[3,17] its use has not been well studied. It is notable that for most studies of the use of convalescent plasma,[4,5,18] there was lack of standardization and procedure control with regard to the donor selection process and the nature or level of antibodies in convalescent plasma units. This may explain the varied therapeutic effects seen across a variety of diseases or even across patients with the same disease. The guidance on convalescent plasma issued by the World Health Organization[11] highlighted the importance of standardized processes and laboratory testing-based quality control of convalescent plasma units, the selection of clinical indications, as well as program deployment to recruit adequate numbers of donors and maintain sufficient inventory.

One of the potential strengths of this study was the controlled process for donor selection and convalescent plasma quality control. A predefined process was used to enroll donors for convalescent plasma collection. Only units with a high titer of S-RBD-specific IgG antibody were used for convalescent plasma treatment in this study.

Limitations

This study has several limitations. First, the sample size was small and the study was terminated early. It is possible that the study was underpowered to detect a clinically important benefit of convalescent plasma therapy. Second, the median time between the onset of symptoms and randomization was 30 days, and it is unclear whether earlier treatment would have resulted in greater benefit. Third, this was an open-label study and the primary outcome was based to some degree on physicians' clinical management decisions. Fourth, the use of standard therapy was allowed in both groups and was not protocolized, which could have potentially influenced outcomes. Fifth, the relatively short 28-day time frame of the study follow-up may have precluded the observation of clinical improvement in patients with severe diseases, especially life-threatening COVID-19, as they may take longer time to respond and recover. Sixth, plasma was not used for the control group, which would have been a more ideal control group, making blinded design possible. Seventh, the study findings should be interpreted cautiously given that practices may vary from country to country, and hospital to hospital, such as the types of standard treatment, supportive care, and thresholds for intubation and hospital admission. The outcomes of this study may be related to a combination of many factors, such as the quality of the convalescent plasma products in terms of potency, the selection of the patients (severe and life-threatening COVID-19), and the timing of convalescent plasma transfusion.

Conclusion

Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not significantly improve the time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tu Y-P, Jennings R, Hart B, et al. Swabs collected by patients or health care workers for SARS-CoV-2 testing. N Engl J Med. DOI: 10.1056/NEJMc2016321

Supplemental Material

Table of Contents

Methods:

Participants self-collected of all three anatomic sites: tongue, nasal and MT and health care worker-collection from the NP. Inclusion criteria included evidence of symptoms suggestive of an upper respiratory illness (subjective and objective fevers, cough, sore throat, fevers, myalgia, or rhinorrhea) indicating higher risk of COVID-19 in this community and the ability to consent and agree to participate in the study. People who were not able to demonstrate understanding of the study, not willing to commit to having all four samples collected, had a history of nosebleed in the past 24 hours, nasal surgery in the past two weeks, chemotherapy treatment with documented low platelet and low white blood cell counts, or acute facial trauma were excluded from the study.

Health care workers used a spoken script to explain the study and give eligible patients the opportunity to decline. Any patient who had all four samples collected is considered as having willingly participated in the study as they allowed the sample collection and the use of the data produced from the sample. This study protocol was deemed to be an operational project by the Office of Human Research Affairs at UnitedHealth Group.

Participants were provided instructions and asked to self-collect tongue, nasal, and MT samples, in that order (see Supplement). Tongue samples were collected with a nylon flocked swab (Copan FLOQSwab 502CS01) via the following steps: 1) Extending the tongue, and 2) firmly but gently brushing the swab along the length of the anterior 2/3 of dorsum of the tongue for 10 seconds. Nasal samples were collected with a foam swab (Puritan 25-1506 1PF100) via the following steps: 1) gently inserting the swab in the vertical position into one nasal passage until there is gentle resistance, 2) leaving the swab in place for 10-15 seconds, rotating the swab, and 3) repeating the procedure on the other side with the same swab. MT samples were collected

with a nylon flocked swab (MDL NasoSwab A362CS02.MDL, 56380CS01 for adults and 56780CS01 for pediatrics) via the following steps: 1) inserting the swab in the horizontal position until gentile resistance was met, 2) leaving the swab in for 10-15 seconds on each side, rotating the swab, 3) repeating in the other nostril with the same swab. After patient sampling was completed, NP samples were collected by a health care worker using a polyester tipped swab on a skinny wire (Puritan 25-800-2PDBG) via the following steps: 1) pass the swab along the floor of the nose until meeting gentle resistance as the swab touches the posterior pharynx, in the nostril corresponding to the patient's dominant hand, and 2) rotate the swab several times and withdraw the swab.

All samples were stored in viral transport media and refrigerated at 4°C before shipping on ice packs to a reference laboratory for rRT-PCR testing (Quest Diagnostics, San Juan Capistrano, CA). Patient results were transmitted back to the clinical practice via the standard lab information system and electronic health record protocol. Additionally, cycle threshold (Ct) values for all samples that tested positive for SARS-CoV-2 were reported back to the clinical sites. A higher Ct value corresponds to a lower viral load.

Three separate analyses were performed: one comparing tongue samples to NP samples, a second comparing nasal samples to NP samples, and a third comparing MT samples to NP samples; all used health care worker-collected NP samples are the comparator. Samples included in the final analysis had RT-PCR results returned for both samples in question (i.e. NP and one patient-collected sample) at the time of data freeze. The Wilson score method was used to calculate all binomial one-sided 97.5% confidence intervals. All statistical analysis was performed using R version 3.6.1.

Results:

We enrolled patients aged 15 months to 94 years old presenting with symptoms indicative of an upper respiratory infection, visiting one of five ambulatory clinical sites in the Puget Sound metropolitan area over five days (March 16 to March 21, 2020). An NP swab plus at least one test location swab were obtained and tested for 530 participants. All four swabs were successfully collected and tested from 449 participants. Additionally, testing results were obtained from all sites except the tongue, anterior nares, and MT for 23, 30, and 22 participants, respectively. Results were obtained from only the NP and nasal swabs for four participants and from only the NP and MT swabs for two participants.

Supplemental Table 1 summarizes the positivity rate in each of the three analysis populations broken out by demographics and self-reported symptoms. Using the NP results, patients had overall positivity rates of 9.8%, 10.0%, and 10.3% for SARS CoV-2 among patients who also returned a tongue, nasal, and MT result, respectively.

Supplemental Tables 2, 3, and 4 show 2x2 tables for test results between health care worker - collected NP samples and the patient-collected tongue, nasal, and MT samples, respectively. These tables also provide the estimated sensitivity of the patient-collected samples and one-side 97.5% confidence intervals.

Supplemental Table 1: Demographics and self-reported clinical symptoms.

	Tongue & NP $\frac{\text{n positive}}{\text{n total}}$ (%)	Nasal & NP $\frac{\text{n positive}}{\text{n total}}$ (%)	MT & NP $\frac{\text{n positive}}{\text{n total}}$ (%)
Total Participants	49/501 (9.8%)	50/498 (10.0%)	52/504 (10.3%)
Sex			
Female	27/299 (9.0%)	27/296 (9.1%)	29/303 (9.6%)
Male	22/200 (10.9%)	23/202 (11.4%)	23/201 (11.4%)
Smoker/Vaper			
Yes	9/112 (8.0%)	10/118 (8.5%)	10/117 (8.5%)
No	38/356 (10.7%)	37/353 (10.5%)	39/354 (11.0%)
Self-report Symptoms			
Fever	15/71 (21.1%)	14/71 (19.7%)	14/74 (18.9%)
Ear Pain/Drainage	10/130 (7.7%)	11/133 (8.3%)	11/135 (8.1%)
Vomiting	2/46 (4.3%)	2/46 (4.3%)	2/46 (4.3%)
Cough	39/385 (10.1%)	39/388 (10.1%)	41/388 (10.6%)
Diarrhea	10/149 (6.7%)	12/151 (7.9%)	12/150 (8.0%)
Difficulty Breathing	25/246 (10.2%)	25/248 (10.0%)	24/253 (9.5%)
Age			
< 30	5/116 (4.3%)	4/115 (3.5%)	5/116 (4.3%)
30 - 39	14/116 (12.1%)	15/118 (12.7%)	14/116 (12.1%)
40 - 49	6/94 (6.4%)	6/86 (7.0%)	7/92 (7.6%)
50 - 59	10/81 (12.3%)	12/88 (13.6%)	13/87 (14.9%)

≥ 60	14/94 (14.9%)		13/91 (14.3%)		13/93 (14.0%)	
	Mean (SD)		Mean (SD)		Mean (SD)	
	Among Pos.	Among Neg.	Among Pos.	Among Neg.	Among Pos.	Among Neg.
Temperature (°F)	98.8 (0.9)	98.5 (0.7)	98.8 (0.9)	98.5 (0.7)	98.8 (0.9)	98.5 (0.7)
Pulse	86.5 (12.8)	84.1 (16.2)	85.3 (12.3)	84.7 (16.0)	86.0 (12.8)	84.4 (16.1)
Days Since First Symptoms	6.8 (5.3)	7.1 (8.0)	6.7 (5.4)	7.1 (7.9)	6.7 (5.2)	6.9 (7.7)

Supplemental Table 2: A 2x2 table of the test results for all patients who had an NP and a Tongue sample tested.

Estimated Sensitivity (97.5% CI): 89.8% (78.2%, 100.0%)		Tongue		
		Negative	Positive	Total
NP	Negative	450	2	452
	Positive	5	44	49
	Total	455	46	501

Supplemental Table 3: A 2x2 table of the test results for all patients who had an NP and a Nasal sample tested.

Estimated Sensitivity (97.5% CI): 94.0% (83.8%, 100.0%)		Nasal		
		Negative	Positive	Total
NP	Negative	447	1	448
	Positive	3	47	50
	Total	450	48	498

Supplemental Table 4: A 2x2 table of the test results for all patients who had an NP and a MT sample tested.

Estimated Sensitivity (97.5% CI): 96.2% (87.0%, 100%)		MT		
		Negative	Positive	Total
NP	Negative	452	0	452
	Positive	2	50	52
	Total	454	50	504

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CORRESPONDENCE

Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing

TO THE EDITOR: The early medical response to the Covid-19 pandemic in the United States was limited in part by the availability of testing. Health care workers collected a swab sample from the patients' oropharynx or nasopharynx according to testing guidelines for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. This procedure potentially increased the risk of transmission of the virus to health care workers who lacked sufficient personal protective equipment (PPE).[1]

In other clinical conditions,[2,3] it is faster to obtain a tongue, nasal, or mid-turbinate sample than a nasopharyngeal sample, with less potential for the patient to sneeze, cough, or gag. In addition, recent data support the validity of non-nasopharyngeal samples for detection of SARS-CoV-2.[4,5] Collection by the patient reduces high exposure of the health care worker to the virus and preserves limited PPE.

We obtained swab samples from the nasopharynx and from at least one other location in 530 patients with symptoms indicative of upper respiratory infection who were seen in any one of five ambulatory clinics in the Puget Sound region of Washington. Patients were provided with instructions and asked to collect tongue, nasal, and mid-turbinate samples, in that order. A nasopharyngeal sample was then collected from the patient by a health care worker. All samples were submitted to a reference laboratory for reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing that yielded qualitative results (positive or negative) and cycle threshold (Ct) values for positive samples only (additional details are provided in the Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Our study was powered on the basis of a one-sided test to determine whether the sensitivities of the non-nasopharyngeal swabs collected by the patients themselves were significantly greater than 90%. We calculated that 48 patients with positive nasopharyngeal samples would be needed for the study, assuming a true sensitivity of 98% with 80% power. Pairwise analyses were conducted to compare each sample collected by the patient with the nasopharyngeal sample collected by a health care worker. Of the 501 patients with both tongue and nasopharyngeal samples, both swabs tested negative in 450 patients, both swabs tested positive in 44, the nasopharyngeal swab was positive and the tongue swab was negative in 5, and the tongue swab was positive and the nasopharyngeal swab was negative in 2. Of the 498 patients with both nasal and nasopharyngeal samples, both swabs were negative in 447, both swabs were positive in 47, the nasopharyngeal swab was positive and the nasal swab was negative in 3, and the nasal swab was positive and the nasopharyngeal swab was negative in 1. Of the 504 patients with both mid-turbinate and nasopharyngeal samples, both swabs were negative in 452, both swabs were positive in 50, and the nasopharyngeal swab was positive and the mid-turbinate swab was negative in 2; none of these patients had a positive mid-turbinate swab and a negative nasopharyngeal swab.

When a nasopharyngeal sample collected by a health care worker was used as the comparator, the estimated sensitivities of the tongue, nasal, and mid-turbinate samples collected by the patients were 89.8% (one-sided 97.5% confidence interval [CI], 78.2 to 100.0), 94.0% (97.5% CI, 83.8 to 100.0), and 96.2% (97.5% CI, 87.0 to 100.0), respectively. Although the estimated sensitivities of the nasal and mid-turbinate samples were greater than 90%, all the confidence intervals for the sensitivity of the samples collected by the patients contained 90%. Despite the lack of statistical significance, both the nasal and mid-turbinate samples may be clinically acceptable on the basis of estimated sensitivities above 90% and the 87% lower bound of the confidence interval for the sensitivity of the mid-turbinate sample being close to 90%. Ct values from the RT-PCR tests showed Pearson correlations between the positive results from the nasopharyngeal swab and the

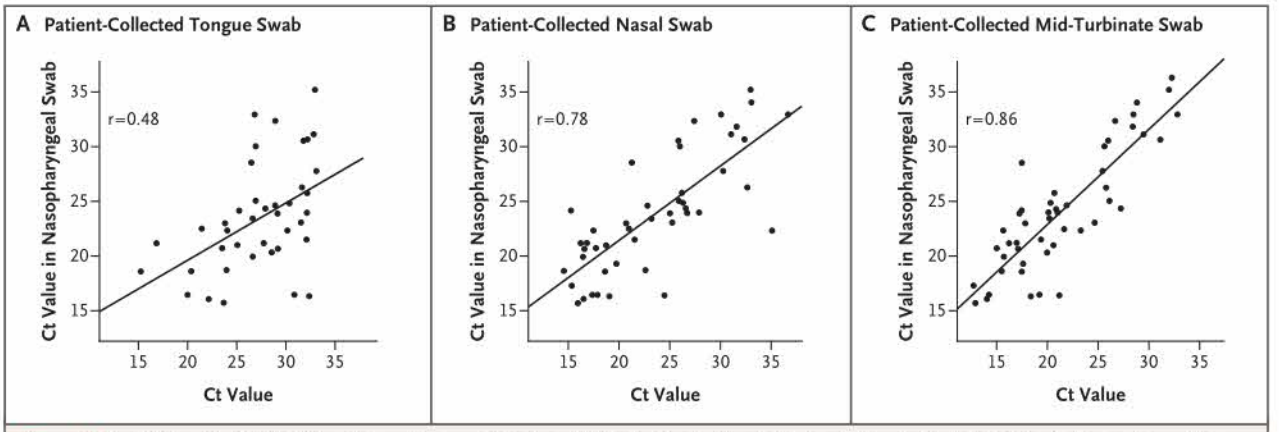

Figure 1. Cycle Threshold (Ct) Values from Tongue, Nasal, and Mid-Turbinate Swabs Collected by Patients Relative to Those from Nasopharyngeal Swabs Collected by Health Care Workers.

The correlation coefficient is superimposed on each panel, along with a trend line estimated with the use of simple linear regression. Plots show the available Ct values for 43 patients who had positive test results from both tongue and nasopharyngeal swabs (Panel A), 46 patients who had positive test results from both nasal and nasopharyngeal swabs (Panel B), and 48 patients who had positive test results from both mid-turbinate and nasopharyngeal swabs (Panel C). Data on 4 patients (1 patient with positive test results from both tongue and nasopharyngeal swabs, 1 patient with positive test results from both nasal and nasopharyngeal swabs, and 2 patients with positive test results from both mid-turbinate and nasopharyngeal swabs) were not included in this analysis because multiple swabs obtained from these patients were labeled with a single test site (i.e., tongue, nasopharynx, nose, or middle turbinate).

positive results from the tongue, nasal, and mid-turbinate swabs of 0.48, 0.78, and 0.86, respectively. Figure 1 shows the Ct values for the sites from the patient-collected swab samples relative to those for the nasopharyngeal swab samples, with a linear regression fit superimposed on the scatterplot. For patients with positive test results from both the nasopharyngeal swab and a tongue, nasal, or mid-turbinate swab, the Ct values for the swabs collected by the patient were less than the Ct values for the nasopharyngeal swab 18.6%, 50.0%, and 83.3% of the time, respectively, indicating that the viral load may be higher in the middle turbinate than in the nasopharynx and equivalent between the nose and the nasopharynx (additional details are provided in the Methods section in the Supplementary Appendix).

Our study shows the clinical usefulness of tongue, nasal, or mid-turbinate samples collected by patients as compared with nasopharyngeal samples collected by health care workers for the diagnosis of Covid-19. Adoption of techniques for sampling by patients can reduce PPE use and provide a more comfortable patient experience. Our analysis was cross-sectional, performed in a single geographic region, and limited to single comparisons with the results of nasopharyngeal sampling, which is not a perfect standard test. Despite these limitations, we think that patient collection of samples for SARS-CoV-2 testing from sites other than the nasopharynx is a useful approach during the Covid-19 pandemic.

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FAST TRACK

Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study

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ABSTRACT

OBJECTIVES

To describe the characteristics of children and adolescents affected by an outbreak of Kawasaki-like multisystem inflammatory syndrome and to evaluate a potential temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DESIGN

Prospective observational study.

SETTING

General paediatric department of a university hospital in Paris, France.

PARTICIPANTS

21 children and adolescents (aged ≤18 years) with features of Kawasaki disease who were admitted to hospital between 27 April and 11 May 2020 and followed up until discharge by 15 May 2020.

MAIN OUTCOME MEASURES

The primary outcomes were clinical and biological data, imaging and echocardiographic findings, treatment, and outcomes. Nasopharyngeal swabs were prospectively tested for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR) and blood samples were tested for IgG antibodies to the virus.

RESULTS

21 children and adolescents (median age 7.9 (range 3.7-16.6) years) were admitted with features of Kawasaki disease over a 15 day period, with 12 (57%) of African ancestry. 12 (57%) presented with Kawasaki disease shock syndrome and 16 (76%) with myocarditis. 17 (81%) required intensive care support. All 21 patients had noticeable gastrointestinal symptoms during the early stage of illness and high levels of inflammatory markers. 19 (90%) had evidence of recent SARS-CoV-2 infection (positive RT-PCR result in 8/21, positive IgG antibody detection in 19/21). All 21 patients received intravenous immunoglobulin and 10 (48%) also received corticosteroids. The clinical outcome was favourable in all patients. Moderate coronary artery dilations were detected in 5 (24%) of the patients during hospital stay. By 15 May 2020, after 8 (5-17) days of hospital stay, all patients were discharged home.

CONCLUSIONS

The ongoing outbreak of Kawasaki-like multisystem inflammatory syndrome among children and adolescents in the Paris area might be related to SARS-CoV-2. In this study an unusually high proportion of the affected children and adolescents had gastrointestinal symptoms, Kawasaki disease shock syndrome, and were of African ancestry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Acute clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are less common and less severe in children than in adults

Recent observations, however, have raised concerns about a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), with shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorders

WHAT THIS STUDY ADDS

Kawasaki-like multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection has characteristics that differ from those of classic Kawasaki disease

The characteristics comprise a higher frequency in children of African ancestry, predominant acute gastrointestinal symptoms, haemodynamic instability, and myocarditis

These clinical findings should prompt high vigilance among primary care and emergency doctors, and preparedness during the coronavirus disease 2019 pandemic in countries with a high proportion of children of African ancestry and high levels of community transmission

Introduction

In children and adolescents, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is mostly responsible for mild respiratory symptoms, in contrast with severe forms reported in adults.[1 2] An association between the disease caused by SARS-CoV-2, coronavirus disease 2019 (covid-19), and late manifestations of vasculitis has been increasingly suspected, especially in young asymptomatic patients, which might be due to post-viral immunological reactions.[3 4]

Kawasaki disease is the most common primary vasculitis in childhood, with medium and small sized arteries predominantly affected.[5] The annual incidence of the disease is highest in Japan, with more than 300 per 100 000 children aged 4 years or younger affected, compared with 25 per 100 000 children aged 5 years or younger in North America.[6 7] One of the most severe complications of Kawasaki disease is coronary artery aneurysm.[7] Kawasaki disease shock syndrome, a rare

form of Kawasaki disease, is often associated with myocarditis and requires critical care support during the acute phase of illness.[8 9] Although the cause of Kawasaki disease remains unclear, the role of a viral trigger in some genetically predisposed children has been hypothesised, as several viral respiratory agents have been associated with Kawasaki disease,[10-12] including seasonal coronavirus in some studies,[13 14] although not all studies.[15 16]

Recently, 17 children with signs and symptoms consistent with Kawasaki disease and laboratory evidence of recent SARS-CoV-2 infection were reported in the United States (n=1), England (n=8), and Italy (n=8).[17-19] These reports included cases with hyperinflammatory syndrome and multiorgan involvement, provisionally named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) in Europe[20] and multisystem inflammatory syndrome in children (MIS-C) in the United States.[21] Given the highly variable prevalence of SARS-CoV-2 infection in Europe, the possibility of an association between Kawasaki disease and positive testing for SARS-CoV-2 needs confirmation.

We evaluated a potential temporal association with SARS-CoV-2 infection in a cluster of 21 children and adolescents with features of Kawasaki disease who were admitted to the general paediatric department of a university hospital in Paris, France between 27 April and 11 May 2020 and followed up until discharge by 15 May.

Methods

We included all children and adolescents (aged ≤18 years) who were admitted to the general paediatric department of Necker Hospital for Sick Children in Paris, France between 27 April and 11 May 2020 and met the criteria for Kawasaki disease.[7] Patients were followed up until discharge by 15 May 2020. This university hospital serves as the regional reference centre for emerging infectious diseases in children. All parents provided written informed consent.

We reviewed the medical files of all the patients to collect personal and clinical data, laboratory test results, and imaging and echocardiographic findings using a standardised study specific form. For the purposes of this study, we used the criteria of the American Heart Association to define the presence of complete and incomplete Kawasaki disease,[7] and the criteria proposed by Kanegaye et al to define Kawasaki disease shock syndrome.[8] From each patient we obtained at least two nasopharyngeal swabs to test for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR; SARS-CoV-2 R-GENE, Argene; bioMerieux, Marcy l'Étoile, France). To exclude hospital acquired SARS-CoV-2 infection, we collected samples from the patients for RT-PCR testing within the first three days of hospital admission. We also took blood samples to test for IgG antibodies against SARS-CoV-2 (Architect SARS-CoV-2 chemiluminescent microparticle immunoassay -CMIA-; Abbott Core Laboratory, IL),[22] and other laboratory tests, such as for inflammatory and cardiac markers. Standard cardiology investigations included regular electrocardiography and echocardiography. We defined a coronary artery dilation to be present if the coronary artery diameter z score was between 2.0 and <2.5 and an aneurysm to be present if the z score was 2.5 or greater.[7] Resistance to intravenous immunoglobulin treatment was defined as persistent or recrudescent fever at least 36 hours and less than seven days after completion of the first immunoglobulin infusion.[7]

We described patients' characteristics using medians and percentages. Differences between groups were assessed by the Mann-Whitney U test. Statistical analysis was carried out using SPSS v25 (SPSS, Chicago, IL).

Patient and public involvement

We acknowledge the importance of public involvement. For this study, limited staff resources and absence of dedicated funding, short delays, and lockdown challenges made involving patients and members of the public, and especially children and adolescents, not possible at this time. We did make sure our participants remained aware of the progress of the ongoing study and its aims.

Results

Evidence of SARS-CoV-2 infection

Between 27 April and 11 May 2020, a total of 21 children and adolescents were admitted with features of Kawasaki disease (table 1). In response to the covid-19 pandemic, France closed schools and began its lockdown on 17 March 2020. According to the parents, all 21 patients reported here had not left home for school, social gatherings, or travel since lockdown was implemented. A recent history of viral-like symptoms was reported in nine of the patients: headache, cough, coryza, fever for less than 48 hours, and, for one patient, anosmia. The median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 (range 18-79) days. A history of recent contact with family members displaying viral-like symptoms was reported in 10 households: parents or grandparents (n=11) and siblings (n=3). Symptoms in five of these family contacts were highly suspicious of covid-19 (ageusia, anosmia, suggestive findings on thoracic computed tomography). One contact had a positive RT-PCR test result for SARS-CoV-2 while symptoms were still present. The median interval between the reported contact and Kawasaki disease was 36 (range 18-45) days. The result of RT-PCR testing for SARS-CoV-2 was positive in eight (38%) of the 21 patients presented here (table 2). All but one of them had no symptoms suggestive of covid-19; one had anosmia that started 24 hours before the symptoms of Kawasaki disease. IgG antibodies against SARS-CoV-2 were detected in 19 of the 21 (90%) patients, with a median IgG index of 5.4 (range 2-9). The two patients with negative IgG results also tested negative

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Table 1 | Clinical characteristics of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are numbers (percentages) unless stated otherwise

Characteristics	Total (n=21)
Personal:	
Median (range) age (years)	7.9 (3.7-16.6)
Girls	12 (57)
Parents country of birth (n=42):	
Sub-Saharan Africa/Caribbean islands	24 (57)
Asia	4 (10)
Europe	12 (29)
Middle East	2 (5)
Kawasaki disease principal clinical criteria:	
Complete presentation (fever >4 days and ≥4 principal criteria)	11 (52)
Lips and oral cavity changes	16 (76)
Bilateral bulbar conjunctival injection	17 (81)
Rash	16 (76)
Changes to extremities	10 (48)
Cervical lymphadenopathy	12 (57)
Median (range) days of fever before intravenous immunoglobulin	5 (0-12)
Kawasaki disease associated clinical features:	
Gastrointestinal symptoms	21 (100)
Perineal or face desquamation	4 (19)
Arthralgia	2 (10)
Irritability	12 (57)
Other neurological features	6 (29)
Myocarditis	16 (76)
Median (range) left ventricular ejection fraction rate	42 (10-57)
Serous effusion	12 (57)

for SARS-CoV-2 by RT-PCR. These two patients with complete and incomplete Kawasaki disease according to the American Heart Association criteria[7] had no myocarditis and did not require intensive care support. Their procalcitonin levels were less than 1µg/L, and coronary artery dilation was detected in one patient. Multiplex PCR targeting human respiratory syncytial viruses, seasonal coronaviruses, parainfluenza and influenza viruses, metapneumovirus, and rhinovirus/enterovirus in nasopharyngeal swabs, was negative in 19 patients tested; serum PCR results for adenovirus, Epstein Barr virus, cytomegalovirus, human herpesvirus 6, and parvovirus B19 were negative in nine patients tested, and one patient with positive anti-SARS-CoV-2 IgG also had a serology suggestive of recent Epstein Barr virus infection.

Clinical features

Table 1 presents the clinical features of the 21 patients admitted with a diagnosis of Kawasaki disease. The ratio of male patients to female patients was 0.75. The median age at presentation was 7.9 (range 3.7-16.6) years. Twelve (57%) patients had at least one parent originating from sub-Saharan Africa or a Caribbean island, and three (14%) from Asia (two from China, one from Sri Lanka). The 21 patients had no relevant personal or family medical history, and none reported living in unhealthy environments or social housing. Sixteen (76%) patients had a body mass index below the 97th centile.

Eleven (52%) of the patients fulfilled the complete criteria for Kawasaki disease, whereas the remaining 10 had incomplete Kawasaki disease. Among the principal criteria for Kawasaki disease, polymorphous skin rash (76%), changes to the lips and oral cavity (76%), and bilateral bulbar conjunctival injection (81%) were the most common signs. All the patients had gastrointestinal symptoms, which occurred early in the course of illness before the onset of the principal manifestations of Kawasaki disease and consisting of acute abdominal pain, often associated with vomiting and diarrhoea (95%). Four patients had peritoneal effusion, with acute surgical abdomen in two of the four. One of them underwent abdominal surgery for suspected appendicitis, but had aseptic peritonitis. Irritability was common (57%), and six (29%) patients presented with headaches, confusion, or meningeal irritation. One of the three patients who underwent lumbar puncture had cerebrospinal fluid pleocytosis. Among other acute manifestations of Kawasaki disease, pericardial effusions occurred in 10 (48%) patients and pleural effusion in three (14%) patients. Myocarditis was diagnosed in 16 (76%) patients, with left ventricular ejection fraction ranging between 10% and 57%. Two of these 16 patients displayed important electrocardiographic changes (increased QT interval and occasional ventricular arrhythmias or diffuse ST-segment elevation) not attributable to any drug for QTc prolongation.

Imaging and laboratory findings

Of the 18 patients who underwent chest imaging (radiography or computed tomography), ground glass opacities, local patchy shadowing, and interstitial abnormalities were present in eight (44%) patients (table 2). Echocardiography detected coronary artery abnormalities in eight (38%) patients after a median of 7.5 (range 5-11) days of fever, which consisted of dilations (z score between 2.0 and 2.5) in five (24%) patients and increased coronary visibility in three (14%) patients. No coronary aneurysms were identified.

All patients had high levels of inflammatory markers, including leucocytosis with a predominance of neutrophils, and high levels of C reactive protein, procalcitonin, and serum interleukin 6 (IL-6; table 2). Seventeen (81%) patients had lymphopaenia, and anaemia was common, with a median haemoglobin level of 86 (range 53-122) g/L. Hyponatraemia (<135 mmol/L) and hypoalbuminaemia (<32 g/L) were observed in 20 (95%) patients. Transient kidney failure was observed in 11 (52%) patients. Moderate increases in serum alanine transaminases and γ-glutamyltransferase levels occurred in 62% and 76% of patients, respectively, and increases in γ-glutamyltransferase occurred after a median of 6.5 (range 5-16) days after disease onset. Lipase was increased in 10/16 (63%) patients tested. D-dimer levels were increased (>500 µg/L) in 19/20 (95%) patients. Increased levels of high sensitivity cardiac troponin I (>26 pg/mL) and B-type natriuretic peptide (>100 ng/L) were found in 17/21 (81%) and 14/18 (78%) patients, respectively.

Table 2 | Imaging and laboratory findings of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are medians (ranges) unless stated otherwise

Characteristics	Total (n=21)
Ultrasound findings on coronary arteries during hospital admission (No (%)):	
Increased visibility	3 (14)
Dilation (z score 2 to <2.5)	5 (24)
Aneurysm (z score ≥2.5)	0
Chest radiography or computed tomography abnormalities (No (%)):	
Ground glass opacity, local patchy shadowing, interstitial abnormalities	8/18 (44)
Biochemistry findings:	
White cell count (×10^9/L)	17.4 (5.4-42.8)
Neutrophil count (×10^9/L)	13.6 (3.3-36.4)
Lymphocyte count (×10^9/L)	1.1 (0.4-5.6)
Haemoglobin (g/L)	86 (53-122)
Platelet count (×10^9/L)	499 (78-838)
C reactive protein (mg/L)	253 (89-363)
Procalcitonin (µg/L)	22.5 (0.1-448)
Interleukin 6 (pg/mL)*	170 (4-1366)
Sterile pyuria (No (%))†	10/16 (63)
Albumin (g/L)	21 (16-37)
Natrium (mmol/L)	130 (116-135)
Creatinine (µmol/L)	63 (27-417)
Alanine aminotransferase (IU/L)	70 (6-257)
γ-glutamyl transferase (IU/L)	59 (10-205)
Lipase (IU/L)†	108 (19-537)
Lactates (mmol/L)*	2.8 (1.6-9)
D-dimers (µg/L)‡	4025 (350-19330)
High sensitivity cardiac troponin I (ng/L)	282 (10-6900)
B-type natriuretic peptide (ng/L)§	3354 (16-16017)
Positive microbiological findings:	
Nasopharyngeal SARS-CoV-2 RT-PCR	8 (38)
Positive SARS-CoV-2 serum serology (IgG)‡	19 (90)
Positive nasopharyngeal PCR for other viruses	0/19

RT-PCR=reverse transcription-polymerase chain reaction; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; IgG=immunoglobulin G.
*Missing data for four patients.
†Missing data for five patients.
‡Missing data for one patients.
§Missing data for three patients.

Treatment and outcomes

All 21 patients received high dose intravenous immunoglobulin (2 g/kg) after fever for a median duration of 5 (range 0-12) days and low dose aspirin (3-5 mg/kg/day) (table 3), and seven patients received concomitant corticosteroids (2-10 mg/kg/day). Five (24%) patients showed resistance to intravenous immunoglobulin and were treated with a second infusion (2 g/kg), with corticosteroids (2 mg/kg/day) in four of these patients. Eighteen (86%) patients received empirical broad spectrum antibiotic treatment, which always included a third generation cephalosporin. Median duration of antibiotic treatment was 6.5 (range 2-13) days. All test results for bacteria (urine, cerebrospinal fluid, and blood culture) were negative.

Seventeen (81%) patients were admitted to an intensive care unit (ICU) for management of haemodynamic instability. After hospital admission for a median 2 (range 1-5) days, 10 of these patients were admitted to the ICU. All presented with the criteria for Kawasaki disease on admission to the ICU. Twelve (57%) patients were considered to have Kawasaki disease shock syndrome: 11 received intravenous fluid resuscitation, and eight received vasoactive agents because of sustained hypotensive shock. Fourteen (67%) patients received inotropic agents for myocarditis with cardiac dysfunction. Median duration of vasoactive or inotropic agents was 3 (range 1-7) days. Eleven (52%) patients needed mechanical ventilation for cardiovascular compromise. Patients admitted to the ICU had higher levels of systemic inflammation markers, with a higher peak procalcitonin level (26 µg/L, range 1.7-448 µg/L), compared with those who did not require admission to the ICU (1 µg/L, range 0.13-4.17 µg/L; P=0.001). Median ICU length of stay was 5 (range 3-15) days. By 15 May 2020, after 8 (range 5-17) days of hospital stay, all patients were discharged home. No deaths were recorded.

Discussion

In this study, the temporal association between the onset of the covid-19 pandemic in France and the results of tests (RT-PCR and IgG antibodies) for SARS-CoV-2 in our patients with Kawasaki-like disease suggests a causal link. Furthermore, only one patient had symptoms suggestive of acute covid-19 and most had positive serum test results for IgG antibodies, suggesting that the development of Kawasaki disease in these patients is more likely to be the result of a post-viral immunological reaction. An association between Kawasaki disease and viral respiratory infections has been suspected,[10 14 23] especially rhinovirus and enterovirus, and various viral agents, including human coronaviruses.[10 13 14] However, no difference has been reported in clinical presentation between patients with Kawasaki disease with and without documented respiratory viral infection.[10]

In our series, we describe a Kawasaki-like multisystem inflammatory syndrome with an over-representation of myocarditis and Kawasaki disease shock syndrome, consistent with recent findings.[18 19] Mild myocarditis is common in the early phase of Kawasaki disease, as shown by cardiac biopsies and scintigraphy,[24 25] and generally improves quickly as inflammation resolves.[24 26] More severe myocarditis with decreased left ventricular contractility can sometimes occur, however, especially in the context of Kawasaki disease shock syndrome. This syndrome is a rare complication that affects 1.5% to 7.0% of patients with Kawasaki disease, and it has a higher incidence in Western countries compared with Asian countries.[9] It results from both myocardial dysfunction and decreased peripheral vascular resistance, usually requiring intravenous fluid resuscitation together with inotropic and vasoactive agent infusion in ICU.[8 27] Kawasaki disease shock syndrome might mimick toxic shock syndrome,[8] justifying systematic antibiotic use in our series. The pathophysiology of Kawasaki disease shock syndrome remains unclear. A high level of circulating pro-inflammatory cytokines might contribute to the distributive component of shock. Indeed, Kawasaki disease shock syndrome has been found associated with high levels of IL-6, C reactive protein, and procalicitonin.[9] In our series, we observed high levels of procalcitonin; 10-fold higher than those recently reported in 27 patients with Kawasaki disease

Table 3 | Treatment and outcomes of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are numbers (percentages) unless stated otherwise

Variables	Total
Treatment:	
Intravenous immunoglobulin (2g/kg) infusion	21 (100)
Intravenous immunoglobulin (2g/kg) retreatment	5 (24)
Steroids (2-10 mg/kg/day)	10 (48)
Aspirin (3-5 mg/kg/day)	21 (100)
Broad spectrum antibiotics	18 (86)
Outcome and serious complications:	
Persistent fever 36 hours after end of initial intravenous infusion	5 (24)
Median (range) length of hospital stay (days)	8 (5-17)
Admitted to intensive care unit	17 (81)
Fluid resuscitation	11 (52)
Vasoactive and inotropic agents*	15 (71)
Mechanical ventilation	11 (52)
Death	0

*Adrenaline, dobutamine, milrinone and/or noradrenaline.

shock syndrome.[9] C reactive protein and IL-6 levels were also high. This major pro-inflammatory state, together with multiorgan dysfunction, recently named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS),[20] might reflect a particularly strong post-viral immunological reaction to SARS-CoV-2 compared with other viral agents.[28] Of note, a cytokine storm syndrome with increased levels of inflammatory markers such as IL-6 was described in adults with covid-19,[29] and it has been associated with fatality.[30]

Besides inflammatory markers, clinical and biological features of our patients were often consistent with the diagnosis of Kawasaki disease shock syndrome. Indeed, older age, higher D-dimer levels, lower haemoglobin and albumin levels, and more severe hyponatraemia were previously found to be associated with Kawasaki disease shock syndrome.[9] In contrast with a recent series,[18] only 24% of our patients had a body mass index above the 75th centile, which does not support the hypothesis of overweight as a risk factor for Kawasaki-like multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection. Resistance to intravenous immunoglobulin treatment and coronary artery abnormalities were less common in our series than in previous series of Kawasaki disease shock syndrome.[8 9] However, these results should be treated with caution as coronary artery abnormalities might appear later during follow-up. Gastrointestinal symptoms were also unusually common, affecting all of our 21 patients. A previous study reported intestinal pseudo-obstruction in only 2% of 310 patients with Kawasaki disease.[31] As previously described, other symptoms of Kawasaki disease appeared after the intestinal ones in all patients, which could have led to diagnostic and therapeutic delays in some children.[32] Suspected mechanisms involve intestinal ischaemia secondary to bowel vessel vasculitis. Rapid resolution of symptoms in all patients after treatment with intravenous immunoglobulin supports this hypothesis.

The observation of a higher proportion of patients of African ancestry is consistent with recent findings,[18] suggesting an effect of either social and living conditions or genetic susceptibility. Kawasaki disease is rarely reported in sub-Saharan Africa, but it might be more common than previously thought.[33] In the United Kingdom and the United States, a 2.5-fold higher incidence was reported in children of Asian ancestry than of European ancestry, with an intermediary 1.5-fold risk for children of African ancestry.[34 35] Besides, African-Americans have been disproportionately affected by the covid-19 pandemic, also suggesting an increased susceptibility to severe SARS-CoV-2 infection.[36 37] Therefore, African countries where the SARS-CoV-2 pandemic has spread might face a potentially large number of children with Kawasaki disease, and supply shortages of intravenous immunoglobulin should be anticipated in such settings. The absence of reported cases of Kawasaki-like multisystem inflammatory syndrome associated with SARS-CoV-2 infection in Asian countries where the covid-19 pandemic started, and where the incidence of Kawasaki disease is the highest, is noteworthy.[38] Ethnic differences in the development of Kawasaki disease shock syndrome were previously reported, with a lower incidence in Asian countries than in Western countries.[89] This warrants future studies investigating underlying genetic and immunological mechanisms.

Table 4 | Main features of classic Kawasaki disease and Kawasaki-like multisystem inflammatory syndrome. Numbers are percentages of people affected unless stated otherwise

Characteristics	Classic Kawasaki disease*	Kawasaki-like syndrome series
High risk population	Asian	African
Age	6 months-5 years	4-17 years
Incomplete form of Kawasaki disease†	5-20	48
Gastrointestinal symptoms	Uncommon	100
Kawasaki disease shock syndrome	2-7	57
Myocarditis with ventricular dysfunction	<1	76
Intensive care support	4	81
Levels of inflammatory markers	Increased	Noticeably increased
Lymphopaenia	Rare	81
Coronary artery dilations/aneurysm	4-13	24
Intravenous immunoglobulin resistance	10-20	24

*Supported by Li et al,[9] Saundankar et al,[40] Makino et al,[6] and McCrindle et al.[7]
†Incomplete form according to American Heart Association criteria[7]: fever ≥5 days, 2 or 3 principal clinical criteria of Kawasaki disease, and echocardiographic or laboratory features of Kawasaki disease.

Limitations of this study

Our study has limitations. Firstly, potential recruitment bias might have contributed to the high number of patients with Kawasaki-like multisystem inflammatory syndrome admitted to the general paediatric department in our hospital. This hospital is the referral centre for paediatric patients with severe covid-19 in the Paris area. Secondly, the low number of patients precluded indepth comparisons of phenotypes with adequate statistical power. Thirdly, a causal link with SARS-CoV-2 infection has not been established, despite a strong suspicion of exposure to SARS-CoV-2. Household members were not systematically tested for SARS-CoV-2 ongoing infection. Besides, a new released kit for antibody testing has been used and false positive results for SARS-CoV-2 IgG assay might occur as a result of cross reactivity from pre-existing antibodies.[39] However, a study recently reported 99.9% specificity and 100% sensitivity for this assay.[22] Also, since Kawasaki-like multisystem inflammatory syndrome might induce immune reactions with multiple antibody production, patients may show transient cross reactive IgG leading to false positive serology results for SARS-CoV-2. IgG antibody levels against SARS-CoV-2 should therefore be monitored.

Conclusions and policy implications

Our study documents an outbreak of Kawasaki-like multisystem inflammatory syndrome in children and adolescents in the Paris area and its association with recent SARS-CoV-2 infection. Further studies are needed to explore potential causality. The patients reported here had characteristics that differ from those of patients with classic Kawasaki disease (table 4): this present form seems to be more common among children of African ancestry, with predominant acute gastrointestinal symptoms, haemodynamic instability, and myocarditis. These clinical findings should prompt high vigilance among primary care and emergency doctors, and preparedness during the covid-19 pandemic in countries with a high proportion of children of African ancestry.

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Data sharing: Code for all the analyses as well as the anonymised database will be made available on reasonable request.

Dissemination to participants and related patient and public communities: We immediately disseminated the work by prepublishing in MedRxiv. We sent the manuscript to some members of the French public health authorities, and The BMJ editorial team sent our findings to the World Health Organization during the reviewing process. WHO and the French public health authorities might, at their discretion, share this further with population groups.

The manuscript's guarantor (MC) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For persons who are exposed, the standard of care is observation and quarantine. Whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure is unknown.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis. We enrolled adults who had household or occupational exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Within 4 days after exposure, we randomly assigned participants to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days). The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days.

RESULTS

We enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was –2.4 percentage points (95% confidence interval, –7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

CONCLUSIONS

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. (Funded by David Baszucki and Jan Ellison Baszucki and others; ClinicalTrials.gov number, NCT04308668.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the global, rapidly emerging virus causing coronavirus disease 2019 (Covid-19).[1] The current public health strategies to mitigate transmission are rapid identification of cases, isolation, contact tracing, and self-quarantine of those exposed. Once a person is exposed, observation and quarantine during a 14-day incubation period is the standard of care. To date, no medication has been shown to prevent SARS-CoV-2 transmission.

Both chloroquine and the derivative molecule hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2.[2,3] Hydroxychloroquine is thought to impair the terminal glycosylation of the angiotensin-converting–enzyme 2 (ACE2) receptor, which is the binding site for the envelope spike glycoprotein and has been shown to inhibit endolysosome function.[2,4] In addition, hydroxychloroquine may have greater in vitro activity against SARS-CoV-2 than chloroquine.[3]

The majority of clinical studies of chloroquine or hydroxychloroquine for Covid-19 have focused on hospitalized patients.[5-8] Yet, to alter the trajectory of the epidemic, it is necessary to break the chain of transmission. The risk of secondary household transmission has been estimated as 10 to 15%.[9,10] Small, nonrandomized, noncontrolled cohort studies have suggested that the use of hydroxychloroquine might reduce or even eliminate this risk.[11] Whether short-term high-dose hydroxychloroquine can prevent disease soon after a high-risk exposure remains unknown. We hypothesized that hydroxychloroquine could potentially be used as postexposure prophylaxis, to prevent symptomatic infection after exposure to Covid-19.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a randomized, double-blind, placebo-controlled trial to evaluate postexposure prophylaxis with hydroxychloroquine after exposure to Covid-19.[12] We randomly assigned participants in a 1:1 ratio to receive either hydroxychloroquine or placebo. Participants had known exposure (by participant report) to a person with laboratory-confirmed Covid-19, whether as a household contact, a health care worker, or a person with other occupational exposures.

Trial enrollment began on March 17, 2020, with an eligibility threshold to enroll within 3 days after exposure; the objective was to intervene before the median incubation period of 5 to 6 days. Because of limited access to prompt testing, health care workers could initially be enrolled on the basis of presumptive high-risk exposure to patients with pending tests; however, on March 23, eligibility was changed to exposure to a person with a positive polymerase-chain-reaction (PCR) assay for SARS-CoV-2, with the eligibility window extended to within 4 days after exposure.

This trial was approved by the institutional review board at the University of Minnesota and conducted under a Food and Drug Administration Investigational New Drug application. In Canada, the trial was approved by Health Canada; ethics approvals were obtained from the Research Institute of the McGill University Health Centre, the University of Manitoba, and the University of Alberta.

PARTICIPANTS

We included participants who had household or occupational exposure to a person with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Participants were excluded if they were younger than 18 years of age, were hospitalized, or met other exclusion criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Persons with symptoms of Covid-19 or with PCR-proven SARS-CoV-2 infection were excluded from this prevention trial but were separately enrolled in a companion clinical trial to treat early infection.

SETTING

Recruitment was performed primarily with the use of social media outreach as well as traditional media platforms. Participants were enrolled nationwide in the United States and in the Canadian provinces of Quebec, Manitoba, and Alberta. Participants enrolled themselves through a secure Internet-based survey using the Research Electronic Data Capture (REDCap) system.[13] After participants read the consent form, their comprehension of its contents was assessed; participants provided a digitally captured signature to indicate informed consent. We sent follow-up e-mail surveys on days 1, 5, 10, and 14. A survey at 4 to

6 weeks asked about any follow-up testing, illness, or hospitalizations. Participants who did not respond to follow-up surveys received text messages, e-mails, telephone calls, or a combination of these to ascertain their outcomes. When these methods were unsuccessful, the emergency contact provided by the enrollee was contacted to determine the participant's illness and vital status. When all communication methods were exhausted, Internet searches for obituaries were performed to ascertain vital status.

INTERVENTIONS

Randomization occurred at research pharmacies in Minneapolis and Montreal. The trial statisticians generated a permuted-block randomization sequence using variably sized blocks of 2, 4, or 8, with stratification according to country. A research pharmacist sequentially assigned participants. The assignments were concealed from investigators and participants; only pharmacies had access to the randomization sequence.

Hydroxychloroquine sulfate or placebo was dispensed and shipped overnight to participants by commercial courier. The dosing regimen for hydroxychloroquine was 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total). If participants had gastrointestinal upset, they were advised to divide the daily dose into two or three doses. We chose this hydroxychloroquine dosing regimen on the basis of pharmacokinetic simulations to achieve plasma concentrations above the SARS-CoV-2 in vitro half maximal effective concentration for 14 days.[14] Placebo folate tablets, which were similar in appearance to the hydroxychloroquine tablets, were prescribed as an identical regimen for the control group. Rising Pharmaceuticals provided a donation of hydroxychloroquine, and some hydroxychloroquine was purchased.

OUTCOMES

The primary outcome was prespecified as symptomatic illness confirmed by a positive molecular assay or, if testing was unavailable, Covid-19–related symptoms. We assumed that health care workers would have access to Covid-19 testing if symptomatic; however, access to testing was limited throughout the trial period. Covid-19–related symptoms were based on U.S. Council for State and Territorial Epidemiologists criteria for confirmed cases (positivity for SARS-Cov-2 on PCR assay), probable cases (the presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders), and possible cases (the presence of one or more compatible symptoms, which could include diarrhea).[15] All the participants had epidemiologic linkage,[15] per trial eligibility criteria. Four infectious disease physicians who were unaware of the trial-group assignments reviewed symptomatic participants to generate a consensus with respect to whether their condition met the case definition.[15]

Secondary outcomes included the incidence of hospitalization for Covid-19 or death, the incidence of PCR-confirmed SARS-CoV-2 infection, the incidence of Covid-19 symptoms, the incidence of discontinuation of the trial intervention owing to any cause, and the severity of symptoms (if any) at days 5 and 14 according to a visual analogue scale (scores ranged from 0 [no symptoms] to 10 [severe symptoms]). Data on adverse events were also collected with directed questioning for common side effects along with open-ended free text. Outcome data were measured within 14 days after trial enrollment. Outcome data including PCR testing results, possible Covid-19–related symptoms, adherence to the trial intervention, side effects, and hospitalizations were all collected through participant report. Details of trial conduct are provided in the protocol and statistical analysis plan, available at NEJM.org.

SAMPLE SIZE

We anticipated that illness compatible with Covid-19 would develop in 10% of close contacts exposed to Covid-19.[9] Using Fisher's exact method with a 50% relative effect size to reduce new symptomatic infections, a two-sided alpha of 0.05, and 90% power, we estimated that 621 persons would need to be enrolled in each group. With a pragmatic, Internet-based, self-referral recruitment strategy, we planned for a 20% incidence of attrition by increasing the sample size to 750 participants per group. We specified a priori that participants who were already symptomatic on day 1 before receiving hydroxychloroquine or placebo would be excluded from the prophylaxis trial and would instead be separately enrolled in the companion symptomatic treatment trial.

Because the estimates for both incident symptomatic Covid-19 after an exposure and loss to follow-up were relatively unknown in early March 2020,[9] the protocol prespecified a sample-size reestimation at the second interim analysis. This reestimation, which used the incidence of new infections in the placebo group and the observed percentage of participants lost to follow-up, was aimed at maintaining the ability to detect an effect size of a 50% relative reduction in new symptomatic infections.

INTERIM ANALYSES

An independent data and safety monitoring board externally reviewed the data after 25% and 50% of the participants had completed 14 days of follow-up. Stopping guidelines were provided to the data and safety monitoring board with the use of a Lan–DeMets spending function analogue of the O'Brien–Fleming boundaries for the primary outcome. A conditional power analysis was performed at the second and third interim analysis with the option of early stopping for futility. At the second interim analysis on April 22, 2020, the sample size was reduced to 956 participants who could be evaluated with 90% power on the basis of the higher-than-expected event rate of infections in the control group. At the third interim analysis on May 6, the trial was halted on the basis of a conditional power of less than 1%, since it was deemed futile to continue.

STATISTICAL ANALYSIS

We assessed the incidence of Covid-19 disease by day 14 with Fisher's exact test. Secondary outcomes with respect to percentage of patients were also compared with Fisher's exact test. Among participants in whom incident illness compatible with Covid-19 developed, we summarized the symptom severity score at day 14 with the median and interquartile range and assessed the distributions with a Kruskal–Wallis test. We conducted all analyses with SAS software, version 9.4 (SAS Institute), according to the intention-to-treat principle, with two-sided type I error with an alpha of 0.05. For participants with missing outcome data, we conducted a sensitivity analysis with their outcomes excluded or included as an event. Subgroups that were specified a priori included type of contact (household vs. health care), days from exposure to enrollment, age, and sex.

RESULTS

PARTICIPANTS

We recruited 821 asymptomatic adult participants who were randomly assigned to the hydroxychloroquine group (414 participants) or the placebo group (407 participants) (Fig. 1). The demographic and clinical characteristics of the participants are provided in Table 1. The median age was 40 years (interquartile range, 33 to 50). Women accounted for 51.6% of the trial participants (424 of 821). A total of 27.4% of the participants (225 of 821) reported chronic health conditions, with hypertension being the most common (99 of 821 [12.1%]), followed by asthma (62 of 821 [7.6%]). Health care workers accounted for 66.4% of the participants (545 of 821), the majority being physicians or physician assistants (342 of 545 [62.8%]) and nurses or nursing assistants (128 of 545 [23.5%]). In the case of health care workers, exposure was predominantly from patients (418 of 545 [76.7%]) or ill coworkers (107 of 545 [19.6%]). Among the 29.8% of the participants (245 of 821) who enrolled as a household contact, the majority reported that their Covid-19 contact exposure was either a spouse or partner (114 of 245 [46.5%]) or a parent (43 of 245 [17.6%]).

Overall, 87.6% of the participants (719 of 821) had high-risk exposures without eye shields and surgical masks or respirators. Of those, 365 received hydroxychloroquine and 354 received placebo. Approximately 60% of the participants reported not wearing any element of personal protective equipment during their Covid-19 exposure.

PRIMARY OUTCOME

Overall, new Covid-19 (either PCR-confirmed or symptomatically compatible) developed in 107 of 821 participants (13.0%) during the 14 days of follow-up (Table 2). The incidence of new illness compatible with Covid-19 did not differ significantly between those receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]) (P=0.35). The absolute difference was –2.4 percentage points (95% confidence interval, –7.0 to 2.2). Figure 2 shows the development of Covid-19 over time. Two hospitalizations were reported (one in each group). No arrhythmias or deaths occurred. There was no meaningful difference in effectiveness according

to the time of starting postexposure prophylaxis or in any of the prespecified subgroups (Fig. S1 in the Supplementary Appendix). Overall, 10.7% of the participants (46 in the hydroxychloroquine group and 42 in the placebo group) did not complete the day 14 survey; among these participants, vital status was unknown for 36 in the hydroxychloroquine group and 33 in the control group. In sensitivity analyses, exclusion of these persons from the denominator or inclusion of them as having had an event did not affect the trial conclusions (Table S1).

Of 113 persons in whom symptomatic illness developed, 16 had PCR-confirmed disease, 74 had illness that was compatible with probable Covid-19 per the U.S. case definition, 13 had possible Covid-19 with compatible symptoms and epidemiologic linkage, and 10 were adjudicated as not having Covid-19 on the basis of the symptom complex (Table S2). Four additional participants had positive PCR tests and were asymptomatic during the 14-day trial period; symptoms eventually developed in 3 of these participants. The median number of symptoms was 4 (interquartile range, 2 to 5) among participants with Covid-19. The most frequent symptoms were cough (44.9% of the 107 participants with Covid-19), fever (34.6%), shortness of breath (18.7%), fatigue (49.5%), sore throat (40.2%), myalgia (37.4%), and anosmia (23.4%). Among participants who were symptomatic at day 14, the median symptom-severity score (on a scale from 0 to 10, with higher scores indicating greater severity) was 2.8 (interquartile range, 1.6 to 5.0) in those receiving hydroxychloroquine and 2.7 (interquartile range, 1.4 to 4.8) in those receiving placebo (P=0.34).

ADHERENCE AND SAFETY

Adherence among the trial participants was moderate. Full adherence to the trial intervention differed according to trial group, with 75.4% of participants in the hydroxychloroquine group (312 of 414) and 82.6% of those in the placebo group (336 of 407) having taken all 19 prescribed tablets over a period of 5 days (P=0.01). The most common reason that participants stopped taking the assigned hydroxychloroquine or placebo was side effects (17 participants in the hydroxychloroquine group and 8 in the placebo group). Side effects were more frequent with hydroxychloroquine than with placebo (Table 3). Among the

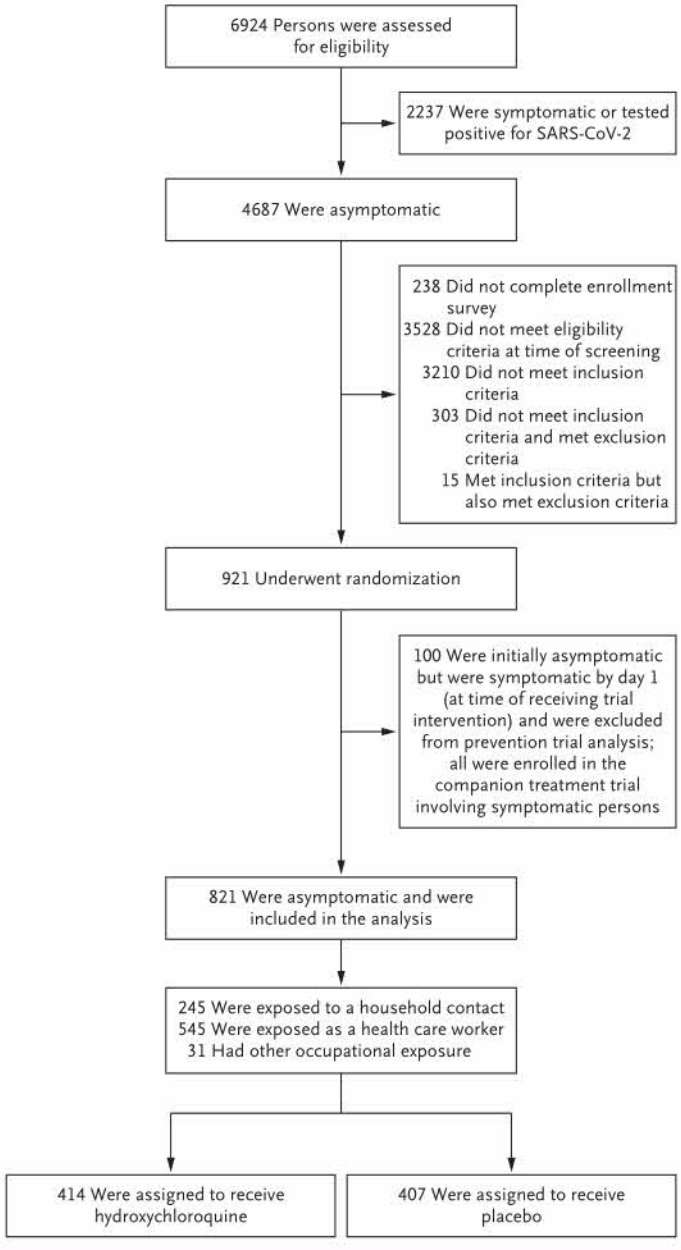

Figure 1. Screening and Randomization.

Of the 821 participants who underwent randomization, 96 did not complete the day 14 follow-up survey, of whom 8 formally withdrew from the trial (4 in each group). Investigators confirmed the vital status and lack of infection in 19 participants (10 in the hydroxychloroquine group and 9 in the control group); 17 completed some follow-up surveys without symptoms before being lost to follow-up (13 in the hydroxychloroquine group and 4 in the control group). A total of 52 participants never completed any surveys after enrollment and did not respond to investigators e-mails, text messages, or telephone calls (23 in the hydroxychloroquine group and 29 in the control group). SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Hydroxychloroquine (N=414)	Placebo (N=407)
Median age (IQR) — yr	41 (33–51)	40 (32–50)
Median weight (IQR) — kg	75 (64–86)	76 (64–91)
Female sex — no. (%)†	218 (52.7)	206 (50.6)
Current smoker — no. (%)	15 (3.6)	12 (2.9)
Health care worker — no. (%)	275 (66.4)	270 (66.3)
High-risk exposure — no. (%)‡	365 (88.2)	354 (87.0)
No PPE worn — no. (%)	258 (62.3)	237 (58.2)
Time from exposure to enrollment — no./total no. (%)		
1 day	77/413 (18.6)	63/407 (15.5)
2 days	100/413 (24.2)	106/407 (26.0)
3 days	98/413 (23.7)	117/407 (28.7)
4 days	138/413 (33.4)	121/407 (29.7)
Coexisting conditions — no. (%)		
None	306 (73.9)	290 (71.3)
Hypertension	51 (12.3)	48 (11.8)
Asthma	31 (7.5)	31 (7.6)
Diabetes	12 (2.9)	16 (3.9)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and PPE personal protective equipment.
† A total of 0.2% of the women (1 of 424) were pregnant and 1.4% (6 of 424) were breast-feeding at the time of enrollment. One woman (0.2%) reported new pregnancy at day 14.
‡ High-risk exposure was defined as exposure to a person with confirmed coronavirus disease 2019 (Covid-19) at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield.

participants who took any hydroxychloroquine, 40.1% (140 of 349) reported a side effect by day 5, as compared with 16.8% (59 of 351) receiving placebo (P<0.001). Nausea, loose stools, and abdominal discomfort were the most common side effects. There were no serious intervention-related adverse reactions or cardiac arrhythmias.

On day 14, we assessed how well the masking of the trial interventions was maintained. Of the 344 participants in the hydroxychloroquine group who completed the day 14 survey question, 160 (46.5%) correctly identified that they received hydroxychloroquine, 151 (43.9%) were unsure, and 33 (10%) believed that they received placebo. Of the 353 participants in the control group who completed the day 14 survey question, 126 (35.7%) correctly identified that they received placebo, 168 (47.6%) were unsure, and 59 (16.7%) believed that they received hydroxychloroquine. Participants who reported any side effect (regardless of trial group) at day 5 were 3.7 times as likely to believe that they received hydroxychloroquine as participants who did not report side effects (122 of 179 participants [68.2%] reporting side effects and 94 of 504 participants [18.7%] not reporting side effects; P<0.001). In the absence of side effects, blinding was well maintained.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, we investigated the efficacy of hydroxychloroquine as Covid-19 postexposure

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

* Symptoms were adjudicated by four infectious disease physicians, who were unaware of the trial-group assignments, in accordance with U.S. Council of State and Territorial Epidemiologists case definition of probable Covid-19 after an epidemiologic link with a close contact.[15] (Descriptions of the symptom complex are provided in the Supplementary Appendix.) The median number of new symptoms reported in the hydroxychloroquine group was 4 (interquartile range, 2 to 6), as compared with 3 (interquartile range, 2 to 5) in the placebo group.

prophylaxis. In this trial, high doses of hydroxychloroquine did not prevent illness compatible with Covid-19 when initiated within 4 days after a high-risk or moderate-risk exposure.

We used a pragmatic approach to recruitment and follow-up of participants through Internet-based self-referral and online follow-up surveys, and we couriered the trial interventions directly to participants' homes. This approach allowed for recruitment across North America, minimized the risk of SARS-CoV-2 infection to researchers, lowered the burden of research participation, and provided a timely answer to this question of whether postexposure prophylaxis was effective. Moreover, this approach allowed broad geographic participation regardless of anyone's physical distance from academic centers, increasing the generalizability of the findings. One result of our approach was that enrolled participants were generally younger and healthier than those at risk for severe Covid-19. Although the risk of severe Covid-19 is related to age and coexisting conditions,[16] the risk of acquiring symptomatic infection is generally still present among adults, regardless of age. Although PCR or serologic testing for asymptomatic infection would have added to the scientific strength of this trial, this was not possible, and we cannot assess an effect on mild or asymptomatic infections. Although a marginal possible benefit from prophylaxis in a more at-risk group cannot be ruled out, the potential risks that are associated with hydroxychloroquine may also be increased in more at-risk populations, and this may essentially negate any benefits that were not shown in this large trial involving younger, healthier participants.

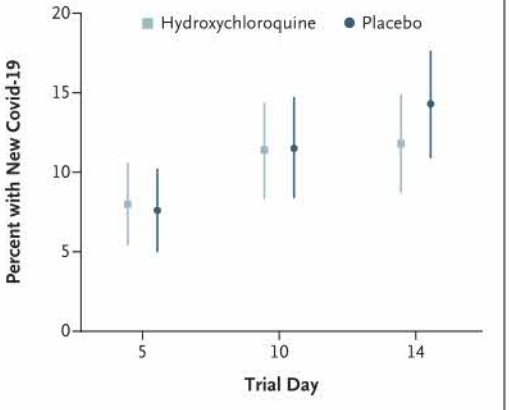

Figure 2. Cumulative Incidence of Illness Compatible with Coronavirus Disease (Covid-19).

The cumulative incidence of illness compatible with Covid-19 was 11.8% in the hydroxychloroquine group (49 of 414 participants) and 14.3% in the placebo group (58 of 407) (P=0.35). The difference equates to a number needed to treat to prevent one infection of 42 persons (lower boundary of the 95% confidence interval for the number needed to treat to prevent one infection, 14 persons; upper boundary of the 95% confidence interval for the number needed to treat to harm 1 person, 50 persons). When we excluded participants who were lost to follow-up, who withdrew, or who were not fully adherent to the trial intervention, the results were similar. When we excluded 13 persons with possible Covid-19 cases who had only one symptom compatible with Covid-19 and no laboratory confirmation, the incidence of new Covid-19 still did not differ significantly between the two groups: 10.4% in the hydroxychloroquine group (43 of 414 participants) and 12.5% in the placebo group (51 of 407) (P=0.38). The vertical bars represent 95% confidence intervals. (Details on symptoms and the adjudication of cases are provided in the Supplementary Appendix.)

We acknowledge that this trial has limitations. Because of the lack of availability of diagnostic testing in the United States, the vast majority of the participants, including health care workers, were unable to access testing. Thus, an a priori symptomatic case definition was used — the U.S. clinical case definition of probable Covid-19.[15] This trial represents real-world implementation after exposure. In the context of a randomized trial design, any non–SARS-CoV-2 viral infection (e.g., influenza, adenovirus, or rhinovirus) should be equally distributed in the trial groups. Owing to the Internet-based approach used to rapidly recruit participants in the context of a pandemic, data were obtained by means of participant report. The types and frequency of symptoms that were observed are similar to those in previous studies involving U.S. health care providers.[17] The U.S. case definition is how probable Covid-19 cases are nationally reportable.[15,18] However, the predictive power of this case definition is unknown, particularly in the younger populations that we studied; given the small number of PCR tests, it remains theoretically possible that hydroxychloroquine therapy limits proven infection. Reproduction of our results in other, ongoing trials would confirm our findings.

This randomized trial did not demonstrate a significant benefit of hydroxychloroquine as postexposure prophylaxis for Covid-19. Whether pre-

Table 3. Participant-Reported Adherence and Side Effects.*

Variable	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
Reported taking any assigned hydroxychloroquine or placebo — no. (%)	349 (84.3)	351 (86.2)	
Reported 100% adherence to trial intervention — no. (%)	312 (75.4)	336 (82.6)	0.01
Reasons that participants did not take all the assigned hydroxychloroquine or placebo — no. (%)			
Side effects	17 (4.1)	8 (2.0)	
Advised to not take hydroxychloroquine	6 (1.4)	2 (0.5)	
Intervention not received from courier	9 (2.2)	2 (0.5)	
Took nontrial hydroxychloroquine	4 (1.0)	0	
Felt no longer at risk	5 (1.2)	3 (0.7)	
Other reason	12 (2.9)	10 (2.5)	
Side effects in participants who started trial intervention — no./total no. (%)			
Any	140/349 (40.1)	59/351 (16.8)	<0.001
Nausea or upset stomach	80/349 (22.9)	27/351 (7.7)	
Diarrhea, abdominal discomfort, or vomiting	81/349 (23.2)	15/351 (4.3)	
Neurologic reaction: irritability, dizziness, or vertigo	19/349 (5.4)	13/351 (3.7)	
Headache	13/349 (3.7)	8/351 (2.3)	
Tinnitus	8/349 (2.3)	3/351 (0.9)	
Visual changes	3/349 (0.9)	0/351	
Skin reaction	4/349 (1.1)	2/351 (0.6)	
Allergic reaction	1/349 (0.3)	1/351 (0.3)	
Fatigue	1/349 (0.3)	1/351 (0.3)	
Taste change or dry mouth	3/349 (0.9)	2/351 (0.6)	
Hot flashes, night sweats, or palpitations	0/349	1/351 (0.3)	

* Values are through day 5, the date of the scheduled completion of the trial intervention. More than one side effect could occur. Ongoing side effects were reported by approximately 3% of the participants in the hydroxychloroquine group at days 10 and 14 and by less than 1% of those in the placebo group. There was no association between the occurrence of side effects and the incidence of Covid-19. Among participants in whom Covid-19 developed, 30.0% (30 of 100) reported a side effect, as compared with 28.2% (169 of 600) reporting a side effect in whom Covid-19 did not develop (P=0.72).

exposure prophylaxis would be effective in high-risk populations is a separate question, with trials ongoing. In order to end the pandemic, a reduction in community transmission is needed.

Supported by David Baszucki and Jan Ellison Baszucki, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, and the University of Minnesota. Ms. Pastick and Ms. Okafor are supported by the Doris Duke Charitable Foundation through a grant supporting the Doris Duke International Clinical Research Fellows Program at the University of Minnesota. Drs. Nicol, Rajasingham, and Pullen are supported by the National Institute of Allergy and Infectious Diseases (K08AI134262, K23AI138851, T32AI055433). Dr. Lofgren is supported by the National Institute of Mental Health (K23MH121220). Dr. Skipper is supported by the Fogarty International Center (D43TW009345). Drs. Lee and McDonald receive salary support from Fonds de Recherche du Québec–Santé. Dr. Zarychanski receives research support as the Lyonel G. Israels Professor of Hematology at the University of Manitoba. In Quebec, funds were received from the Clinical Practice Assessment Unit of the McGill University Health Centre and the McGill Interdisciplinary Initiative in Infection and Immunity Emergency Covid-19 Research Funding Program. In Manitoba, research support was received from the Manitoba Medical Service Foundation and Research Manitoba. In Alberta, the trial was funded by the Northern Alberta Clinical Trials and Research Centre Covid-19 Clinical Research Grant. Purolator Canada provided in-kind courier support for the participating Canadian sites. The REDCap software was supported by the National Institutes of Health National Center for Advancing Translational Sciences (grant UL1TR002494).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants who consented to participate in this randomized trial; the members of the data and safety monitoring board (Drs. George Thompson III, Andrej Spec, Tom Chiller, and Bozena Morawski) for their thoughtful, generous service; and Drs. Jakub Tolar, Alexis Turgeon, Brad Benson, Tim Schacker, and Peter Igarashi for institutional support. Dr. Boulware thanks Drs. Paul Bohjanen and Ed Janoff for their mentorship.

APPENDIX

The authors' full names and academic degrees are as follows: David R. Boulware, M.D., M.P.H., Matthew F. Pullen, M.D., Ananta S. Bangdiwala, M.S., Katelyn A. Pastick, B.Sc., Sarah M. Lofgren, M.D., Elizabeth C. Okafor, B.Sc., Caleb P. Skipper, M.D., Alanna A. Nascene, B.A., Melanie R. Nicol, Pharm.D., Ph.D., Mahsa Abassi, D.O., M.P.H., Nicole W. Engen, M.S., Matthew P. Cheng, M.D., Derek LaBar, Pharm.D., Sylvain A. Lother, M.D., Lauren J. MacKenzie, M.D., M.P.H., Glen Drobot, M.D., Nicole Marten, R.N., Ryan Zarychanski, M.D., Lauren E. Kelly, Ph.D., Ilan S. Schwartz, M.D., Ph.D., Emily G. McDonald, M.D., Radha Rajasingham, M.D., Todd C. Lee, M.D., M.P.H., and Kathy H. Hullsiek, Ph.D.

The authors' affiliations are as follows: the University of Minnesota (D.R.B., M.F.P., A.S.B., K.A.P., S.M.L., E.C.O., C.P.S., A.A.N., M.R.N., M.A., N.W.E., R.R., K.H.H.) and M Health Fairview Investigational Drug Service Pharmacy (D.L.), Minneapolis; and the Research Institute of the McGill University Health Centre and the Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montreal (M.P.C., E.G.M., T.C.L.), the Department of Internal Medicine, University of Manitoba (S.A.L., L.J.M., G.D., N.M., R.Z.), the Research Institute in Oncology and Hematology, CancerCare Manitoba, University of Manitoba (R.Z.), and the George and Fay Yee Centre for Healthcare Innovation (L.E.K.), Winnipeg, and the University of Alberta, Edmonton (I.S.S.) — all in Canada.

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From: Datta, Deblina (CDC/DDPHSIS/CGH/GID)
Sent: Thu, 20 Aug 2020 01:32:48 +0000
To: De Perio, Marie A. (CDC/NIOSH/OD); Raizes, Elliot (CDC/DDPHSIS/CGH/DGHT); Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Cc: Iskander, John (CDC/DDPHSS/OS/OD)
Subject: appreciate if you give your inputs on the Hot Topics slides, v short but impactful
Attachments: HotTopicsMichaelMelgar_2020.08.19.DDedits.pptx

Take a look in Notes view, pay special attention to slide 10 notes which is the main point of the presentation.

These were my feedback notes to John/Michael so not final yet, but v close.

Kind thanks.

S. Deblina Datta, MD FIDSA (she/her)
CAPT, USPHS
On temporary assignment to:
Lead, Clinical Team
Health Systems and Worker Safety Task Force
COVID 19 Emergency Operations Center (EOC)
Centers for Disease Control and Prevention, Atlanta, GA

A Proposed Framework for Three Clinical Syndromes over the Time Course of SARS CoV-2 Infection

Hot Topics Meeting

Michael Melgar, MD & John Iskander, MD, MPH

Friday, 21 August 2020

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Page 0310

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From: Oster, Matt (CDC/DDNID/NCBDDD/DBDID)
Sent: Fri, 11 Sep 2020 18:06:48 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Subject: FW: myocarditis in athletes after COVID
Attachments: Rajpal - Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection - 2020.pdf

I'm sure your team is all over this, but here's the article just published on myocarditis in athletes.

Matthew Oster, MD, MPH
CDC COVID-19 MIS-C Working Group, HSWS Clinical Team Special Investigations Unit
CDC Center on Birth Defects and Developmental Disabilities
Pediatric Cardiologist, Sibley Heart Center, Children's Healthcare of Atlanta
Emory University School of Medicine | Emory University Rollins School of Public Health
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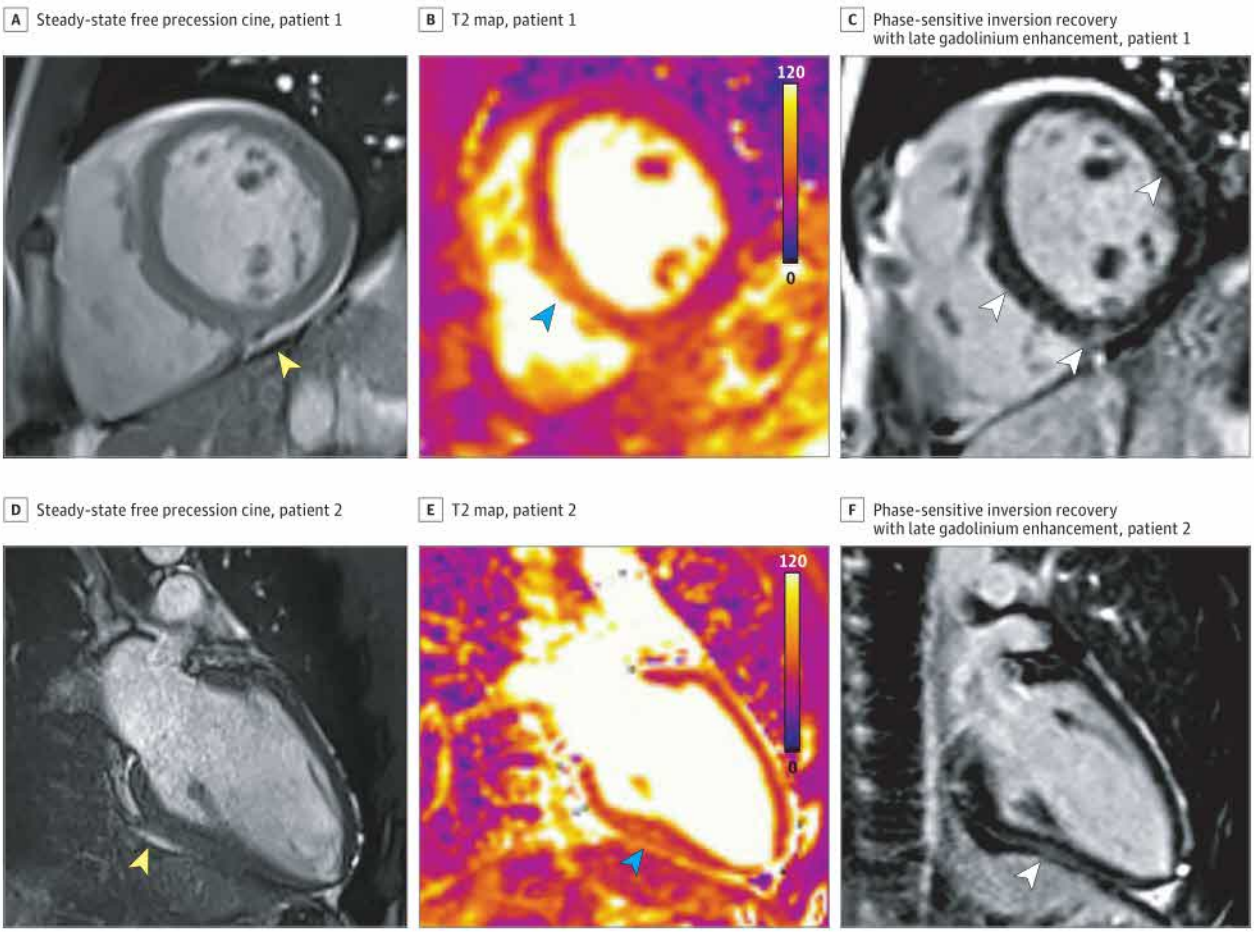
RESEARCH LETTER

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Myocarditis is a significant cause of sudden cardiac death in competitive athletes and can occur with normal ventricular function.[1] Recent studies have raised concerns of myocardial inflammation after recovery from coronavirus disease 2019 (COVID-19), even in asymptomatic or mildly symptomatic patients.[2] Our objective was to investigate the use of cardiac magnetic resonance (CMR) imaging in competitive athletes recovered from COVID-19 to detect myocardial inflammation that would identify high-risk athletes for return to competitive play.

Methods | We performed a comprehensive CMR examination including cine, T1 and T2 mapping, extracellular volume fraction, and late gadolinium enhancement (LGE), on a 1.5-T scanner (Magnetom Sola; Siemens Healthineers) using standardized protocols,[3] in all competitive athletes referred to the sports medicine clinic after testing positive for COVID-19 (reverse transcriptase–polymerase chain reaction) between June and August 2020. The Ohio State University institutional review board approved the study, and informed consent in writing was obtained from participating athletes. Cardiac magnetic resonance imaging was performed after recommended quarantine (11-53 days). Electrocardiogram, serum troponin I, and transthoracic echocardiogram were performed on day of CMR imaging.

Figure. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From Coronavirus Disease 2019 Infection



A, Cine mid short-axis images showing pericardial effusion indicated by yellow arrowhead. B, T2 map with color overlay mid short-axis showing myocardial edema (elevated T2, 61 milliseconds) indicated by blue arrowhead. C, Short-axis view showing late gadolinium enhancement in the mid inferoseptum, right ventricular insertion point, and mid anterolateral wall indicated by white arrowheads. D, Cine 2-chamber long-axis view showing pericardial effusion indicated by yellow arrowhead. E, T2 map with color overlay myocardial edema (elevated T2, 58 milliseconds) indicated by blue arrowhead. F, Right 2-chamber long-axis view showing epicardial late gadolinium enhancement in the inferior wall indicated by white arrowhead.

Table. Demographic Features and Echocardiographic and Cardiovascular Magnetic Resonance Parameters in Competitive Athletes Recovering From Coronavirus Disease 2019[a]

Athlete No.	Sex	Symptoms	Time CMR performed after positive test result, d	Echocardiography, mL/m^2		CMR, %		Native T1, ms	ECV, %	Maximal T2, ms, (AHA segments)	LGE (pattern/AHA segments)	CMR (updated Lake Louise Criteria)
				LVEDV	RVEDV	LVEF	RVEF					
1	Male	No	21	Not done	Not done	60	49	1034	21	51 (9)	Yes (RV insertion; 9)	Normal
2	Male	No	22	51	46	56	59	964	24	48 (9)	Yes (patchy; 6, 8)	Normal
3	Male	No	22	65	60	60	64	953	22	48 (10)	Yes (patchy, 5)	Normal
4	Male	No	15	65	48	59	54	905	20	48 (9)	Yes (linear; 8, 12)	Normal
5	Male	No	17	66	57	55	54	994	24	55 (9)	Yes (epicardial; 3, 9)	Myocarditis
6	Male	Yes	23	73	52	61	62	947	26	63 (3, 9)	Yes (patchy; 3, 9)	Myocarditis
7	Male	Yes	53	66	64	53	52	991	25	49 (7, 9)	Yes (linear, patchy; 8, 9, 12)	Normal
8	Male	No	20	76	36	56	53	963	17	51 (10)	No	Normal
9	Male	Yes	18	60	71	56	52	964	24	52 (7)	Yes (patchy; 3, 9)	Normal
10	Male	Yes	11	67	70	61	58	929	25	58 (8, 9)	Yes (patchy; 2, 3, 8, 9)	Myocarditis
11	Male	No	23	57	49	63	60	987	22	53 (7)	No	Normal
12	Male	Yes	28	72	59	50	53	966	28	53 (7, 8)	No	Normal
13	Male	No	28	81	52	33	53	925	25	53 (7, 8)	No	Normal
14	Male	No	11	46	41	65	54	989	24	53 (8)	No	Normal
15	Male	No	48	56	51	59	57	1003	25	53 (7)	Yes (RV insertion; 9)	Normal
16	Female	Yes	23	68	50	64	58	1001	26	52 (8)	No	Normal
17	Female	Yes	23	55	56	57	60	1030	28	48 (10)	No	Normal
18	Female	No	21	53	35	65	66	1008	25	48 (9)	No	Normal
19	Female	Yes	17	60	32	63	57	978	26	53 (8)	No	Normal
20	Female	No	31	62	51	58	59	1002	25	52 (8)	No	Normal
21	Female	Yes	31	52	40	60	60	946	28	53 (8)	No	Normal
22	Female	Yes	30	67	49	59	64	1000	27	52 (8)	Yes (linear; 12)	Normal
23	Female	Yes	30	58	57	57	55	964	26	53 (11)	No	Normal
24	Female	Yes	26	52	49	55	57	1010	30	53 (10)	No	Normal
25	Female	No	31	56	36	56	56	1027	28	50 (7)	No	Normal
26	Male	No	12	80	44	60	53	969	21	61 (8)	Yes (linear; 8, 9)	Myocarditis

Abbreviations: AHA, American Heart Association; CMR, cardiovascular magnetic resonance imaging; ECV, extracellular volume fraction; EDV, end-diastolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular.

[a] Symptoms refer to symptoms during short-term infection. Echo volumes were calculated by 3-dimensional method. Cardiovascular magnetic resonance imaging–derived left and right ventricular volumes and function were measured from contiguous short-axis cine images using semiautomated software for endocardial segmentation using endocardial and epicardial contours at end systole and end diastole per standard protocol. Cardiovascular magnetic resonance imaging–derived myocardial T1 and T2 mapping and ECV were done per standard guidelines. Mean (SD) native T1 less than 999 (31) milliseconds, native T2 of less than 53 milliseconds, and ECV of less than 29% were considered normal per institutional protocol based on phantom and human volunteer experiments. T2 and LGE were only considered significant if seen in 2 orthogonal planes.

Results | We performed CMR imaging in 26 competitive college athletes (mean [SD] age, 19.5 [1.5] years; 15 male [57.7%]) from the following sports: football, soccer, lacrosse, basketball, and track. No athletes required hospitalization or received COVID-19–specific antiviral therapy. Twelve athletes (26.9%; including 7 female individuals) reported mild symptoms during the short-term infection (sore throat, shortness of breath, myalgias, fever), while others were asymptomatic. There were no diagnostic ST/T wave changes on electrocardiogram, and ventricular volumes and function were within the normal range in all athletes by transthoracic echocardiogram and CMR imaging. No athlete had elevated serum levels of troponin I. Four athletes (15%; all male individuals) had CMR findings consistent with myocarditis based on the presence of 2 main features of the updated Lake Louise Criteria: myocardial edema by elevated T2 signal and myocardial injury by presence of nonischemic LGE (**Figure**).[4] Pericardial effusion was present in 2 athletes with CMR evidence of myocarditis. Two of these 4 athletes with evidence of myocardial inflammation had mild symptoms (shortness of breath), while the other 2 were asymptomatic. Twelve athletes (46%) had LGE (mean of 2 American Heart Association segments), of whom 8 (30.8%) had LGE without concomitant T2 elevation (**Table**). Mean (SD) T2 in those with suspected myocarditis was 59 (3) milliseconds compared with 51 (2) milliseconds in those without CMR evidence of myocarditis.

Discussion | Of 26 competitive athletes, 4 (15%) had CMR findings suggestive of myocarditis and 8 additional athletes (30.8%) exhibited LGE without T2 elevation suggestive of prior myocardial injury. COVID-19–related myocardial injury in competitive athletes and sports participation remains unclear. Cardiac magnetic resonance imaging has the potential to identify a high-risk cohort for adverse outcomes and may, importantly, risk stratify athletes for safe participation because CMR mapping techniques have a high negative predictive value to rule out myocarditis.[4] A recent study by Puntmann et al[2] demonstrated cardiac involvement in a significant number of patients who had recovered from COVID-19. A recent expert consensus article recommended 2-week convalescence followed by no diagnostic cardiac testing if asymptomatic and an electrocardiogram and transthoracic echocardiogram in mildly symptomatic athletes with COVID-19 to return to play for competitive sports.[5] However, emerging knowledge and CMR observations question this recommendation. Cardiac magnetic resonance imaging evidence of myocardial inflammation has been associated with poor outcomes, including myocardial dysfunction and mortality.[6] Study limitations include lack of baseline CMR imaging and variable timing of CMR imaging from a positive COVID-19 test result. Athletic cardiac adaptation could be responsible for these abnormalities; however, in this cohort, mean (SD) T2 in those with suspected myocarditis was 59 (3) milliseconds vs 51 (2) milliseconds in those without, favoring pathology. Additionally, the rate of LGE (42%) is higher than in previously described normative populations. To conclude, while long-term follow-up and large studies including control populations are required to understand CMR changes in competitive athletes, CMR may provide an excellent risk-stratification assessment for myocarditis in athletes who have recovered from COVID-19 to guide safe competitive sports participation.

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Author Contributions: Drs Rajpal and Daniels had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Rajpal, Tong, Borchers, Obarski, Simonetti, Daniels.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rajpal, Tong, Simonetti.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Rajpal, Tong, Obarski.
Administrative, technical, or material support: Rajpal, Tong, Zareba, Simonetti, Daniels.
Supervision: Rajpal, Tong, Borchers, Daniels.

Conflict of Interest Disclosures: Dr Simonetti reports grants from Siemens, Myocardial Solutions, and Cook Medical outside the submitted work. No other disclosures were reported.

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From: CDC IMS 2019 NCOV Response Policy Partnerships
Sent: Mon, 4 May 2020 18:55:44 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Cc: CDC IMS 2019 NCOV Response Policy Partnerships; Gunn, Janelle P. (CDC/DDNID/NCCDPHP/DNPAO); CDC IMS 2019 NCOV Response CICP Policy
Subject: Materials for Tomorrow's American Heart Association
Attachments: 05-04-20 CI Special Topic - HYPERTENSION.pdf, American-Heart-Association_JBrooks_QAs_5.5.2020.docx, AHA.COVID.runofshow updated 5.1.20.docx

Hi Dr. Brooks,

Attached are three documents to assist with tomorrow's American Heart Association call.

- **AHA.COVID.runofshow updated 5.1.20:** This is the run of show with notes reflecting the prep call last week.
- **American-Heart-Association_JBrooks_QAs_5.5.2020:** These are an outline of the remarks you mentioned during the prep call and background information on the planned Q&A.
    - Please note, (b)(5) (b)(5)
- **05-04-20 CI Special Topic – HYPERTENSION:** This is a pull of all the hypertension clinical inquiries has received. Warning – it is a lot!

I will update if we hear back with additional details.

Around 1,900 people are already registered and they have bumped up the total capacity to 3,000. The world await Cosmo's cameo.

Best,
Wendy

****

Wendy Ruben
Policy and Partnership Unit
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
eocevent337@cdc.gov

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From: Kamb, Mary (CDC/DDPHSIS/CGH/DPDM)
Sent: Sat, 16 May 2020 04:02:01 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Subject: FW: COVID-19 Infection or Autoimmunity
Attachments: COVID-19 Infection or Autoimmunity 5.15.2020.docx, Transplant Survival 1990 to 2016.pdf, Dr. Icenogle CV 2020.docx

Hi John,

OK, (b)(5)

I'm on call and was referred an inquiry from a cardiothoracic and transplant surgeon in Spokane (formerly director of the transplant program there, I believe it's affiliated with the Univ of Washington).

(b)(5)

(b)(5) so he submitted a paper describing this to an immunology journal.
Today he worried that would be a slow process and decided to share with CDC/NIH in case people here thought the treatment might have merit. I spoke with him earlier this evening and (b)(5)

(b)(5)

Anyway, paper attached (he also sent his CV as he feared we might not take him seriously; he's published a bit).

From: CDC IMS 2019 NCOV Response MCCM Clinical Inquiries <eocevent12@cdc.gov>
Sent: Friday, May 15, 2020 11:26 PM
To: Kamb, Mary (CDC/DDPHSIS/CGH/DPDM) <mlk5@cdc.gov>
Subject: Fw: COVID-19 Infection or Autoimmunity

Clinical Team Inquiries
COVID-19 Response
Medical Care and Countermeasures Task Force
U.S. Centers for Disease Control and Prevention

From: Timothy Icenogle (b)(6)
Sent: Friday, May 15, 2020 11:14 PM
To: CDC IMS 2019 NCOV Response Clinical On-Call Unit <eocevent185@cdc.gov>; CDC IMS 2019 NCOV Response MCCM Clinical Inquiries <eocevent12@cdc.gov>; eocevent@cdc.gov <eocevent@cdc.gov>

Cc: [redacted] [redacted]
Subject: COVID-19 Infection or Autoimmunity

Dr. Kamb,

I wish to thank-you for returning my call to the CDC of May 15, 2020. As per our conversation, I have enclosed a copy of my paper, "COVID-19: Infection or Autoimmunity" that I submitted to Frontiers in Immunology. I did ask Dr. Sally Huber, Professor Emeritus in Pathology, University of Vermont to read the paper before I submitted it to ensure that my immunology material was correct. She conveyed to me that the paper has merit. Unfortunately, Frontiers in Immunology's website states that they have a three month turn around time for papers, which given the current pandemic, is just too long to wait.

I have also enclosed my CV and a Kaplan-Meier survival curve comparing the survival rate of the program that I led for 25 years compared to the international survival rates from the International Society of Heart and Lung Transplantation. I did this to support the understanding that I have had admirable experience treating some of the sickest patients in medicine.

The purpose of the paper is to illustrate that more effective immunosuppressive agents probably exist for COVID-19 than have been tried to date. I review the basic science of viral induced hypersensitivity reactions in relation to viral myocarditis. The literature shows that T cell depleting agents were shown to be effective in stopping the autoimmune reaction and improve survival despite the presence of virus in several murine models. We used this information to justify an IRB approved protocol in the early 1990s to treat fulminant viral myocarditis with lymphocytic infiltrates by endomyocardial biopsy. We reported this experience in 2004. Patients frequently showed clinical improvement within 8 to 12 hours. Later, upon the desire of the IRB, we changed this to an "Art of Medicine" protocol. We did notice that several patients with flaccid hearts had no lymphocytic infiltrates on large left ventricular cores removed during the emergent implantation of cardiac assist devices. This led us to believe that the patients had an antibody mediated attack on the heart and not a T cell mediated attack. We modified the protocol to add rituximab to deplete naïve B cells to keep them from becoming plasmablasts and the combination of RATG and rituximab has been shown to reduce CD 27 bearing lymphocytes, the phenotypic marker of memory B cells, in the human spleen. These medications are not even mentioned in most current guideline recommendations, but once one understands the immunology of viral induced disease, they should understand why corticosteroids, azathioprine, cyclosporine and IVIG are ineffective.

I believe a pilot study using T cell depleting agents and possibly rituximab should be entertained in some patients in the ICU with COVID-19. An antiviral should also be given to shorten the time of viral shedding.

I wish to thank the CDC for their time in reviewing my submission.

Regards,

Tim Icenogle MD

COVID-19:

INFECTION OR AUTOIMMUNITY

Timothy Icenogle MD

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COVID-19:

Infection or Autoimmunity

Abstract

The clinical and laboratory features of COVID-19 are reviewed with attention to the immunologic manifestations of the disease. Recent COVID-19 publications describe myocarditis and a hemophagocytic lymphohistiocytosis like syndrome that suggest an overexuberant autoimmune component of the disease. Yet, the immunosuppressive regimens that have been utilized show little efficacy in COVID-19. Review of the immunology of viral induced Type II and Type IV hypersensitivity reactions reveals why these medications lack efficacy. The disconnect between the immunology literature and clinical understanding is explored. There is potential use of T cell depleting therapies and possibly anti-CD20 therapy for COVID-19 and clinical research using these medications is warranted.

COVID-19: Infection or Autoimmunity

Tim Icenogle MD FACS, FACC, FCCP

INTRODUCTION:

The SARS-CoV-2 virus, as of May 1, 2020, has infected more than 3,278,000 people worldwide and resulted in over 234,000 deaths. It has spread to all continents except Antarctica and continues to spread. Fortunately, most cases are mild and self-resolve. Approximately 14% are classified as severe, (dyspnea, respiratory frequency $\geq$ 30/min, blood arterial oxygenation $\leq$ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or infiltrates > 50% within 24 to 48 hours), and 5% are critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[1] The current US mortality rate is 5.8% percent[2], but roughly double that number become severely ill requiring ICU care.

The clinical features and pathophysiology of this disease are reviewed with attention to the autoimmune features exhibited by myocarditis and an hemophagocytic lymphohistiocytosis like syndrome. Type IV and possibly Type II hypersensitivity autoimmune responses in COVID-19 are compared with the Type IV and Type II responses seen in other viral induced autoimmune diseases. Studies in the immunology literature point to a different pathophysiology than that accepted by most clinicians, explaining the lack of efficacy of the immunosuppressive regimens used to date. The potential use of other therapies based on immunology and clinical research deserve study in COVID-19.

CLINICAL FEATURES AND PATHOPHYSIOLOGY OF COVID-19

The clinical features of the disease and pathophysiology are areas of ongoing study. Pathologic analyses of patients with severe COVID-19 disease and SARS reveal a complex overexuberant inflammatory response.[3,4] ICU patients with COVID- 19 had higher plasma levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα compared to non-ICU patients with COVID-19.[5] COVID-19 patients were noted to have high amounts of IL1B, IFNγ, IP10 and MCP1 probably leading to activated T-helper-1 (Th1) responses. These responses suggest the cytokine storm is associated with disease severity. Sixty- three percent of hospitalized patients had lymphocytopenia in one study,[4] while another study that focused only on ICU

patients documented an 85% incidence of lymphocytopenia.[5] Those authors suggested that severity of the lymphocytopenia reflects the severity of the disease.

In a report of one patient who died, post-mortem biopsies noted that the pulmonary tissue resembled that seen in severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS).[6] Pulmonary findings included ARDS, edema, hyaline membranes, interstitial mononuclear infiltrates, multinucleated syncytial cells with atypical enlarged pneumocytes but no intranuclear or intracytoplasmic viral inclusions were seen. Flow cytometry performed on peripheral blood revealed that counts of CD 4 and CD 8 T cells were substantially reduced, but those present were highly activated as evidenced by high proportions of HLA-DR, (CD3) and CD 28 double fractions present. There was also an increased concentration of CCR6+ and Th17 in the CD4 T cells. CD8 T cells had high concentrations of cytotoxic granules in which 31.6% of cells were perforin positive, 64.2% were granulysin positive and 30.5% were granulysin and perforin double positive. The authors felt the findings implied the overactivation of T cells as manifested by the increase in Th17 and high cytotoxicity of the $CD8^+$ T cells.[6]

A Chinese study of 49 patients admitted to a single institution sought to determine which factors were associated with the progression to severe disease.[7] Univariate analysis revealed that comorbidity, age >50, lymphocyte counts < 1500/μL and serum ferritin > 400 ng/ml were predictive of progression to severe disease. The findings of lymphopenia and hyperferritinemia are suggestive of secondary hemophagocytic lymphohistiocytosis (HLH) which was seen in both SARS and MERS patients. [8,9,10,11,12]

Myocarditis:

Evidence of myocarditis in COVID patients is evident from multiple studies.[4,5,13,14,15,16,17,18,19] Cardiac injury as demonstrated by troponin I levels above the 99th percentile upper reference limit or new echocardiographic or electrocardiography was seen in 12% of severely ill patients demonstrating virus related injury to other organ systems than the lungs.[4] In a study of 416 hospitalized patients with COVID-19, 82 (19.7%) had evidence of myocardial injury evidenced by elevation of high-sensitivity troponin I (TnI) levels.[16] A similar retrospective study of 187 hospitalized patients with COVID-19 disease revealed that 52 (27.8%) had myocardial injury by elevated levels of troponin T (TnT).[17] The patients with cardiac injury had higher rates of mortality and evidenced severe systemic inflammation with increased leukocyte counts, increased levels of C-reactive protein and procalcitonin.

Hemophagocytic Lymphohistiocytosis:

Patients with COVID have been noted to have symptoms of fever, findings of a cytokine storm, and elevated ferritin,[3,4,5,6,7,13] suggestive of hemophagocytic lymphohistiocytosis (HLH). HLH is a syndrome characterized by excessive cytokine production, subsequent immune dysregulation, and tissue damage and may be the result of an inherited disorder of the immune system or may be secondary to infections.[20] Secondary HLH, a form of Type IV Hypersensitivity, is associated with viral syndromes and was first reported by Risdall et al. in 1979.[21] The dysregulated inflammatory response causes fever, hepatomegaly, splenomegaly, cytopenias (affecting one or more of three lineages in the peripheral blood),neutropenia, hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent natural killer (NK)-cell activity, and elevated soluble

CD 25 (interleukin [IL]-2 receptor).[20] Excessive cytokine production, (cytokine storm) by macrophages, NK cells, and cytotoxic T lymphocytes (CTLs) is thought to be the primary mediator of tissue damage.[22,23] A number of viruses have been linked to secondary HLH including avian influenza A subtype H1N1, SARS-CoV, Ebstein Barr, and rotavirus.[24] Secondary HLH is differentiated from primary HLH which is caused by genetic disorders and is more prevalent in children but may be seen in adulthood.

The diagnosis of secondary HLH is made based on both clinical and laboratory findings, none of which by themselves are diagnostic. Five of the following eight findings are considered to be diagnostic of HLH as outlined in the HLH-2004 guidelines:[25,26]

1. Fever $\geq$ 38.5°C
2. Splenomegaly
3. Peripheral Blood cytopenia, with at least two of the following: hemoglobin<9g/dl; platelets < 100,000/microL; absolute neutrophil count < 1000/microL
4. Hypertriglyceridemia (fasting triglycerides>265 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph node or liver
6. Low or absent NK cell activity
7. Ferritin>500ng/mL
8. Elevated soluble CD 25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted lab specific normal

The finding of hemophagocytosis is not necessary to make the diagnosis of HLH. Other findings include a histological picture of chronic persistent hepatitis, decreased fibrinogen, coagulopathies, and elevated levels of cytokines (IFN-γ, IL-10, and IL-6).[20]

It is sometimes difficult to diagnose HLH so a diagnostic score was developed called the HScore.[26] The HScore can be used to estimate an individual's risk of having hemophagocytic syndrome. The scoring system is available online at http://saintantoine.aphp.fr/score/ or in MedCalc®. These diagnostic tools are most often applied to pediatric patients with primary HLH but can be applied to patients with secondary HLH.

Infection versus Autoimmunity:

The overexuberant immune response seen in COVID-19 raises the question as to the pathophysiology of the disease: Is the lethality related to an infection with the SARS-CoV-2 virus or to an uncontrolled autoimmune response induced by the virus. Viruses can induce Type II and Type IV hypersensitivity reactions in addition to a viral cytopathic effect.

Type II hypersensitivity occurs when autoantibodies secondary to the viral infection cause tissue damage. Type IV Hypersensitivity reactions occur when T cells primed to fight the viral infection induce inflammation or directly kill target cells of the host. These reactions can occur even if the virus has little or no cytopathic effect. Findings in patients with COVID-19 are consistent with those Type IV reaction and possibly a Type II reaction.

Immunomodulating therapy should be considered in the treatment regimen. Corticosteroids have been part of the treatment regimen for some patients with COVID-19 despite any real evidence of efficacy. Further study of Type IV and Type II hypersensitivity reactions secondary to viruses reveals that other medications have a higher probability of providing benefit. Examination of the pathophysiology of myocarditis from the immunology literature provides light for potential solutions for the current pandemic. This review will focus on two clinical facets seen in COVID-19: 1. Treatment of myocarditis and 2. hemophagocytic lymphohistiocytosis (HLH) and then propose a change in therapeutic strategy.

Type IV hypersensitivity in myocarditis:

Woodruff first established that T cells have a critical role in the pathogenesis of myocarditis in 1974 using CD1 and Balb/c mice.[27] In the CD-1 mouse, pre-treatment with rabbit anti-thymocyte serum greatly suppressed the inflammation and tissue injury after coxsackie B3 (CVB3) infection. In the Balb/c mouse, deprivation of T cells by lethal irradiation and thymectomy led to a decrease in inflammation, necrosis, and mortality. Viral growth curves in both strains were not different than normal immunologically intact animals, this lead the investigators to conclude that, while the virus may initiate the immune response and even with high titers within the heart, the T cells were the important mediators in the severity of inflammation and tissue injury.

Other investigators expanded on these observations. Huber showed that cytotoxic T cells from DVB3 infected mice would lyse virus infected myocardial cells *in vitro* independent of viral cytopathology.[28] The Huber lab at the University of Vermont later showed that cytotoxic T lymphocytes derived from CVB3 mice were cytotoxic to uninfected Balb/c myocyte monolayers grown in culture. When T cells induce cardiac injury of uninfected cells, myocarditis becomes an autoimmune disease.[29] Additionally, when control DBA/2 and Balb/c mice were infected with CVB3, they developed myocarditis, but if anti-thymocyte serum was administered immediately prior to and after inoculation, then myocarditis was prevented.[30] From these studies and others, T cell depletion therapies seemed most likely to have a reasonable probability for successful treatment of myocarditis.

Treatment of Type IV hypersensitivity manifested by HLH:

Treatment for HLH is often directed to the pediatric patients with primary HLH. These patients have a genetic defect that results in the syndrome and recurs unless the patient receives a stem cell transplant. Supportive therapies prior to transplant include steroids, IVIG, immune cell depletion using etoposide, anti-thymocyte globulin, or alemtuzumab. These therapies have little support for adults with secondary HLH, a form of Type IV hypersensitivity. There is an anecdotal report of a critically ill 31-year old man with secondary HLH due to influenza A/H1N1 who improved with etoposide and steroids in addition to antiviral therapy.[31] The authors emphasize that patients with secondary HLH should be considered for therapy only after they have met the diagnostic guidelines in HLH-2004. The therapy was directed at the HLH and was part of the HLH-94 protocol. The unique approach of this paper to treat a critically ill influenza A/H1NI patient with a powerful cytotoxic regimen aimed at modulating the immune system cannot be understated. The virus initiated a severe autoimmune attack that was successfully treated

with immunotherapy directed at a broad range of immunologically active cells. Treating an infection with powerful immunosuppression is a paradox with medical tradition and understanding.

UNREALIZED TREATMENT OPPORTUNITIES FOR COVID-19:

T cell depleting therapies in myocarditis and HLH:

Gilbert et al. reported the first use of a T cell depleting therapy for myocarditis in 1988 using OKT3.[32] Muromonab-CD-3, (Orthoclone OKT3, Centocor Ortho Biotech Products, LP Raritan, NJ), a T cell depleting agent that is now discontinued in the US, was reported in over ten studies to have efficacy in human myocarditis.[33] A viral prodrome was present in 68.8% of the patients in these studies. Full or partial recovery was seen in 82.5% of the patients. It should be noted that other immunosuppressives like corticosteroids, cyclophosphamide, cyclosporine, azathioprine and IVIG were also used and the dose of OKT3 was also variable. OKT3 was approved for transplantation but was associated with a cytokine release syndrome shortly after being administered. It was also associated with late occurring lymphomas so its use in transplantation gradually waned.

Icenogle et al. reported the first use with rabbit thymocyte globulin (RATG), a T cell depleting medication, in six patients with fulminant viral myocarditis and hemodynamic instability in 2004. They were treated with either locally manufactured or with the commercial preparation, Thymoglobulin (Anti-Thymocyte Globulin [rabbit] intravenous administration. Genzyme, Cambridge, MA), once it became available. All patients had pre and post treatment heart biopsies which showed resolution of the myocarditis, and five of the six survived, all without heart transplantation.[34] Five years after the initial report there was a report with five cases of fulminant myocarditis treated with a similar polyclonal anti-T cell medication, Atgam, (Lymphocyte Immune Globulin, Anti-Thymocyte Globulin [Equine] Sterile Solution. Pfizer, New York, NY) that revealed similar results with the patients making rapid recovery.[35]

RATG has also been used to treat primary HLH in pediatric patients as part of a stabilization regimen prior to stem cell transplant.[36,37] These studies documented the nearly immediate improvement in symptoms leading to remission of an extremely ill group of patients. The genetic defects with primary HLH invariably lead to recurrence, but RATG alleviates the immediate life-threatening immunologic dysfunction in preparation for stem cell transplant.

Pharmacology of RATG:

Thymoglobulin (RATG) is produced by inoculating pathogen-free New Zealand rabbits with fresh human thymocytes. The thymocytes are derived from thymus tissue removed during pediatric cardiac surgery. The thymus lies anterior to the heart and blocks the surgeon's view of the heart and so a portion is removed to allow visualization. After inoculation, the rabbits make a polyclonal antibody response to the human thymocytes and this is then purified and pasteurized.

There are a variety of cells in the human thymus, so Thymoglobulin has antibodies to numerous immunologically active cells, immune response antigens, adhesion and cell trafficking molecules, and molecules involved in heterogenous pathways.[38]

RATG has anti-T-cell properties causing complement mediated T-cell death in peripheral blood and apoptosis in the spleen and lymph nodes.[38] RATG also has antibodies to CD20, CD27, CD28 CD38, HLA Class I and Class II, and a host of adhesion molecules, i.e. CD11a/CD18 (LFA-1), CD49/CD29 (VLA-4), CD50 (ICAM-3), CD54 (ICAM-1), CD58 (LFA-3), CD102 (ICAM-2), CD195 (CCR5), and has demonstrated anti-B cell properties *in vitro* and *in vivo.*[38,39,40]

The literature in myocarditis and immunosuppression:

The papers using T cell depleting therapies focus on patients presenting with fulminant myocarditis and the use of T cell depleting therapies is rarely mentioned in clinical reviews of myocarditis except in the treatment of giant cell myocarditis.[41,42,43,44] No T cell depleting therapies have ever been part of a randomized prospective trial in myocarditis. While most reviews consider, "immunosuppression", and mention the prospective randomized trials of steroids, cyclosporine, azathioprine, and IVIG which have generated conflicting results. Yet none of these immunosuppressive medications have a profound effect on T cell dynamics so it is not surprising that they have been inconclusive or even contraindicated in viral induced autoimmune disease. These reviews also stress that immunosuppression should not be given unless the patient has been determined to be virus free, a view that appears to represent a consensus statement. This is a contradiction to the numerous animal studies that found that myocarditis was related to the manifestations of T cell mediated injury and not active infection or the presence of viral genome in the heart. The virus infection may initiate the autoimmune process but might otherwise be irrelevant to the outcome. The caveat might be that the murine studies focus on the acute pathophysiology of the disease which, in the human, presents as fulminant myocarditis while the non-T cell depleting therapies might be more appropriate for a chronic disease state.

Additional effects of RATG:

The cytokine storm that accompanies some patients with COVID-19 and HLH changes the endothelium of blood vessels from an anti-adhesive to a pro-adhesive status. Selectins and integrins on the surfaces of lymphocytes and the endothelium are critical to these events.[38] The antibodies in Thymoglobulin attach to these adhesion molecules and the antigen-antibody complex is then internalized by the cell. The internalization of the antigen-antibody complex, called modulation, is a major function of Thymoglobulin and the related pathway is then inhibited, (down-modulation). The down modulation effect of Thymoglobulin has been demonstrated in the experimental animal in an ischemia-reperfusion experiment.[45]

B cell depleting therapies in viral induced autoimmune disease:

The B cell lineage produce antibodies and viruses may induce an antibody mediated autoimmune process, (Type II hypersensitivity). Animal models in myocarditis research point to the considerable impact that B cells and their resultant antibodies have in the pathophysiology.[46,47,48,49,50,51] Autoantibodies may be produced by an immune response to viral antigens that then react with self-antigens in a process called molecular mimicry and direct viral damage to myocardial cells which then

release self-antigens.[52] Antibodies may be made against cell surface antigens as well as intracellular and even intra-mitochondrial antigens.[49,51] Making the diagnosis of antibody mediated myocarditis can be challenging in that immunohistochemical studies may be difficult to obtain in community hospitals and the endomyocardial biopsy may be normal. While autoantibodies are well documented in some patients with lymphocytic myocarditis, it is currently unknown, although likely, that autoantibodies play a role in the pathophysiology of COVID-19. Autoantibodies are a product of the adaptive immune system wherein T cells and B cells interact to form antibody. A brief review of antigen recognition and antibody production and immunologic memory may reveal new strategies to remove harmful antibodies in COVID-19.

When SARS-CoV-2 enters the body via the respiratory system or gastrointestinal tract it is likely to be taken up by antigen presenting cells (APCs), e.g. dendritic cells, macrophages, epithelial cells, and B cells. Dendritic cells that capture the virus become activated and express major histocompatibility antigens (MHCs) that present small fragments of virus polypeptides in a groove in the MHC. They also present co-stimulatory molecules on their surface that work to activate naïve T cells. The dendritic cells travel to lymph nodes where they will meet naïve T cells, a few of which are specific for the MHC-peptide complex. In response to the MHC-peptide recognition, the naïve T cells then become activated, secrete cytokines, undergo clonal expansion, and differentiate into effector and memory subsets. The effector T cells work to eliminate the virus while memory T cells are long lived, move out of the lymph nodes to sites where they may encounter viral antigens and rapidly respond to subsequent encounters with the virus. There are two major types of effector T cells, $CD4^+$ T cells, or helper T cells, that help B cells to make antibodies to the SARS-CoV-2 virus and $CD8^+$ T cells that are able to kill virus infected cells.

The SARS-CoV-2 virus will also attach to a B cell receptor that is bound to the membrane of a mature naïve B cell. These cells express CD20 on their surface and are usually located in a lymph node that drains the respiratory or gastrointestinal tract. The B cell, with help from other cells and cytokines may then become activated and it can travel to the germinal center part of the lymph node and engage with a $CD4^+$ helper T cell. The virus, on the surface of the B cell is internalized, broken apart and a peptide fragment from the virus is then presented in an MHC II molecule on the surface of the B cell. The SARS-CoV-2 activated B cells then meet with the independently activated SARS-CoV-2 $CD4^+$ T cells and the $CD4^+$ T cell then recognizes the MHC II-peptide complex on the B cell. Once a B cell becomes further activated by a $CD4^+$ T cell, it loses its CD 20 surface molecule, and it may become a short-lived plasma cell and generate antibody, or it can enter a geminal center where it can undergo somatic hypermutation with affinity maturation and isotype switching. The B Cell can then differentiate into a plasmablast and secrete antibody or can become a memory B cell, that has CD 27 on its surface, which is long lived. Some plasmablasts may find a survival niche in the bone marrow and become a long-lived plasma cells.[52]

The elimination of viral induced autoantibodies requires reduction or elimination of the plasmablasts and the short-lived plasma cell populations responsible for making the antibody. It also involves the reduction or elimination of memory B cells to autoantigens that are primed to become high affinity plasmablasts or plasma cells upon re-exposure to autoantigens. The population of pre-sensitized memory T cells, that are capable of re-stimulating B cells to differentiate into plasmablasts and

autoantibody producing plasma cells, also need to be eliminated. A successful plan to eliminate autoantibody must address two of the three systems for immunologic memory: memory T cells and memory B cells. The third system of immunologic memory, the long-lived plasma cells that are held within protective niches within the bone marrow, probably doesn't need to be addressed since COVID-19 is an acute disease and there is not enough time for long-lived plasma cells to compete for a survival niche.

Thymoglobulin has T cell depleting activity via antibodies to several T cell antigens including CD3, CD4, CD8, CD28, and CD 45.[38,40] It also has antibodies to HLA-ABC and HLA-DR and the B cell specific surface proteins CD19, CD20, CD80, and CD 40 and the plasma cell surface protein CD138.[40] It has been shown to induce apoptosis of stimulated B cells and plasma cells in vitro, but does not delete plasma cells from the human spleen.[54]

Rituximab, an anti-CD20 monoclonal antibody, (Rituxan (Rituximab) Genentech, South San Francisco, CA), was first approved to B cell lymphomas and has found efficacy in treating multiple sclerosis, rheumatoid arthritis, and other autoimmune diseases. It binds to human CD20 on mature naïve B cells and depletes B cells in circulation for 4 to 12 months.[55] In a murine model it was shown to decrease autoreactive short-lived plasma cells thus reducing serum autoantibodies while not affecting total antibody titers.[56] Plasma cells in bone marrow niches do not display CD20, so antibody titers from these cells are not affected.

Thymoglobulin and rituximab have been used together in highly sensitized kidney transplant recipients who also underwent splenectomy as part of the protocol.[38] There was a decrease in $CD27^+$ cells, the phenotype of the memory B cell when compared with giving rituximab and IVIG, or IVIG alone, or control patients. These findings support the use of rituximab in patients with autoreactive antibodies and its use in combination with Thymoglobulin when a T cell mediated autoimmune process is part of the pathophysiology.

DISCUSSION:

The key issue with therapy for COVID-19 is whether the pathophysiology is primarily infective or autoimmune. The fact that eighty percent of patients infected have no symptoms or mild symptoms intimates that the disease response is secondary to host factors. Viral induced Type II and Type IV hypersensitivity reactions are well described, and COVID-19 fits with other viral induced autoimmune disease pathologies. The immunology literature would lead to the use of a T cell depleting agent above other forms of immunosuppression but the current clinical literature, particularly in myocarditis, fails to even mention T cell depleting therapies. To date, case reports of using T cell depleting therapies for COVID-19 have not been reported and should be considered an area for investigation. It seems likely that autoantibodies will be discovered in the study of COVID-19 and then consideration should be towards adding an anti-CD20 medication. Clinical studies utilizing these agents should be considered soon. These medications, however, do not have any efficacy in removing the offending virus and antiviral therapies should be employed to decrease the time of viral shedding. Remdesivir should probably be considered as part of a treatment regimen in COVID-19.

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47. Neu N, Craig SW, Rose NR, Alvarez F, Beisel KW. Coxsackievirus induced myocarditis in mice: cardiac myosin autoantibodies do not cross-react with the virus. Clin. Exp. Immunol 1987;69:566-574.
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52. Zhao L, Fu Z. Roles of host immunity in viral myocarditis and dilated cardiomyopathy. J Immun Res. 2018 Article ID 5301548.
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54. Ramos EJ, Pollinger HS, Stegall MD, et al. The effect of desensitization protocol on human splenic B cell populations *in vivo*. Am J Transplant 2007;7:402-407.
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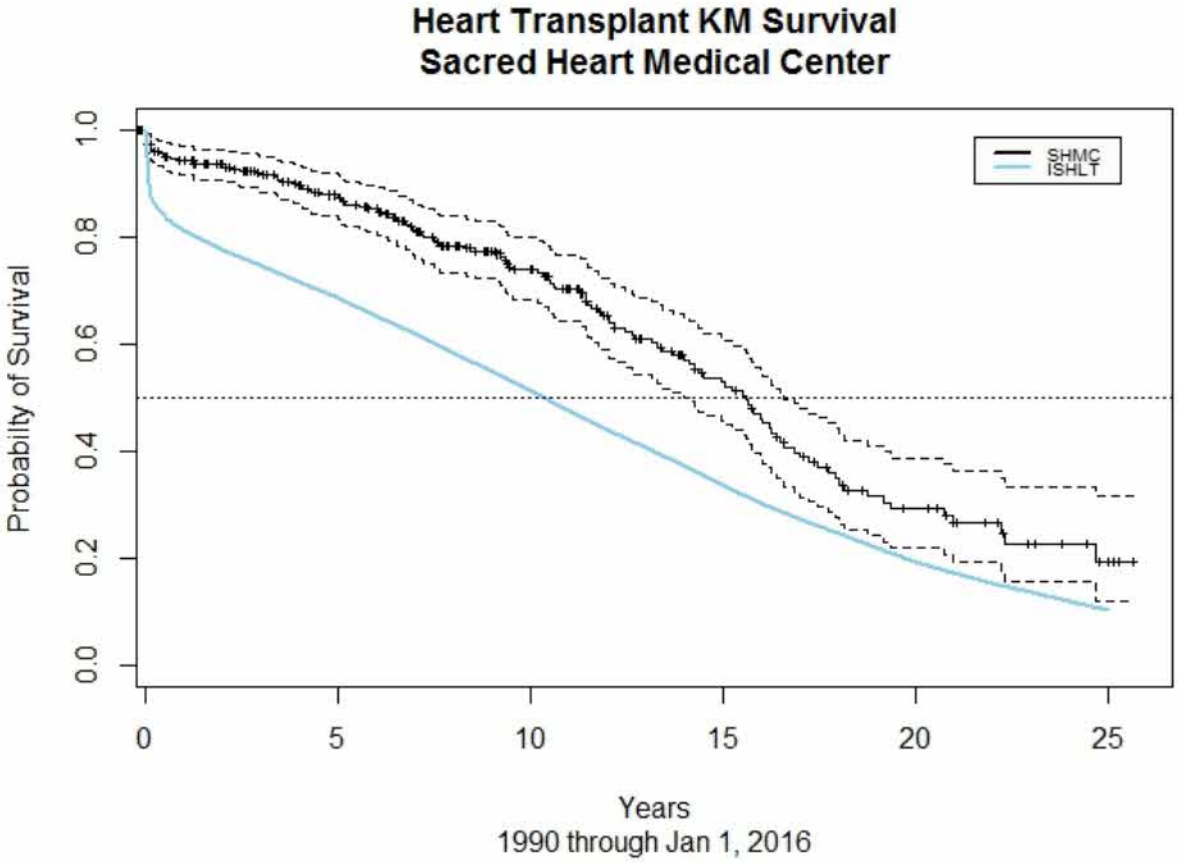
56. Huang H, Benoist C, Mathis D. Rituximab specifically depletes short-lived autoreactive plasma cells in a mouse model of inflammatory arthritis. PNAS. 2010;107(10): 4658-4663.


Heart Transplant KM Survival
Sacred Heart Medical Center
SHMC
ISHLT
Probabilty of Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Years
1990 through Jan 1, 2016

April 14, 2020

CURRICULUM VITAE

TIMOTHY B. ICENOGLE, MD, FACC, FCCP, FACS

Date of Birth: (b)(6)

Birthplace: (b)(6)

Marital Status: (b)(6)

Address: (b)(6)

Phone: (b)(6)

Work Address: Tim Icenogle MD PLLC
3415 W. Horizon Ave.
Spokane, Washington 99208
Tel.: (b)(6)
Email: (b)(6)

EDUCATION:

1971-1973	Casper College, Casper, Wyoming, A.S.
1973-1975	Baylor University, cum laude, Waco, Texas, B.S.
1975-1979	University of New Mexico School of Medicine Albuquerque, New Mexico- M.D.

PROFESSIONAL AND ACADEMIC APPOINTMENTS:

1979-1983	Resident, Phoenix Integrated Surgical Residency Program, Phoenix, Arizona
1983-1984	Chief Resident, Phoenix Integrated Surgical Residency Program, Phoenix, Arizona
1984-1985	Resident, Section of Cardiothoracic Surgery, University of Arizona, Tucson, Arizona
1985-1986	Chief Resident, Section of Cardiothoracic Surgery, University of Arizona, Tucson, Arizona

June 1986 to June 1989: Assistant Professor, Department of Surgery, University of Arizona, Tucson, Arizona

EMPLOYMENT:

Sept 1989 to Feb 1992: Cardiothoracic Surgeon, Cardiovascular and Thoracic Surgical Associates Spokane, Washington

Sept. 1989 to June 2016: Director of Thoracic Organ Transplantation, Director of Heart Assist Program, Providence Sacred Heart Medical Center, Spokane, WA

Feb 1992 to Feb 2014: President, Northwest Cardiothoracic and Transplant Surgeons PS

Feb 2014 to Aug 2016: Cardiothoracic Surgeon, Providence Northwest Heart and Lung Surgical Associates, Spokane, WA

October 2016 to Present: Locum tenens as Tim Icenogle MD PLLC

Work Schedule

2016

Harrison Medical Center, Bremerton, WA Oct 17-24

Harrison Medical Center, Bremerton, WA Nov 14-21

Harrison Medical Center, Bremerton, WA Dec 5-12

St. Joseph's Medical Center, Bellingham, WA Dec 15-23

St. Joseph's Medical Center, Bellingham Dec 27-Jan 1,2017

2017

Yakima Regional Medical Center, Yakima, WA Jan 20-27

Yakima Regional Medical Center, Yakima, Jan 30-Feb 5

Yakima Regional Medical Center, Yakima, Feb 13-Feb 20

Marshfield Clinic, Marshfield, WI March 17-31

Kalispell, MT April 3-17

Marshfield Clinic, Marshfield, WI April 21-28

Marshfield Clinic, Marshfield, WI May 18-31

Marshfield Clinic, Marshfield, WI June 16-30

Marshfield Clinic, Marshfield, WI July 17-31

Marshfield Clinic, Marshfield, WI Sept 18 Oct 1

Astria Regional Medical Center, Yakima: October 8-10,

Harrison Medical Center, Bremerton: October 19- 28, 2017

Astria Regional Medical Center, Yakima: Nov 10-12

Astria Regional Medical Center, Yakima Nov 13-19

Astria Regional Medical Center, Yakima Nov 20-21

Harrison Medical Center, Bremerton: November 30, 2017, Thursday (5pm) - December 9, 2017, Saturday (7am) – 9 Days

Harrison Medical Center, Bremerton: December 27, 2017, Wednesday (7am) – January 3, 2017, Wednesday (7am) – 7 Days

2018

Astria Regional Medical Center, Yakima Jan 15 to Jan 24

Harrison Medical Center Society of Thoracic Surgeons: Jan 26th to Jan 31st

Harrison Medical Center, Bremerton: February 19th (7am) to February 26th (7am)

Essentia Fargo, Fargo, ND March 12 to 16th

Harrison Medical Center, Bremerton: March 19, 2018, Monday (7am) - March 26, 2018, Monday (7am) – 7 Days

Essentia Fargo, Fargo, ND April 4 (7am) to 16th (7am)

Essentia Fargo, Fargo, ND May 4 to May 14 (7am) Bremerton May 24 (7am) to May 29 (7am)

Essentia Fargo, Fargo, ND June 4 to June 15 (7am)

Essentia Fargo, Fargo, ND July 6 to July 23 (7am)

Essentia Fargo, Fargo, ND Aug6(7am) to Aug 20(7am)

Multicare Deaconess Hospital, Spokane, WA Aug 30-31, Sept 1-3

Essentia Fargo, Fargo, ND Sept 7 (7am) to Sept 21(7am)

Essentia Fargo, Fargo, ND Sept 28 (7am) to Oct 12 (7am)

Multicare Deaconess Hospital, Spokane, WA Nov 2,3,4

Astria Regional Medical Center, Yakima, WA November 25 (noon) to November 28 (7am)

Multicare Deaconess Hospital, Spokane, WA December 14,15,16

Astria Regional Medical Center, Yakima, WA December 28 to December 31

2019

Astria Regional Medical Center, Yakima, WA Jan 1 to Jan 7

Multicare Deaconess Hospital, Spokane, WA Jan 11 to 13

Astria Regional Medical Center Yakima Jan 25 to Jan 31

Harrison Medical Center,Bremerton, WA Feb 14 (7am) to Feb 18 (7 am)

Multicare Deaconess Hospital, Spokane, WA March 8 to 10

Multicare Deaconess Hospital, Spokane, WA March 29 to April 7

Salina Regional Health Center, Salina, KS April 22 to May 8

Multicare Deaconess Hospital, Spokane, WA May 10-12, 13th

Multicare Deaconess Hospital, Spokane, WA May 24-27

Salina Regional Health Center, Salina, KS June 3 to 14

Salina Regional Health Center, Salina June 17 to 28

Virginia Mason Medical Center, Seattle, WA July 19 to 29

Virginia Mason Medical Center, Seattle, WA Sept. 6 to 16

Astria Regional Medical Center, Yakima, WA Sept. 27 to Oct 14

Astria Regional Medical Center, Yakima, WA Nov. 1 to 16

Astria Regional Medical Center, Yakima, WA Dec. 9 to 17

Astria Regional Medical Center, Yakima, WA Dec 28 to Dec 31

2020

Astria Regional Medical Center, Yakima, WA Jan 1 to Jan 3

University of Kansas, St. Francis Campus, Topeka, KS Feb 21 to Mar 9

University of Kansas, St. Francis Campus, Topeka, KS April 5 to April 6 (Interrupted by family emergency)

RESEACHGATE RATING: 32.69 (Top 90% of ResearchGate Investigators)

MEDICAL LICENSURE:

July 18, 1986	Arizona - #16192 Expired 05/08/2017
August 1, 1989	Washington - #0026659 Expires 05/08/2020
July 19, 1996	Montana - #8034 Expires 05/08/2020
Jan 01,2016	Oregon - #138652 Inactive Expires 12/31/2020

July 16, 2009	Idaho - # MC-0401, Expires 06/30/2021
	Idaho Controlled Substance CS13684 Expired 12/31/2016
March 14, 2017	Wisconsin # 67062-20, Expired 10/31/2019
March 29, 2018	North Dakota – 14997, Expires 5/8/2020
April 18, 2019	Kansas #04-42031 Expires July 31, 2021
May 15, 2019	Mississippi #26751 Expires June30, 2020
	Colorado

BOARD CERTIFICATION:

7/04/80	American Board of Medical Examiners - #212680
5/16/87	American Board of Thoracic Surgery - #4535
12/31/97	American Board of Thoracic Surgery Recertified - #4535
2/28/07	American Board of Thoracic Surgery Recertified - #4535
2015	American Board of Thoracic Surgery Recertified -4535 to Dec. 31, 2027

MEDICAL SOCIETY MEMBERSHIPS:

11/06-Present:	American Board of Thoracic Surgery-Diplomat
02/88-Present:	American College of Cardiology – Fellow
02/88-Present:	American College of Chest Physicians – Fellow
10/92-Present:	American College of Surgeons – Fellow
07/86-Present:	International Society for Heart & Lung Transplantation – Member
01/99-Present:	The Society of Thoracic Surgeons
01/10-Present:	Washington State Chapter of American College of Surgeons – Fellow
07/05-Present:	Western Thoracic Surgical Association

PATENT:

A Mobile Intensive Care Patient Handling Transport System Apparatus and Method of Using Same. TB Icenogle, WF Machamer, RJ Nelson, S Mikitish Jr, R Davis. Patent applied for. Patent Number 4,957,121. Date of Patent: September 18, 1990.

SERVICE ACTIVITES:

09/86-07/89:	Admissions Committee, University of Arizona, College of Medicine – Interviewer
02/87-07/89:	Intensive Care Unit Committee, University Medical Center, Member

11/86-07/89:	Education Committee, University of Arizona Heart Center, Member
01/87-07/89:	CCU/CTICU User Group, University Medical Center, Member
03/90-Present:	Sacred Heart Medical Center Thoracic Transplant Committee
07/91-Present:	Surgery Committee, Sacred Heart Medical Center, Member
08/91-07/95:	Research Committee. The Heart Institute of Spokane, Member
08/95-Present:	Regional Representative, UNOS Thoracic Transplantation, Executive Committee Member
02/96-Present:	LifeCenter Northwest Organ Procurement Agency, Medical Advisory Board Member
02/96-05/2003:	LifeCenter Northwest Organ Procurement Agency, Board of Directors, Member

Special Conferences and Lectures

08/19/86:	"Heart transplantation at University Medical Center"-Cardiology Grand Rounds, Good Samaritan Hospital, Phoenix, AZ
08/23/86:	"Cardiac transplantation: Future goals and expectations"- Lincoln Health Foundation Meeting, Tucson, AZ
10/24/86:	"Cardiac transplantation and artificial heart: Tucson experience"-Riverside Methodist Hospital's 3rd Annual Cardiovascular Symposium, Columbus, OH
11/06/86:	"Surgical management of coronary artery disease"-ACP 3rd Annual Update in Clinical Medicine, Scottsdale, AZ
12/04/86:	"Update on thoracic organ transplantation" – Surgical Ground Rounds, Good Samaritan Medical Center, Phoenix, AZ
01/24/87:	"Medical complications following transplantation"-Treatment Options in End Stage Cardiac Disease, Section of Cardiovascular and Thoracic Surgery
02/21/87:	"Role of mechanical support in the transplant center"-Surgical Grand Rounds
03/28/87:	"Transport of the cardiac patient"- Professional Aeromedical Transport

Association (PATA) Spring Meeting, Phoenix, AZ

04/29/87: "Blood bank and HLA management of Bernadette Chayrez"-American Society for Medical Technology/Arizona State Society for Medical Technology Annual Meeting, Tucson, AZ

05/01/87: "Laboratory's role in cardiac transplantation"-American Society for Medical Technology/Arizona State Society for Medical Technology Annual Meeting, Tucson, AZ

5/12/87: "Long distance transport of cardiac patients in extremis: the MOBI concept"-Aerospace Medical Association Scientific Meeting, Las Vegas, NV

07/24/87: "Update on transplantation"-Coconino Medical Society Summer Medical Seminar, Flagstaff, AZ

08/15/87: "Difficult chest problems"-Surgical Grand Rounds

10/23/87: "Heart and heart/lung transplantation"-St. Joseph's Hospital and Medical Center, Phoenix, AZ

11/24/87: "Postop cardiac surgery complication"-University of Florida College of Medicine, Lake Buena Vista, FL

11/24/87: "Mechanical aids for the failing heart"-University of Florida College of Medicine, Lake Buena Vista, FL

01/25/88: "Bridge to transplantation: The Arizona experience"-Symposium on Circulatory Support, University of Arizona Heart Center

02/13/88: "Current status of cardiac transplantation"-Texas Tech University Health Sciences Center Cardiology Update '88, El Paso, TX

02/13/88: "Update on valvular prostheses: Long-term management & complications"-Texas Tech University Health Sciences Center Cardiology Update '88, El Paso, TX

02/20/88: "Heart Transplantation"-Minneapolis Heart Institute & University of Arizona Heart Center, Tucson, AZ

02/20/88: "Heart Transplantation: Past, present & future"-Southwestern Clinic Pharmacy Symposium, Tucson, AZ

03/16/88: "Postoperative management after cardiac transplantation"-26th Annual

Symposium on Critical Care Medicine-Last Vegas, NV

03/17/88: "Artificial heart as a bridge to transplantation"-26th Annual Symposium on Critical Care Medicine, Las Vegas, NV

03/17/88: "Selection & management of critically ill patients for transplantation"-26th Annual Symposium on Critical Care Medicine, Las Vegas, NV

3/17/88: "Cardiac transplantation"-26th Annual Symposium on Critical Care Medicine, Las Vegas, NV

04/09/88: "Management of specific medical problems in the air: Cardiovascular & Transplant patients"-Professional Aeromedical Transport Association (PATA) Seminar, New Orleans, LA

04/30/88: "Organ donor"-Prescription for Health-Pima County Medical Society, Tucson, AZ

07/19/88: "Surgical aspects of non-small cell lung cancer:"-Tumor Board, Department of Radiation

08/31/88: "Alveolar Cell Carcinoma"-Radiation and Surgical Oncology Conference, Department of Surgery

09/22/88: "Transport of the critically ill cardiac patients: the MOBI Concept"-1988 Airmed Scientific Session, Boston, MA

09/30/88: "Extracorporeal pump complications in cardiac transplant patients"-Neurology/ Neurosurgery Grand Rounds

12/13/88: "Cardiac transplantation and use of mechanical assist devices"-Surgical Grand Rounds, Louisiana State University Medical Center, Shreveport, LA

01/26/89: "Evaluation of patients for cardiac transplantation"-American College of Physicians Postgraduate Courses: Clinical Recognition and Management of Heart Disease-1989, Tucson, AZ

03/12/89: "Transport of the cardiac patient"-Professional Aeromedical Transport Association Annual Meeting, Arlington, WA

05/08/89: "Long distance transport of the asystolic patient"-60th Annual Scientific Meeting Of the Aerospace Medical Association, Washington, DC

09/19/89: "Current status of thoracic organ transplantation"-Benton County Medical

	Society, Tri-Cities, WA
10/27/89:	"Update on cardiac transplantation:-Cardiovascular Conference, Sacred Heart Medical Center, Spokane, WA
11/21/89:	"Thoracic Organ Transplantation"-Whitman County Medical Society, Pullman, WA
12/19/89:	"Thoracic Organ Transplantation"-Medical Staff Conference, Kennewick General Hospital, Kennewick, WA
1/17/90:	"Heart Retrieval and Transplantation"-Sacred Heart Medical Center Operating Staff, Sacred Heart Medical Center, Spokane, WA
01/22-23/90:	"Heart Transplantation"-Providence Auditorium, Sacred Heart Medical Center, Spokane, WA
03/06/90:	"Heart Transplantation"-St. Luke's Medical Staff, Spokane, WA
03/20/90:	"Heart Transplantation and the Spokane Program"-Kootenai Medical Staff, Kootenai Memorial Hospital, Coeur d'Alene, ID
04/09/90:	"Heart Transplantation"-Grant-Adams County Medical Association, Moses Lake, WA
4/16/90:	"Heart Transplantation Update"-Inland Empire Nurses Assoc., Sacred Heart Medical Center, Spokane, WA
04/19/90:	"Heart Transplantation in Spokane"-VA Medical Staff, VA Medical Center, Spokane, WA
06/16/90:	"Heart and Heart-Lung Transplantation"-Surgical Tech Conference, Spokane, WA
09/08/90:	"Heart Transplant Program in Spokane"-Kootenai County Medical Staff, Coeur d'Alene, ID
09/11/90:	"Heart Transplant Program"-Holy Family Hospital Physicians, Spokane, WA
09/28/90:	"Heart Transplant Update"-AACN Fall Symposium, Sacred Heart Medical Center, Spokane, WA
10/30/90:	"Transplant Talk" Including valve procurement-Cardiac Symposium, Missoula, MT

01/18/91:	"Transplants in Malignancies"-Cancer Conference, Sacred Heart Medical Center, Spokane, WA
01/23/91:	"Thoracic Organ Transplantation"-Cardiac Cath Conference, St. Patrick's Hospital Missoula, MT
02/09/91:	"Heart Transplantation"-Administration of Hospital, physician, and public, Whitman Hospital, Colfax, WA
02/14/91:	"Heart Transplant Services"-Sacred Heart Medical Center, Providence Auditorium, Conjoined Conference, Spokane, WA
02/18/91:	"Heart Transplant Program"-Good Samaritan Hospital, Portland, OR
04/23/91:	"Heart Transplantation"-Donate Life Foundation, Richland, WA
09/14/91:	"HeartMate, Left Ventricular Assist Device"-Amsect, Coeur d'Alene, ID
05/08/92:	"Advances in Cardiac Surgical Technology"-Deaconess Medical Center, Spokane, WA
12/18/92:	"Ventricular Assist Protocol"-Sacred Heart Medical Center, Spokane, WA
01/16/93:	"Heart and Lung Transplantation"-WTS Chest Conference Lung Day XXIII and WTS Annual Meeting-Leavenworth, WA
01/21/93:	"Mechanical Assist Device: HeartMate"-Clinical Coordinators Session of the UNOS, Region 6 Meetings, Vancouver, BC
09/10/93:	"New Directions in Cardiac Transplantation"-Sacred Heart Medical Center, Spokane, WA
10/01/93:	"Update on Cardiovascular Surgery; Thoracic Organ Transplantation"-Cardiovascular Update 93, The Heart Institute, Spokane, WA
12/08/93:	"Long Term Outcome of Aortic Valve Replacement-Ross Procedure" Cardiology Conference, Deaconess Medical Center, Spokane, WA
08/25/94:	"Organ and Tissue Donation"-Wyoming Trauma Conference, Cheyenne, WY
09/08/94:	"The Healthy Heart"-Wellness Conference '94, Spokane, WA

12/14/94:	"Mechanical Assist Devices 1994"-Cardiology Conference, Deaconess Medical Center, Spokane, WA
02/04/95:	"Heart Transplantation and the Role of Mechanical Assist Devices"-Association Of Surgical Technicians, Spokane, WA
05/09/95:	"Selective Pulmonary Artery Vasodilator"-Chest Conference, Sacred Heart Medical Center, Spokane, WA
06/09/95:	"The Undiscovered County: Mechanical Cardiac Assist Therapy in the Twenty First Century"-Critical Care Conference, Sacred Heart Medical Center, Spokane, WA.
06/13/96:	"Ventricular Assist Devices: The Future is Now"-Fourth Annual Pacific Northwest Cardiovascular Symposium, Providence Medical Center, Seattle, WA
12/03/96:	"Bridge to Transplantation"-BENESIF Health Care Conference, Montana Deaconess Medical Center, Great Falls, MT
12/05/96:	"Surgical Management of End Stage Heart Disease: Mechanical Assist Devices And Cardiac Transplantation"-Cardiovascular Update 1996, The Heart Institute, Spokane, WA
03/26/97:	"Minimally Invasive CABG: Therapeutic or Salesmanship?" Cardiology Conference, Sacred Heart Medical Center, Spokane, WA
10/3-4/97:	"Cardiovascular Update 1997", The Heart Institute of Spokane, Program Chairman
10/11/97:	"Mechanical Support Using the HeartMate and Thoratec Ventricular Assist Devices", The American Society of Extracorporeal Technology, Coeur d'Alene, ID
12/9/98:	"Mechanical Heart Update", St. Patrick Hospital, The International Heart Institute of Montana, Missoula, MT
03/10-11/00:	"Discharge of HeartMate IP LVAD to Home: a Feasibility Study"-Tokyo, Japan
09/24-26/00:	"PHADE: Pneumatic HeartMate Assist as Destination Evaluation (study update)"-HeartMate Investigator & User Meeting, Thermocardio Systems, Tampa, FL
05/03/01:	"Surgical Intervention for Heart Failure-2001"-Madigam Army Medical Center, Ft. Lewis, Tacoma, WA

5/15-16/01:	"Update on Mechanical Assist Devices"-LifeCenter, Billings, MT
11/9-10/01:	"Gortex Pocket for Intraperitoneal LVAD Implant"-International Society for Heart and Lung Transplantation's 3rd Fall Education Meeting, Mechanical Cardiac Support and Replacement II, Hyatt Regency, Orange County, Anaheim, CA
12/9-10/01:	"Clinical Review of LVAD Procedure and Investigational Review of Inhaled Nitric Oxide"-INO Therapeutics, San Francisco, CA
03/15/02:	"Advances in Cardiac Assist Devices"-LifeCenter Team Meeting, Seattle, WA
03/08/04:	"Treatment of Fulminant Myocarditis with Rabbit Antithymocyte Globulin: A Pilot Study"-American College of Cardiology, 53rd Annual Scientific Session, New Orleans, LA
06/28/06:	"Case presentation interesting cases of chest tumors", Chest Tumor Board
03/15/06:	"Mechanical Assist Devices for End-Stage Heart Disease"-Cardiovascular Conference Presentation, Heart Institute of Spokane, Spokane, WA
04/13/07:	"Transplantation and Mechanical Cardiac Assist Therapy" Tacoma General Hospital, Tacoma, WA
04/19/07:	"Mechanical Cardiac Assist Therapy" Yakima Regional Hospital, Yakima, WA
05/24/07:	"Abiomed Ventricular Assist Device", Providence Alaska Medical Center, Anchorage, Alaska
07/11/07:	"Thromboelastography (TEG)" Cardiovascular Conference Presentation, Heart Institute of Spokane, Spokane, WA
11/07/07:	"Interesting Cardiac Cases Venous ECMO" Cardiovascular Conference Presentation, Heart Institute of Spokane, Spokane, WA
11/18/09:	"Saphenous Vein Harvesting; Techniques & Controversies" Cardiovascular Grand Rounds, Sacred Heart Medical Center, Spokane, WA
06/05/10:	"Heart Failure Crossfire-Assist Devices with be Cost-Effective and Replace Medical Therapy and Transplantation" American College of Cardiology, 7th Annual Oregon Cardiovascular Symposium, Portland, OR
10/23/10:	"Cardiology and Electrophysiology- Concepts and Controversies" Mercy Heart &

Vascular Symposium, Portland, OR

12/02/10: "Management of Acute and Chronic Heart Failure" Grand Rounds, Overlake Hospital, Bellevue, WA

12/22/10: "Treatment of Advanced Heart Failure" Providence St. Vincent Medical Center, Portland, OR

12/12/11: "Surgical Treatment of Advanced Heart Failure" Benefis Heart and Vascular Institute, Great Falls, MT

03/03/12: "Mechanical Support in Failing Fontans, Children's Hospital of Wisconsin, Milwaukee, WI

03/09/12: "Open Heart Update" Providence Sacred Heart Medical Center, Spokane, WA

04/18/12: "Initial Experience-Cost of Quality Adjusted Life Years for Patients Supported by Ventricular Assist Devices for Destination Therapy Indication", Poster Presentation-International Society for Heart & Lung Transplantation 32nd Annual Meeting, Prague, CZK

05/19/12: "Case Study #2: HeartMate II in the Adult Congenital Patient; Advanced Heart Failure Therapy in the New Era" Thoratec Annual Meeting, Las Vegas, NV

09/09/12: "Joint Session with ICCAC-VAD", Session Moderator-Heart Failure Society Of America 16th Annual Scientific Meeting, Seattle, WA

10/23/12: "Trauma, Morbidity & Mortality Conference" Providence Sacred Heart Medical Center, Spokane, WA

03/17/13: "Aortic Valve Closure for Severe Aortic Insufficiency Following LVAD Placement" Thoratec Destination Life 2013 Conference, Orlando, FL

04/26/13: "Meeting INR Targets for the Left Ventricular Assist Device Patient", Poster Presentation, International Society for Heart & Lung Transplantation 33rd Annual Meeting, Montreal Canada

007/26/13: "Primary Transplant, Destination and Device Therapy" Rocky Mountain Valve Symposium, Missoula, MT

07/26/14: "Characterization of Readmissions in the LVAD-Supported Heart Failure Population" Oral Presentation-International Academy of Cardiology, 19th

World Congress on Heart Disease, Boston, MA

04/16/15: "Can Thrombolysis Safely Avert LVAD Exchange? A Single Center Experience" Poster Presentation (co-author)-International Society for Heart & Lung Transplantation 35th Annual Meeting, Nice, France

04/17/15: "Cost Analysis of Leading Causes for LVAD Patient Readmissions", Poster Presentation-International Society for Heart & Lung Transplantation 35th Annual Meeting, Nice, France

BIBILIOGRAPHY

BOOK CHAPTERS

1. Emery RW, Icenogle T, Copeland JG. Managing the cardiac transplant patient. In Brown BR (ed): Anesthesia and Transplantation Surgery, Contemporary Anesthesia Practice, Vol. 10. Philadelphia, F.A. Davis Company. 1987; pp 73-90.

2. Copeland JG, Emery RW, Levinson MM, Icenogle T. Immunosuppression following cardiac transplantation. In Brown BR (ed): Anesthesia and Transplantation Surgery, Contemporary Anesthesia Practice, Vol. 10. Philadephia, F.A. Davis Company. 1987; pp 233-240.

3. Icenogle TB, Meister ND, Copeland JG. Clinical results following heart transplantation. In Emery RW (ed): Cardiac Surgery: State of the Art Reviews Vol 3 (1), Philadelphia, Hanley & Belfus, Inc. 1988; pp 575-579.

4. Icenogle TB, Emery RW, Copeland JG. Donor operation-Myocardial protection: Current and future practice. In Wallwork J (ed): Heart and Heart-Lung Transplantation, Philadephia, W.B. Saunders Company. 1989; pp 107-118.

5. Icenogle TB, Copeland JG. Experience with the total artificial heart as a bridge to transplantation. In Unger F (ed): Assisted Circulation 3, Berlin Springer-Verlag. 1989; pp 260-268.

6. Icenogle TB, Smith RG, Sato D, Crane S, Nelson R, Mikitish SA, Copeland JG. Transport of the critically ill end-stage cardiac patient. In Emerg RW, Pritzker MR, Eales F (ed): Cardiac Surgery: State of the Art Reviews, Vol 3 (3), Philadelphia, Hanley and Belfus, Inc. 1989; pp 499-505.

7. Icenogle TB, Sato DJ, Smith RG, Cleavinger M, Loffing D, Mikitish SA. In Ott RA Gutfinger DE, Gazzaniga AD, (ed): Cardiac Surgery: State of the Art Reviews Vol 7 (2), Philadephia, Hanley and Belfus, Inc. 1993; pp 241-247.

Proceeding:

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2. Levinson MM, Smith RG, Gallo J, Cork RC, Emery RW, Icenogle TB, Ott RA, Copeland JG. Diastolic vacuum augments medical therapy of pulmonary edema following Jarvik-7 (TAH) implantation. Int'l Biomedical Engineering Symposium and Exposition, Salt Lake City, UT, January 20-23, 1986.

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PRINCIPAL INVESTIGATOR FOR THE FOLLOWING PROJECTS:

Note: All medical research was approved by the local Institutional Review Board.

1. IRB#237-Rabbit Antithymocyte Globulin for Immunosuppressive Induction
   Approved 12/89 to 12/99

2. HeartMate Pneumatic-Left Ventricular Assist Device
   Approved 1991 to 10/94

3. IRB #223-Temporary Left and Right Ventricular Support with Thoratec Laboratory Corporation Ventricular Assist Device (for Acute Heart Failure)
   Approved 11/91 to 3/98

4. Thoratec-Biventricular Assist Device, Sacred Heart Medical Center
   Approved 1992 to 12/95

5. IRB#181-Intravenous Ribavirin to Treat Life Threatening Viral Infections
   Approved 9/93 to 3/05

6. IRB#222-Thermo Cardiosystems HeartMate VE LVAS Study
   Approved 11/93 to 11/98

7. HeartMate VE-Left Ventricular Assist Device
   Approved 1994 to 9/98

8. IRB#196-Thermo Cardiosystems HeartMate VE LVAS Study, Supplement: Patient Release Program
   Approved 10/94 to 11/98

9. IRB#6-Thermo Cardiosystems HeartMate IP LVAS Patient Release Program Study

Approved 1/95 to 5/97

10. IRB#145-Inhaled Nitric Oxide as a Selective Pulmonary Vasodilator
Approved 6/95 to 4/04

11. IRB#60-Thermo Cardiosystems HeartPak Portable Pneumatic Driver
Approved 3/96 to 11/01

12. IRB#286-Thermo Cardiosystems HeartMate IP LVAS Patient Release Program Study
Approved 6/97 to 12/05

13. IRB#503-Pneumatic HeartMate Assist as Destination Evaluation (PHADE) (G990020)
Approved 3/99 to 11/02

14. IRB#692-Home Discharge Clinical Evaluation of the Thoratec TLC-II Driver in the VAD System (2000-02)
Approved 03/01 to 03/05.

15. IRB#713-Clinical Evaluation of the Thoratec Implantable Ventricular Assist Device (IVAD) Registry
Approved 6/01 to 10/07

16. IRB#759-Hall Sensor Repair Device for the HeartMate Implanted Pneumatic LVAD, Single Patient
Approved 12/01 to 11/02

17. IRB#869-ISHLT Mechanical Circulatory Support Device (MCSD) Registry
Approved 11/02 to 6/06

18. IRB#870-The Role to Titin in Heart Function and Disease
Approved 11/02 to Present

19. IRB#954-A Registry for Pre-Sensitized Cardiac Transplant Patients Treated with Plasmapheresis, Photopheresis, IV Immune Globulin and Rituximab to Combat Humoral Rejection
Approved 8/03 to 9/12

20. IRB#1027-HeartMate XVE as Destination Therapy Registry
Approved 2/04 to 12/06

21. IRB#1028-Clinical Investigation of the DeBakey VAD® with Comparison to a Performance Goal to Establish Safety and Effectiveness of the Device as a Left Ventricular Support in Patients Awaiting Cardiac Transplantation (PG-007)

Approved 3/04 to 12/06

22. IRB#1031-Randomized Clinical Trial of the Safety and Efficacy of the DeBakey VAD as Destination Therapy in Patients with End-Stage Heart Failure (DEST-008)
Approved 3/04 to 11/06

23. IRB#1032-Post-market Data Collection of an ePTFWE Inflow Conduit with the Novacor Left Ventricular in Patients with End-Stage Heart Failure (DEST-008)
Approved 3/04 to 11/06

24. IRB#1055-Randomized Evaluation of the Novacor LVAS in a Non-Transplant Population (RELIANT) (IDE G990288/S23)
Approved 5/04 to 12/06

25. IRB#1083-DeBakey VAD Child for Humanitarian Use in Pediatrics (L00124 REV.C)
Approved 7/04 to 10/11

26. IRB#1142-Thoratec HeartMate II LVAS Pivotal Study Protocol
Approved 2/05 to 4/12

27. IRB#1261-The Epidemiology of Ventricular Assist Device-Related Infections (LVAD SCCOR Inf)
Approved 3/06 to 10/09

28. IRB#1262-The Epidemiology of Bleeding and Clotting in Patients Undergoing Heart Transplantation and Implantation of Left Ventricular Assist System (LVAS)
Approved 3/06 to 6/07

29. IRB#1270-Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS)
Approved 4/06 to present

30. IRB#1400-Evaluation of the VentraAssist™ Left Ventricular Assist Device as a Bridge To Cardiac Transplantation-Pivotal Trial (IDE G050003)
Approved 7/12/07 to 6/23/09

31. IRB#1402-Evaluation of the VentraAssist™ Left Ventricular Assist Device for Treatment Of Advanced Heart Failure Destination Therapy (IDE G060246)
Approved 7/12/07 to 6/23/09

32. IRB#1561-Evaluation of the HeartWare LVAD System for the Treatment of Advanced Heart Failure (IDE G070199)
Approved 4/29/09 to 7/13

33. IRB#1581-The Effect of Intramyocardial Injection of Mesenchymal Precursor Cells on Myocardial Function in LVAD Bridge to Transplant Patients (IND 13967)
Approved 8/17/09 to 5/11/10

34. IRB#1588-A Randomized Clinical Trial of Intrinsic Pathway Antagonists in Patients Undergoing Implantation of Left Ventricular Assist Devices (IND 101,833)
Approved 8/21/09 to 5/11/10

35. IRB#1606-Evaluation of the Safety and Effectiveness of the DuraHeart Left Ventricular Assist System in Patients Awaiting Transplantation (IDE G070168)
Approved 1/13/10 to 8/11

36. IRB#1629-The Destination Therapy Evaluation for Failing Fontan Study (DEFINE Study)
IDE G090176, NCT01149603
Approved 7/8/10 to 05/01/2016

37. IRB#1658-A Prospective, Randomized, Controlled, Un-blinded, Multi-Center Clinical Trial to Evaluate the HeartWare® Ventricular Assist System (VAS) for Destination Therapy of Advanced Heart Failure (IDE G090253)
Approved 11/22/10 to 05/01/2016

38. IRB#1773-Multi-Drug Desensitization for Heart Transplant Candidates
IND 110875
Approved 1/10/13 to 05/01/2016

39. IRB#1832-Driveline Silicon Skin Interface (SSI) Registry
Approved 10/26/12 to 05/01/2016

40. IRB#1858-A Multi-Center, Post Approval Study Providing Continued Evaluation and Follow-up on Patients Who Received a HeartWare® Ventricular Assist System During IDE Trials for Treatment of Advanced Heart Failure.
Approved 1/28/2013 to 05/01/2016

41. IRB#1902-A Prospective, Randomized, Controlled, Un-blinded,, Multi-Center Clinical Trial To Evaluate the HeartWare® Ventricular Assist Device System for Destination Therapy of Advanced Heart Failure.
Approved 7/13 to 05/01/2016

42. IRB#2015-A Prospective, Randomized, Multi-Center Clinical Trial to Evaluate the Safety And Efficacy of the HeartAssist 5 VAD System Compared to the HeartMate II VAD and HVAD For Left Ventricular Support in Patient's Awaiting Cardiac Transplantation.
Approved 7/1/15 to 05/01/2016

From: Kim, Lindsay (CDC/DDID/NCIRD/DVD)
Sent: Tue, 19 May 2020 14:21:50 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Subject: RE: Echo findings in MIS-C
Attachments: Task Org 10 May.pptx

Here's the organogram for HSWS as of May 10. Matt Stuckey emailed this to us. And thanks for heads-up on Sapna. I know her from my EIS time in TB.

Lindsay Kim, MD, MPH
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office: 404-639-5218
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From: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Sent: Tuesday, May 19, 2020 9:41 AM
To: Kim, Lindsay (CDC/DDID/NCIRD/DVD) <iyn2@cdc.gov>
Cc: Garg, Shikha (CDC/DDID/NCIRD/ID) <izj7@cdc.gov>; Acosta, Anna (CDC/DDID/NCIRD/DBD) <vhy8@cdc.gov>; Oster, Matt (CDC/DDNID/NCBDDD/DBDID) <IGP8@cdc.gov>
Subject: RE: Echo findings in MIS-C

PS: do you have an organogram, for HSWS? Seem huge and I can't figure out who is where doing what!

And nothing in the literature I am of aware yet other than the attached…

Sapna is really interest in the whole hyperimmune/immune-mediated phenomenon across the whole age spectrum and how it is express physiologically (e.g., myocarditis, renal injury, derm, hypercoaguability...). Have you connected with her?

-john

John T. Brooks, MD

Chief Medical Officer, CDC COVID-19 Response
Email: zud4@cdc.gov
Apologies for errors in my messages that may be due to my need to dictate.

http://intranet.cdc.gov/library/covid19/index.html

From: Kim, Lindsay (CDC/DDID/NCIRD/DVD) <iyn2@cdc.gov>
Sent: Tuesday, May 19, 2020 9:30 AM
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
Cc: Garg, Shikha (CDC/DDID/NCIRD/ID) <izj7@cdc.gov>; Acosta, Anna (CDC/DDID/NCIRD/DBD) <vhy8@cdc.gov>
Subject: Echo findings in MIS-C

Hi John:

First, can I just say this photo below is AH-MAZING?!? Nice.
Second, we are working on looking at (b)(5) (b)(5) We've heard abnormal echo findings are seen in MIS-C. Do you know what echo findings specifically are being documented in the literature? We're happy to delve into the literature ourselves, but wondering if your team has put together something (maybe one of those Science Reports that I used to get weekly)? As you know, there is just not enough time in the day!

Thanks, and hope you and kitty are staying well,
Lindsay

Lindsay Kim, MD, MPH
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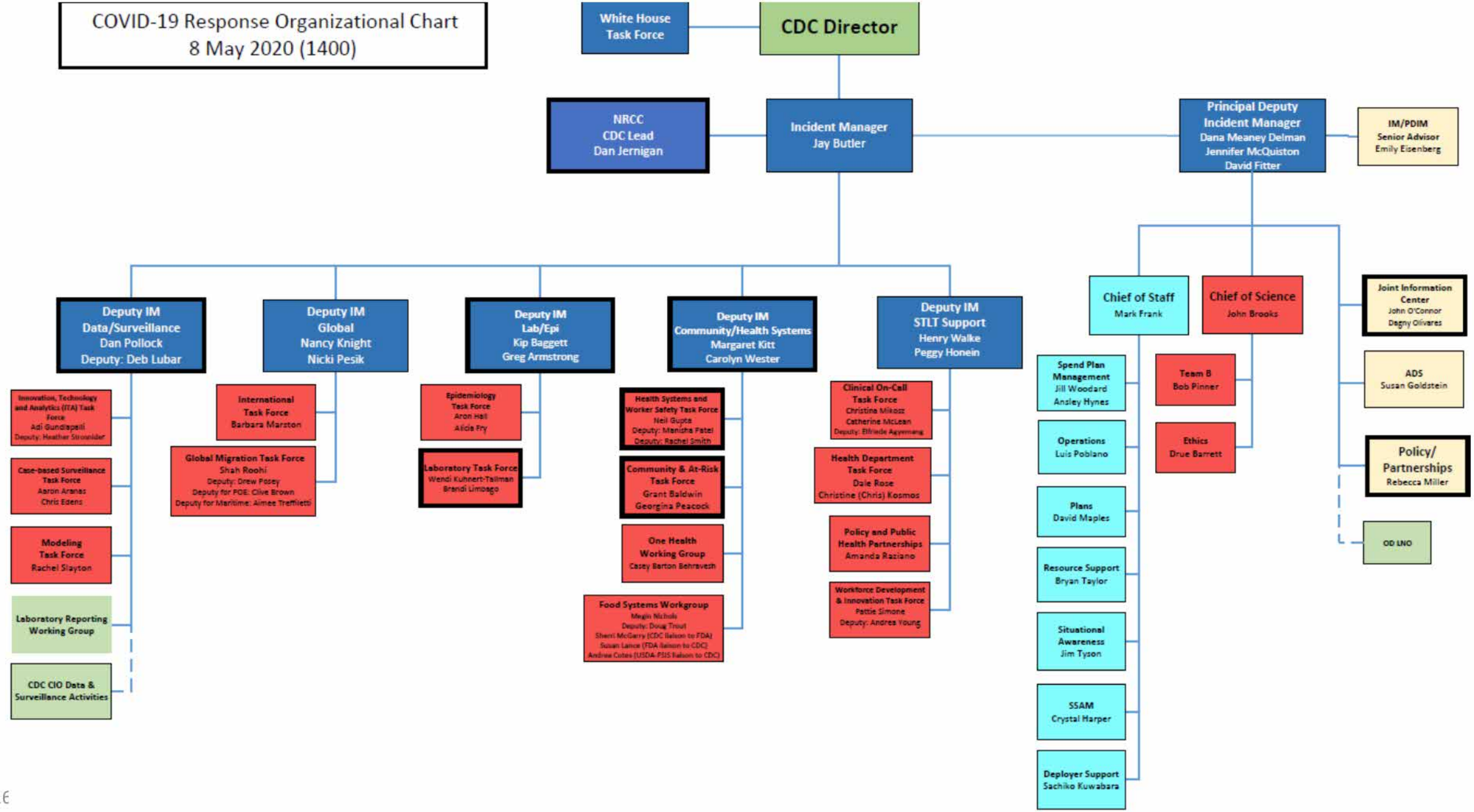
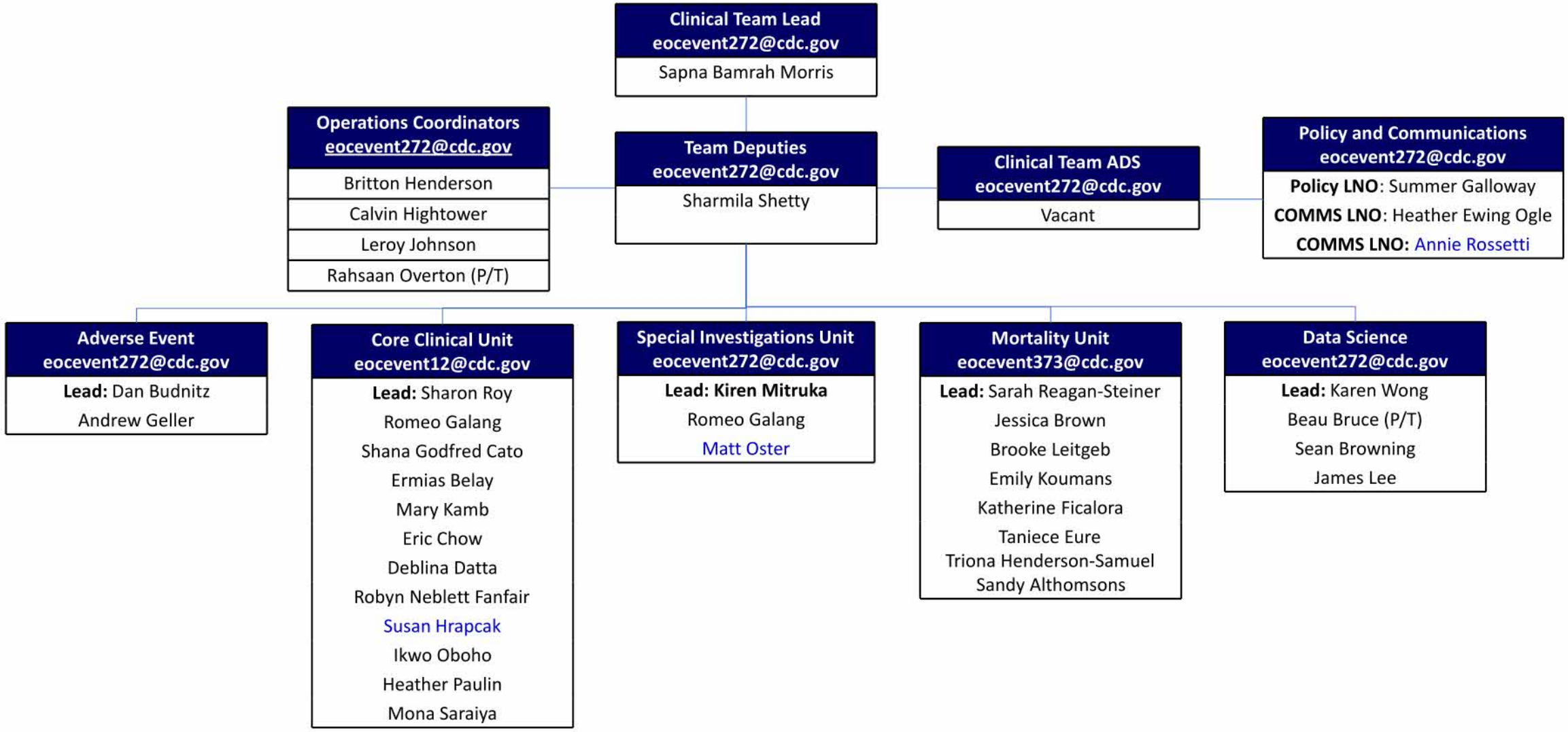
Health Systems and Worker Safety Task Force

May 10, 2020

COVID-19 Response Organizational Chart
8 May 2020 (1400)

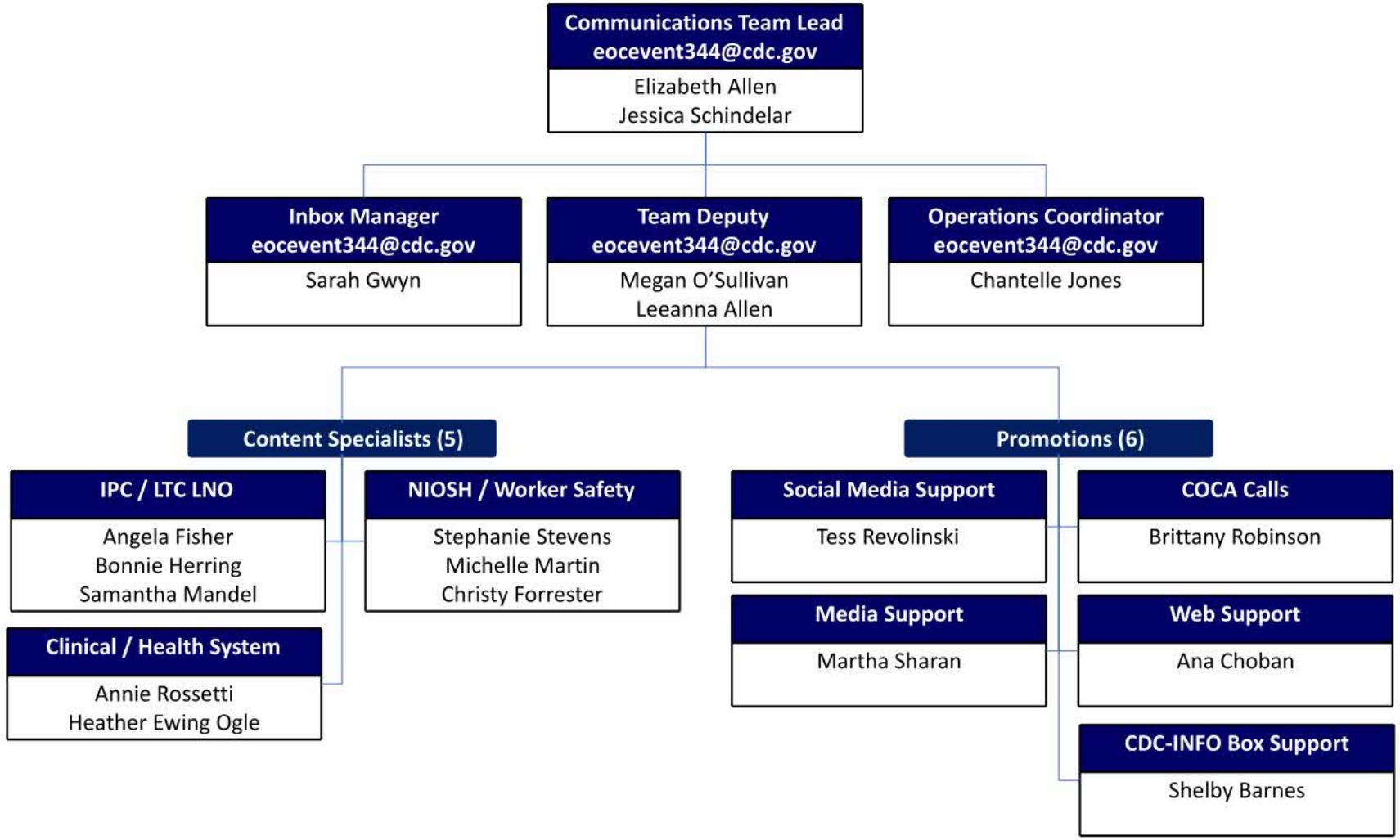


Health Systems and Worker Safety Task Force
Clinical Team



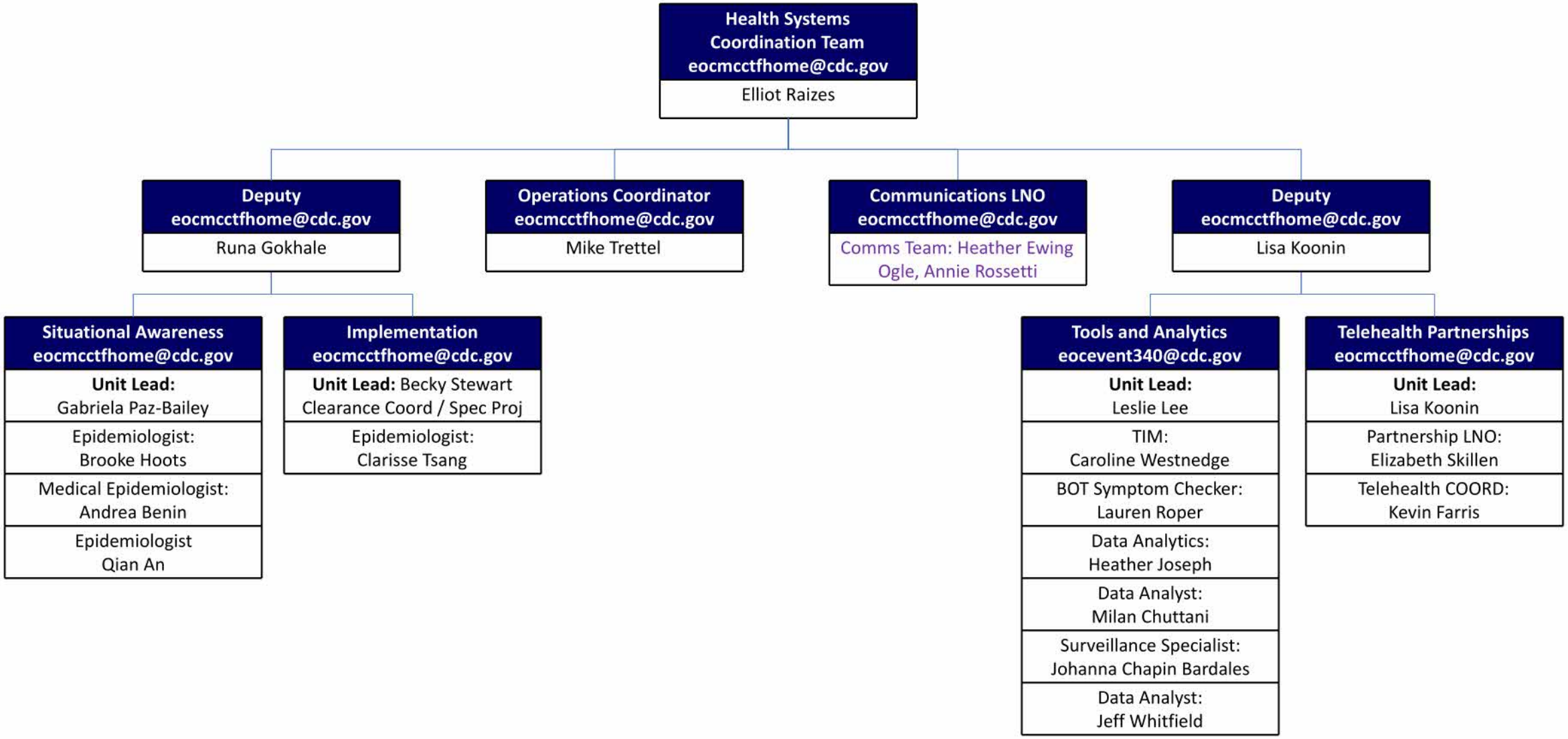
As of 10May 4:06 p.m.

Health Systems and Worker Safety Task Force
Communications Team



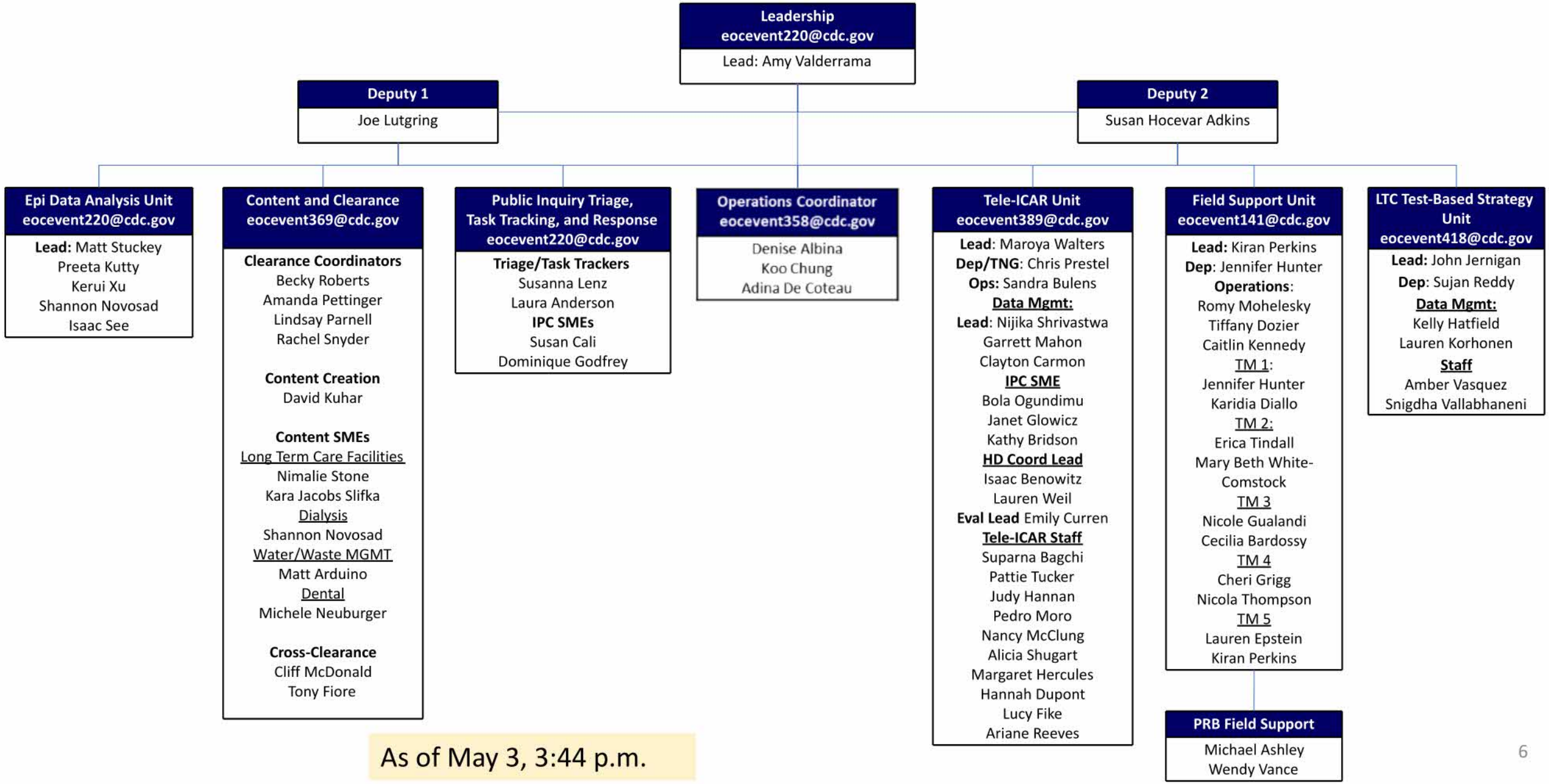
As of May 8, 3:50 p.m.

Health Systems and Worker Safety Task Force
Health Systems Coordination Team



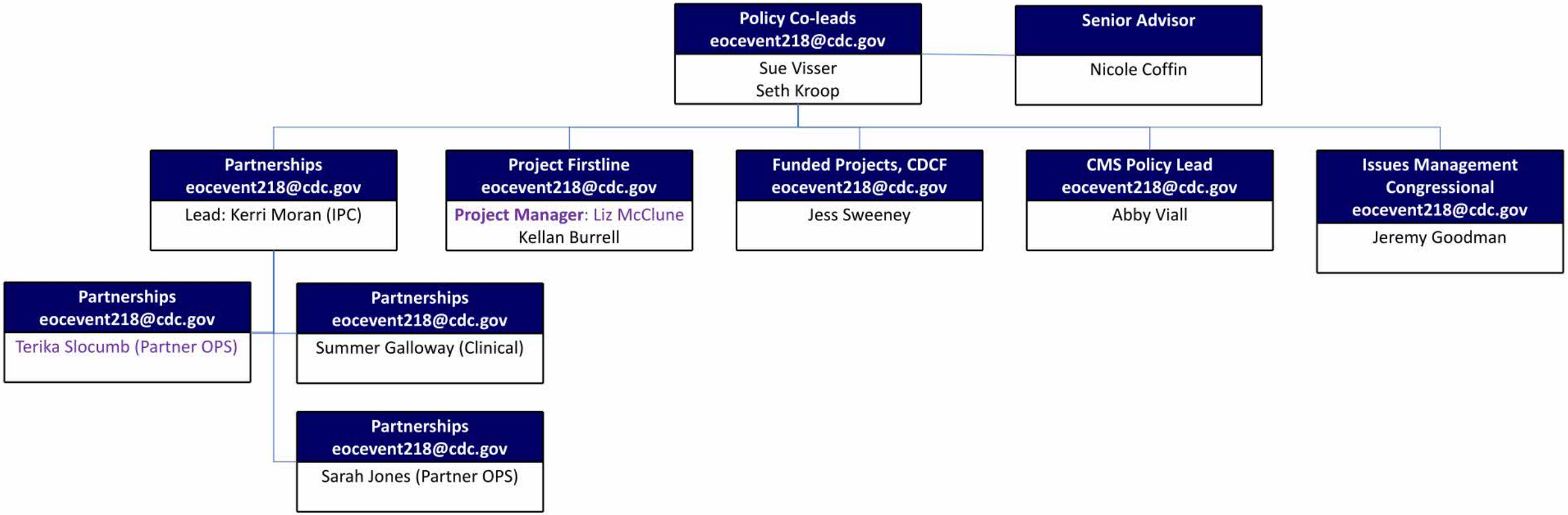
As of 1 May 3:28 p.m.

Health Systems and Worker Safety Task Force
Infection Prevention and Control Team



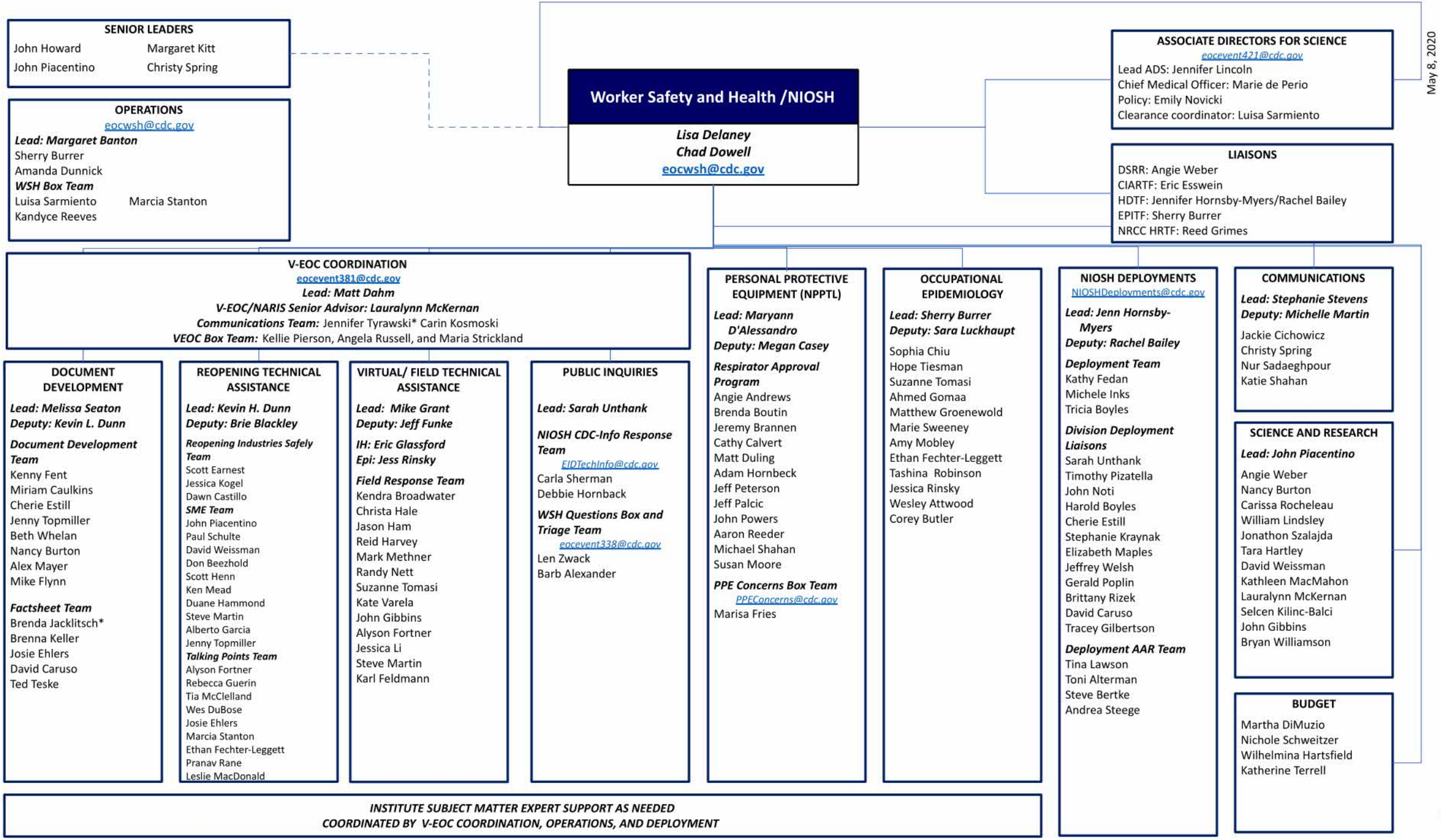
As of May 3, 3:44 p.m.

Health Systems and Worker Safety Task Force
Policy and Partnership Team



Supporting; Not Rostered

As of May 5, 5:00 p.m.


SENIOR LEADERS
John Howard
Margaret Kitt
John Piacentino
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Lead: Margaret Banton
Sherry Burrer
Amanda Dunnick
WSH Box Team
Luisa Sarmiento
Marcia Stanton
Kandyce Reeves
Worker Safety and Health /NIOSH
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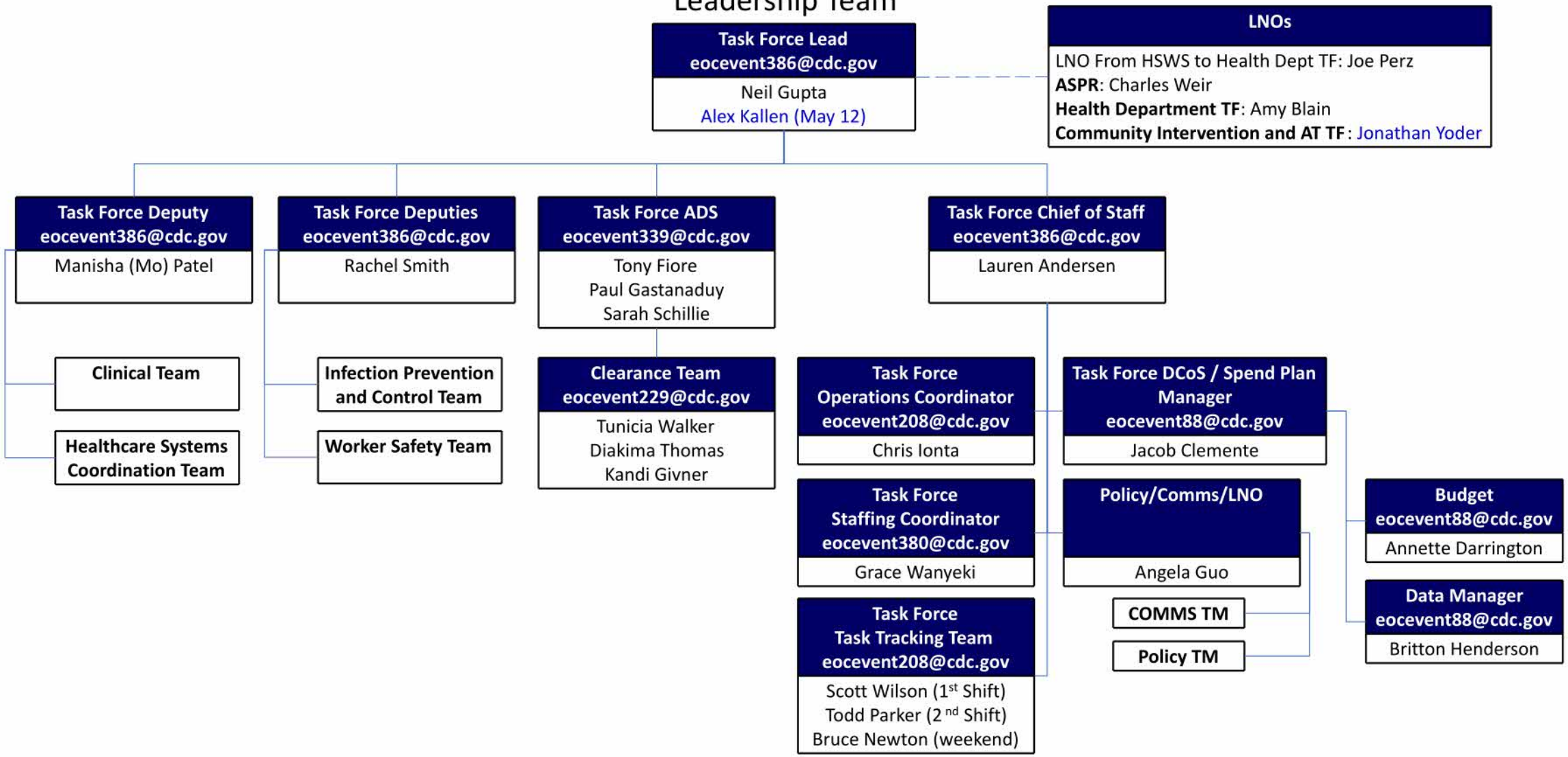

From: Vitek, Charles (CDC/DDPHSIS/CGH/DGHT)
Sent: Sun, 23 Aug 2020 00:24:49 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Subject: Increasing circulation (of info)
Attachments: COVID and vascular disease.pdf

John,
I know you're on vacation but just passing these 2 along for your future pleasure and increased worry.

1 page summary of data on COVID-19 affecting vasculature.

Link to case report of fatal myocarditis in 11 y.o. with visualization of virus in heart. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30257-1/fulltext?dgcid=hubspot_email_newsletter_tlcoronavirus20&utm_campaign=tlcoronavirus20&utm_medium=email&_hsmi=93691430&_hsenc=p2ANqtz-_e6SAHsah4KDy8a6GtBqePVpA3g_FoGBFHTd8psblrLJgdLPPHf9j40wKlDDpi1oYF6kkz0sgqfeB9BShrcOy8JxiuGw&utm_content=93685298&utm_source=hs_email

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COVID-19 and vascular disease

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was originally characterised as a novel respiratory coronavirus and was thought to primarily target pulmonary tissues in infected patients, similar to its close relative SARS-CoV, which was responsible for the epidemic of SARS in 2003. This preconception turned out to be an underestimation. Although SARS-CoV-2 does indeed infect pulmonary epithelial cells, it might also infect many other cell types, causing systematic inflammation with cytokine release and affecting multiple critical organs besides the lungs in severe cases.

In some patients, SARS-CoV-2 appears to attack the cardiovascular system, causing numerous cardiovascular complications. Back in January 2020, clinicians from Wuhan (Hubei, China) reported myocardial injury in patients with COVID-19 in a study published by *The Lancet*. In another study, published in *The Lancet Respiratory Medicine* on February 17, researchers observed interstitial mononuclear inflammatory infiltrates in the heart tissue of a deceased patient with COVID-19. Furthermore, myocardial damage and heart failure have been reported to contribute to causes of death that were linked to COVID-19 complications. In addition to inducing an overreactive inflammatory response, recent studies have shown that SARS-CoV-2 might also directly attack vascular endothelial cells and disrupt vascular barrier, leading to disseminated intravascular coagulation and inflammatory cell infiltration. As our understanding of the disease pathology improves, evidence is emerging that vascular pathology could have a substantial role in COVID-19 disease outcome.

In a *Lancet* paper published on April 20, 2020, Frank Ruschitzka and colleagues from University Hospital Zürich (Zürich, Switzerland) observed direct SARS-CoV-2 infection of endothelial cells and diffuse endothelial inflammation in vascular beds of different organs in patients with COVID-19. Indeed, the angiotensin converting enzyme 2 (ACE2) receptor required for SARS-CoV-2 infection is expressed on the surface of endothelial cells. Shortly after their study was published, several other post-mortem studies showed similar patterns of vascular damage in deceased patients who had COVID-19. For example, two studies published in *The New England Journal of Medicine* on May 21 and *The Lancet Respiratory Medicine* on May 27 showed distinctive vascular features of severe endothelial injury, widespread thrombosis with microangiopathy, and increased vascular angiogenesis in the lungs of patients with COVID-19. Thrombosis not only occurs in the infected lung, but also in other organs including the heart and kidneys, as Amy Rapkiewicz and colleagues reported in *EClinicalMedicine* on June 25. All these data indicate that vasculopathy is likely to be important in COVID-19 pathogenesis and endothelial cells could themselves have a role in orchestrating the destructive intravascular coagulopathy associated with SARS-CoV-2 infection.

Immune mechanisms have been proposed to explain COVID-19-associated intravascular coagulopathy. Injured endothelial cells cause vascular leakage, trigger uncontrolled blood clotting, and recruit different types of immune cells and immunological factors that result in widespread inflammation and further vascular damage, forming a vicious cycle. In a single-centre, cross-sectional study published in *The Lancet Haematology* on June 30, George Goshua and colleagues from Yale University (New Haven, CT, USA) determined the role of endotheliopathy in COVID-19-associated coagulopathy pathogenesis and provided novel mechanistic insights into COVID-19-associated endotheliopathy. The authors discovered increased concentrations of plasma von Willebrand factor (VWF) in patients with COVID-19, which increased with disease severity. Plasma concentrations of soluble thrombomodulin correlated with clinical outcomes, with in-hospital mortality significantly lower in patients with low soluble thrombomodulin than in patients with high soluble thrombomodulin. Only endothelial cells and megakaryocytes can produce VWF, which has a major role in blood coagulation. As commented by O'Sullivan and colleagues in the same issue, these data support a mechanistic model in which alterations of plasma VWF and thrombomodulin concentrations following endothelial cell injury caused by SARS-CoV-2 infection lead to clinical prothrombotic manifestations of coagulopathy in patients with COVID-19. In other words, released VWF binds to platelets, neutrophils, and monocytes to initiate microvascular thrombosis; meanwhile, thrombomodulin further promotes a procoagulant and proinflammatory local milieu within the injured vasculature.

An increasing appreciation of the role of endothelial cells in COVID-19 pathogenesis has prompted research into vascular normalisation and anticoagulation strategies. For instance, bevacizumab, a monoclonal antibody targeting VEGF, can inhibit its vessel-permeabilizing activity and could help to maintain vasculature integrity in patients with COVID-19. Clinical trials (NCT04344782, NCT04275414, and NCT04305106) are exploring the effect of targeting this vascular factor on COVID-19 disease. One Phase 3 trial from Canada (NCT04362085) is recruiting patients to test the effect of therapeutic anticoagulant heparin in patients who are hospitalised with COVID-19. We await results of these trials with hope.

Our understanding of COVID-19 has evolved rapidly over the past few months and new therapies have been proposed and tested. Nevertheless, many mysteries remain. Future scientific discoveries will shed new light on our understanding of COVID-19. In particular, we at *EBioMedicine* look forward to seeing translational and clinical studies that could accelerate the diagnosis, management and treatment of this devastating disease.

EBioMedicine

https://doi.org/10.1016/j.ebiom.2020.102966

From: Oster, Matt (CDC/DDNID/NCBDDD/DBDID)
Sent: Thu, 9 Jul 2020 17:12:49 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE)
Subject: Return to competitive sports
Attachments: Phelan - Resumption of Sport and Exercise After Coronavirus Disease 2019 (COVID-19) Infection - 2020.pdf

See attached. (b)(5)

(b)(5)

Thoughts?

Matthew Oster, MD, MPH
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From: Matt Oster <OsterM@kidsheart.com>
Sent: Thursday, July 9, 2020 1:04 PM
To: Oster, Matt (CDC/DDNID/NCBDDD/DBDID) <IGP8@cdc.gov>
Subject: FW: Town Hall Question: Sibley Feedback

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From: Matt Oster
Sent: Thursday, July 9, 2020 12:24 PM
To: Timothy Slesnick <SlesnickT@kidsheart.com>; William Mahle <MahleW@kidsheart.com>; William Border <Borderw@kidsheart.com>

Cc: Ritu Sachdeva <sachdevar@kidsheart.com>
Subject: RE: Town Hall Question: Sibley Feedback

Looping Ritu into this as I'm not sure this really jives with AUC. Ritu, see attached and below.

I'm on the ACC webinar right now and, to be fair, they are at least having some panelists with alternative viewpoints to this. And they readily acknowledged that this is a very conservative approach based on hypothetical concern, not data.

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From: Matt Oster
Sent: Tuesday, July 7, 2020 9:02 AM
To: Timothy Slesnick <SlesnickT@kidsheart.com>; William Mahle <MahleW@kidsheart.com>; William Border <Borderw@kidsheart.com>
Subject: RE: Town Hall Question: Sibley Feedback

Here's the article. It's a viewpoint article. 2 things to note:

1. Our friend Jonathan Kim at Emory is a co-1st author on this. The ACC Sports and Exercise council endorsed the viewpoint, and he also wrote a piece for ACC regarding the article: https://www.acc.org/latest-in-cardiology/articles/2020/05/13/12/53/return-to-play-and-covid-19
2. The authors readily acknowledge that there is zero evidence regarding those who weren't hospitalized:
    a. "Whether the increased risk of myocardial injury in hospitalized patients with COVID-19 translates to mildly ill nonhospitalized patients is unknown but underscores the need to carefully consider the possibility of cardiac injury among nonhospitalized patients with COVID-19."

Personally I feel that before you implement a recommendation to screen all mildly ill nonhospitalized patients for cardiac problems, you should first demonstrate that the problem exists and that it can be detected via labs/imaging. I don't think that's been done.

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From: Timothy Slesnick <SlesnickT@kidsheart.com>
Sent: Monday, July 6, 2020 9:40 PM
To: William Mahle <MahleW@kidsheart.com>; Matt Oster <OsterM@kidsheart.com>; William Border <Borderw@kidsheart.com>
Subject: RE: Town Hall Question: Sibley Feedback

Agree that this seems aggressive. The algorithm actually says "mild symptoms", not even mild / moderate! As you both said, not sure there is true data to support this rather than just being conservative since we still don't know a lot about the virus. Having said that, if ACC put this out, it's hard to not support it unless we actually have data to refute it. I suspect we may be stuck here.
Tim
PS I do also worry that at 2 weeks out, while we think people are not contagious anymore, I'm not sure that we actually have all the data to support that (Matt can correct me if I'm wrong). Pts with more severe symptoms who get repeated testing have stayed positive for longer periods (see also our CAVC first pt). While I get that they have more aggressive disease, since most people don't get a fu test to prove they are negative, I worry that this may be setting our clinics up for lots of exposures.

From: William Mahle
Sent: Monday, July 06, 2020 6:50 PM
To: Matt Oster; William Border; Timothy Slesnick
Subject: RE: Town Hall Question: Sibley Feedback

Here it is by algorithm

B

From: William Mahle
Sent: Monday, July 06, 2020 6:41 PM
To: Matt Oster; William Border; Timothy Slesnick
Subject: Fwd: Town Hall Question: Sibley Feedback

Seems kind of crazy. Mild to moderate symptoms could be anything

Thoughts?

Bill

Sent from my iPhone

Begin forwarded message:

From: "Johnson, Kate" <kate.johnson@choa.org>
Date: July 6, 2020 at 6:09:29 PM EDT

To: William Mahle <MahleW@kidsheart.com>
Subject: Town Hall Question: Sibley Feedback

Hi—hope you enjoyed the holiday weekend! The below question was received during last week's MD Town Hall. Do you have a response we can include as part of our FAQs? (Please feel free to forward me along to someone else in the practice). Thanks!

> The American College of Cardiology's Sports & Exercise Cardiology Council, with input from national leaders in sports cardiology, have provided a consensus expert opinion clinical framework on return to play in the era of COVID-19. They recommend sensitive cardiac biomarkers (troponin), EKG and echo prior to return to play for any athlete with COVID-19 who had mild -moderate symptoms. Is the Sibley Cardiology group in agreement with this and prepared to accommodate the large number of student athletes who may require this testing? If not, what recommendations/guidelines are in place locally for clearing these athletes to return to sports?

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VIEWPOINT

A Game Plan for the Resumption of Sport and Exercise After Coronavirus Disease 2019 (COVID-19) Infection

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Coronavirus disease 2019 (COVID-19) is associated with significant mortality and morbidity, including adverse cardiovascular sequelae.[1] As public health policy begins to guide the resumption of recreational and competitive sport, clinicians are charged with determining when competitive athletes and highly active individuals who have been infected with COVID-19 and recovered are medically appropriate to return to play. There are limited data establishing the epidemiologic and clinical metrics required to facilitate this process. Specifically, the prevalence of asymptomatic COVID-19 cases in the community, the prevalence of cardiac injury among nonhospitalized individuals with COVID-19, and long-term outcomes attributable to COVID-19 cardiac injury remain unknown. Recognizing these limitations, members of the American College of Cardiology's Sports & Exercise Cardiology Council, with input from national leaders in sports cardiology, provide a consensus expert opinion clinical framework on return to play in the era of COVID-19.

Significant cardiac morbidity has been observed among hospitalized patients with COVID-19. Acute cardiac injury, defined as troponin levels more than the 99th percentile, electrocardiographic and/or echocardiographic abnormalities, occur in up to 22% of hospitalized patients with COVID-19,[2] which is significantly higher compared with the approximately 1% prevalence in non–COVID-19 acute viral infections. Myocarditis from myocyte invasion by the virus could result in cardiac dysfunction, arrhythmias, and death. In the acute phase, exercise could result in accelerated viral replication, increased inflammation and cellular necrosis, and a proarrhythmic myocardial substrate. Return to play after myocarditis is predicated on normalization of ventricular function, absence of biomarker evidence of inflammation, and absence of inducible arrhythmias. Risk stratification may occur after 3 to 6 months of exercise restrictions[3] and is based on extensive testing including echocardiography, stress testing, and rhythm monitoring.

Evidenced-based recommendations for return-to-play guidelines are currently limited and clearly subject to change as further data are obtained in concert with improved COVID-19 case identification. Acknowledging these imperfections, our recommendations are exclusive to cardiovascular considerations and concomitant pulmonary limitations also require consideration. The duration of illness has proved critical in the clinical course of patients infected with COVID-19, with increased risk of clinical deterioration after the first week of symptoms. As such, we recommend an emphasis on the temporal progression of confirmed infection and have incorporated time-based benchmarks in our recommendations (**Figure**).

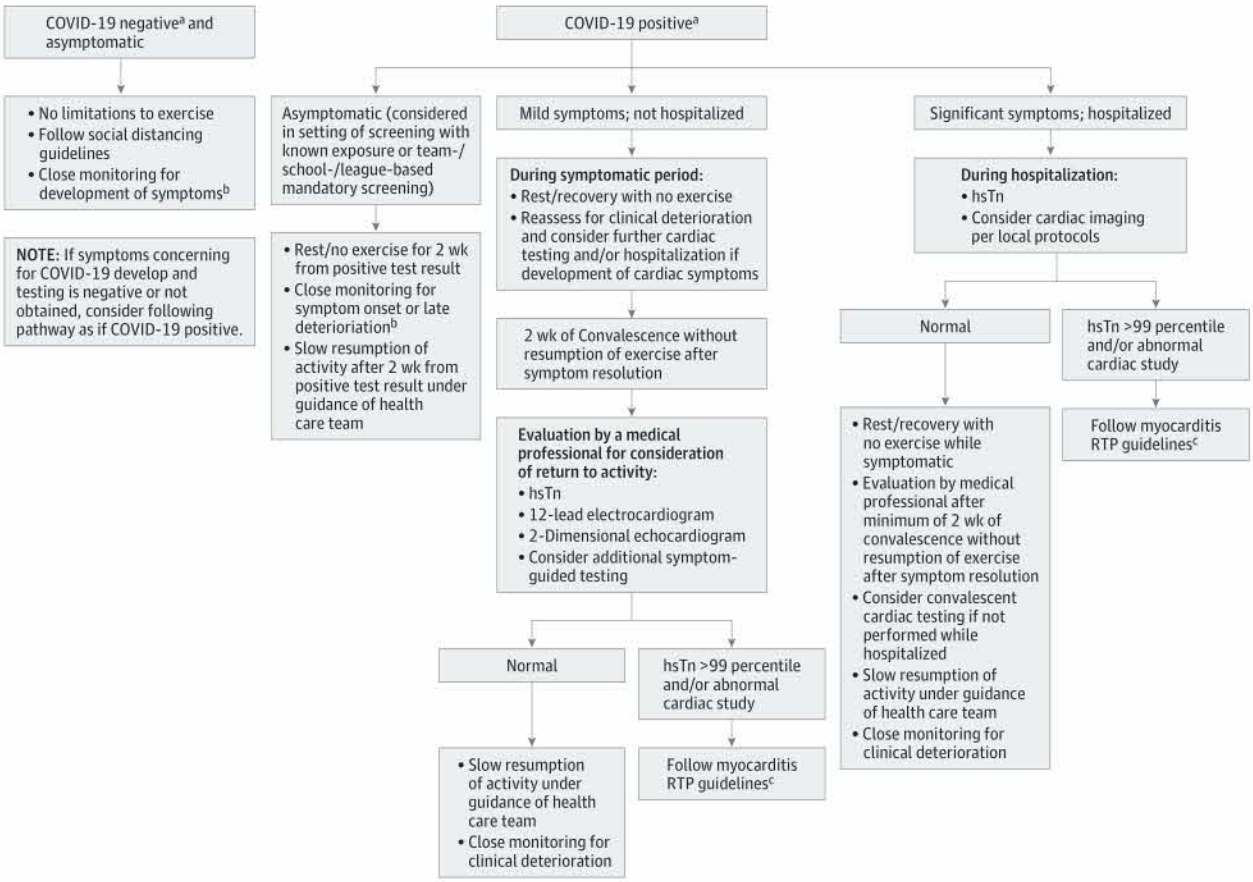
For athletes who remain asymptomatic and are negative for COVID-19, return to exercise training is permissible without additional testing. However, asymptomatic athletes who test positive for COVID-19 antigen (active infection) should refrain from exercise training for at least 2 weeks from the date of positive test result and follow strict isolation guidelines. If athletes remain asymptomatic, slow resumption of activity should be guided under direction from their medical professional. For those asymptomatic individuals with detected COVID-19 antibodies in response to prior infection, we recommend similar evaluation as the asymptomatic athlete with positive COVID-19 test results, and cardiac testing should be considered if there is concern for cardiac involvement.

For athletes who are positive for COVID-19 and develop mild or moderate symptoms, we recommend a minimum of 2 weeks' cessation of any exercise training from symptom resolution. Whether the increased risk of myocardial injury in hospitalized patients with COVID-19 translates to mildly ill nonhospitalized patients is unknown[1] but underscores the need to carefully consider the possibility of cardiac injury among nonhospitalized patients with COVID-19. For recovered individuals ready to resume training after temporal restrictions, we recommend a careful, clinical cardiovascular evaluation in combination with cardiac biomarkers and imaging. Further adjunctive testing with cardiac magnetic resonance imaging, exercise testing, or ambulatory rhythm monitoring should be based on the clinical course and initial testing. With no symptoms and no objective evidence of cardiac involvement, a return-to-exercise training with close clinical follow-up would be reasonable. If testing suggests cardiac involvement, return to play should be based on myocarditis return-to-play guidelines.[3]

Previously hospitalized or more severely ill patients with COVID-19 represent a higher-risk cohort. Acknowledging that myocarditis might not represent the underlying etiology for all hospitalized patients with COVID-19–associated cardiac injury, we recommend following myocarditis return-to-play recommendations.[3] For those who were hospitalized with COVID-19 but whose cardiac biomarkers and imaging studies were normal, we recommend a minimum of 2 weeks' rest after symptom resolution before they undergo careful clinical cardiovascular evaluation with consideration of repeated cardiac testing, followed by a graded resumption of exercise.

Recommendations regarding resumption of intense exercise training and competition requires careful consideration of the severity of prior infection and the likelihood of cardiovascular involvement. The approach provided in this Viewpoint is intended to assist clinicians in this process.

Figure. COVID-19 Return-to-Play Algorithm for Competitive Athlete and Highly Active People



COVID-19 indicates coronavirus disease 2019; hsTn, high-sensitivity troponin I; RTP, return to play.

[a] Typical testing obtained via a nasopharyngeal swab. All athletes with positive testing should be isolated for 2 weeks regardless of symptoms.

[b] If clinical and/or cardiac symptoms develop, follow appropriate clinical pathway.

[c] Given lack of clean pathophysiology, we recommend American College of Cardiology/American Heart Association athlete myocarditis guidelines.

Given the clinical uncertainty regarding the prevalence and magnitude of postinfectious complications, we acknowledge that our proposed approach is conservative and subject to change when the prevalence of cardiac injury in nonhospitalized athletes is better defined. We emphasize the critical need for widespread antigen testing, the development and dissemination of antibody testing, and ultimately vaccination to prevent disease. These important public health objectives coupled with rigorous surveillance of long-term clinical outcomes among athletes will be required to ensure the safe global resurrection of a thriving sport and athletic industry.

ARTICLE INFORMATION

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Author Contributions: Drs Phelan and Kim contributed equally as co-first authors.

Conflict of Interest Disclosures: Dr Kim receives compensation for his role as team cardiologist for the Atlanta Falcons. No other disclosures were reported.

Additional Contributions: This Viewpoint is endorsed by the American College of Cardiology Sports and Exercise Cardiology Section. In addition, the Section acknowledges contributions from Aaron L. Baggish, MD (Massachusetts General Hospital, Boston); Michael S. Emery, MD (Indiana University School of Medicine, Indianapolis); Benjamin D. Levine, MD (University of Texas Southwestern Medical Center, Dallas); and Mathew W. Martinez, MD (Atlantic Health System, Morristown, New Jersey). These individuals were not compensated for their effort and contributed to all recommendations put forth in this expert consensus document

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From: Oster, Matt (CDC/DDNID/NCBDDD/DBDID)
Sent: Tue, 5 May 2020 02:55:26 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP); Chatham-Stephens, Kevin (CDC/DDNID/NCBDDD/DHDD)
Subject: FW: Slides for PIMS-TS
Attachments: PIMS-TS 05042020_final.pptx

Sharing these slides from the Core Clinical Unit…

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From: Chow, Eric (CDC/DDID/NCIRD/ID) <okl9@cdc.gov>
Sent: Monday, May 4, 2020 10:42 PM
To: Oster, Matt (CDC/DDNID/NCBDDD/DBDID) <IGP8@cdc.gov>; Godfred Cato, Shana (CDC/DDNID/NCBDDD/DBDID) <nzt6@cdc.gov>; Kimball, Anne (CDC/DDID/NCHHSTP/DSTDP) <opu7@cdc.gov>
Subject: Slides for PIMS-TS

Hey Matt,

Here are some slides that we are presenting within our team tomorrow. Feel free to use as needed. They are based off the data that was presented on Saturday.

Eric

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Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

- April 26 - the Pediatric Intensive Care Society (UK) tweeted about a newly recognized inflammatory syndrome in children with Kawasaki-like features that was thought to be temporally associated with SARS-CoV-2
- 100+ cases identified so far across multiple European countries; Number of cases increasing about 2 weeks after peak of COVID-19 cases
- May 2 - Pediatric Intensive Care Society COVID-19 International Collaborative call coordinated by Boston Children's

Possible association with SARS-CoV-2: Some children are positive for SARS-CoV-2, others SARS-CoV-2 IgG positive and others have family members who have had COVID-19.

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Royal College of Paediatrics and Child Health (RCPCH) Case Definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.

3. SARS-CoV-2 PCR testing may be positive or negative

Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Clinical Signs/Symptoms (From the UK, N = 38)

- 75% have shock
- 57% with abdominal involvement – normal lap appy
- 51% have myocardial involvement
- 54% have rash
- 38% with AKI; 1 requiring RRT
- 32% with respiratory symptoms
- 30% with conjunctivitis
- 20% with mucous membrane involvement

Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Lab Findings (From the UK, N = 38)

- In total, 23/38 of patients have positive SARS-CoV-2 PCR or IgG

- Commonly will have:
  - Inc CRP
  - Inc neutrophils
  - Lymphopenia
  - Inc D-Dimer
  - Anemia
  - Inc troponin
  - Inc Ferritin
  - Inc BNP
  - Dec albumin

Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Phenotypic Classification (Proposed)

1. Kawasaki (outbreak in the setting of COVID-19 pandemic)

2. COVID-19 associated/triggered “Kawasaki Syndrome” (in COVID-19 + patients)

3. COVID-19 shock syndrome/toxic shock syndrome (in COVID-19 + patients)
   a. With normal cardiac function (with or without coronary aneurysms)
   b. With impaired cardiac function (with or without coronary aneurysms)

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Possible Mechanisms:

1. Immune complexes that activate inflammation through FC Gamma Receptors or activate neutrophils, macrophages and/or platelets

2. Antibodies enhance disease by facilitating viral entry into tissues (like Dengue)

3. Antibodies that directly damage tissue through complement or neutrophil activation

Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Interesting Findings:

1. No apparent increase in Kawasaki Disease or Kawasaki like Illness in Japan, Taiwan or Korea; China has not published on this topic

2. In UK cohort, 46% are Black, Black-Caribbean, Black-British

Y

Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

Path Forward:

- Call with CSTE on May 4, 2020 (Matt Oster (CDC) presented UK case definition)
- Collaboration with ARTF, possibly Epi TF, and Kawasaki Disease group (DHCPP)
- Work group? Call for cases? Special projects?

From: Oster, Matt (CDC/DDNID/NCBDDD/DBDID)
Sent: Tue, 19 May 2020 13:54:41 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE); Kim, Lindsay (CDC/DDID/NCIRD/DVD)
Cc: Garg, Shikha (CDC/DDID/NCIRD/ID); Acosta, Anna (CDC/DDID/NCIRD/DBD)
Subject: RE: Echo findings in MIS-C
Attachments: Belhadjer - Heart failure in MIS-C in France and Switzerland - 2020.pdf

Not really seeing aneurysms. Often seeing decreased cardiac function. Best article to date summarizing cardiac findings is attached. I've also pasted a key table below:

Table 2. Cardiac signs

	n (%)
Clinical signs	
Chest pain	6 (17)
Cardiogenic shock with collapse	28 (80)
Ventricular arrhythmia	1 (3)
Systolic blood pressure at admission (percentile (IQR))	1 (1-10)
Coronary artery dilatation Z-score > +2	6 (17)
Aneurysms at day 10 (echography only)	0 (0)
Left ventricular ejection fraction at baseline, n (%)	
<30%	10 (28)
30-50%	25 (72)
Evolution of LVEF (median±SD)	
Baseline (35 patients)	32±9
Day 3 (23 patients)	52±10
Day 7 (34 patients)	60±6
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Time to full recovery, days (median and range)	2 (2-5)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Matthew Oster, MD, MPH
CDC COVID-19 MIS-C Working Group, HSWS Clinical Team Special Investigations Unit
CDC Center on Birth Defects and Developmental Disabilities
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From: Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE) <zud4@cdc.gov>
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Subject: RE: Echo findings in MIS-C

PS: do you have an organogram, for HSWS? Seem huge and I can't figure out who is where doing what!

And nothing in the literature I am of aware yet other than the attached…

Sapna is really interest in the whole hyperimmune/immune-mediated phenomenon across the whole age spectrum and how it is express physiologically (e.g., myocarditis, renal injury, derm, hypercoaguability...). Have you connected with her?

-john

John T. Brooks, MD
Chief Medical Officer, CDC COVID-19 Response
Email: zud4@cdc.gov
Apologies for errors in my messages that may be due to my need to dictate.

http://intranet.cdc.gov/library/covid19/index.html

From: Kim, Lindsay (CDC/DDID/NCIRD/DVD) <iyn2@cdc.gov>
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Subject: Echo findings in MIS-C

Hi John:

First, can I just say this photo below is AH-MAZING?!? Nice.
Second, we are working on looking at (b)(5) (b)(5) We've heard abnormal echo findings are seen in MIS-C. Do you know what echo findings specifically are being documented in the literature? We're happy to delve into the literature ourselves, but wondering if your team has put together something (maybe one of those Science Reports that I used to get weekly)? As you know, there is just not enough time in the day!

Thanks, and hope you and kitty are staying well,
Lindsay

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Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic

Running title: *Belhadjer et al.; Pediatric acute heart failure and SARS-CoV-2 infection*

Zahra Belhadjer, MD, et al.

The full author list is available on page 13

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Abstract

Background: Cardiac injury and myocarditis have been described in adults with COVID-19. SARS-CoV-2 infection in children is typically minimally symptomatic.
We report a series of febrile pediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection and the multisystem inflammatory syndrome in children (MIS-C) as defined by the US Centers for Disease Control.
Methods: Over a two-month period contemporary with the SARS-CoV-2 pandemic in France and Switzerland, we retrospectively collected clinical, biological, therapeutic, and early outcomes data in children who were admitted to pediatric intensive care units in 14 centers for cardiogenic shock, left ventricular dysfunction and severe inflammatory state.
Results: Thirty-five children were identified and included in the study. Median age at admission was 10 years (range 2-16 years). Co-morbidities were present in 28% including asthma and overweight. Gastrointestinal symptoms were prominent. Left ventricular ejection fraction was <30% in one third; 80% required inotropic support with 28% treated with ECMO. Inflammation markers were suggestive of cytokine storm (interleukin 6 median 135 pg/mL) and macrophage activation (D-dimer median 5284 ng/mL). Mean brain natriuretic peptide was elevated (5743 pg/mL). Thirty-one/35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swab or serology. All patients received intravenous immune globulin, with adjunctive steroid therapy used in one third. Left ventricular function was restored in the 25/35 of those discharged from the intensive care unit. No patient died, and all patients treated with ECMO were successfully weaned.
Conclusion: Children may experience an acute cardiac decompensation due to severe inflammatory state following SARS-CoV-2 infection (multisystem inflammatory syndrome in children - MIS-C). Treatment with immune globulin appears to be associated with recovery of left ventricular systolic function.

Key Words: heart failure; inflammatory cardiomyopathy; SARS-CoV-2; children; COVID-19; atypical Kawasaki disease

Non-standard Abbreviations and Acronyms

MIS-C	Multi-System Inflammatory Syndrome in Children
PICU	Pediatric intensive care unit

Clinical perspective

What is new?

- Multisystem inflammatory syndrome in children (MIS-C) is a new syndrome that is temporally related to previous exposure to the SARS-CoV-2.
- MIS-C shares similarities with atypical Kawasaki disease but prominent clinical signs are largely different.
- Myocardial involvement with acute heart failure is likely due to myocardial stunning or edema rather than to inflammatory myocardial damage.

What are the clinical implications?

- Whereas the initial presentation may be severe with some patients requiring mechanical circulatory and respiratory assistance, rapid recovery with the use of immune globulin and steroids is currently observed.
- Additional study is needed to determine the full spectrum of illness and whether long-term cardiac complications may arise.

Introduction

SARS-CoV-2 infection in children is thought to be relatively mild compared with adult patients, and often asymptomatic or minimally symptomatic (1-3). To date, limited awareness has been afforded to possible SARS-CoV-2-related cardiovascular injury in the pediatric population. However, we recently observed an unexpectedly large number of children hospitalized in intensive care units for cardiogenic shock or acute left ventricular dysfunction in the setting of a multisystem inflammatory state, with a large proportion of those testing positive for SARS-CoV-2.

We describe here a new complex syndrome in 35 children admitted for acute heart failure in febrile patients that is temporally related to previous exposure to SARS-CoV-2 (multisystem inflammatory syndrome in children - MIS-C). We discuss similarities and differences with other pediatric inflammatory diseases with cardiac involvement, as well as current management and preliminary data on early outcomes.

Methods

Study population

The study was approved by the local ethics committee of our institution, which waived the need for patient consent. We will make the data and methods used in the analysis, and materials used to conduct the research available to other researchers for purpose of reproducing the results or replicating the procedures.

We retrospectively collected data for all children with acute left ventricular systolic dysfunction or cardiogenic shock and associated multisystem inflammatory state, admitted to 12 hospitals in France and one hospital in Switzerland from March 22, 2020 to April 30, 2020. All of these institutions are located within the most active COVID-19 pandemic areas in France. The inclusion criteria were the presence of fever (>38.5°C), cardiogenic shock or

acute left ventricular dysfunction (left ventricular ejection fraction <50%) with inflammatory state (C-reactive protein > 100 mg/mL).

Demographic characteristics, clinical data (comorbidities, delay between symptom onset and hospital admission, baseline symptoms and physical signs), laboratory findings (including leukocyte and neutrophil counts, BNP or NT-pro-BNP levels, troponin I levels, IL-6 levels, C-reactive protein, D-dimer), results of cardiac examination (ECG and echocardiography), medical treatments, need for invasive or non-invasive respiratory support, need for mechanical circulatory support, and outcome, were retrieved from patients' files.

COVID-19 diagnosis

All patients were tested for SARS-CoV2 during the hospital course by several means: nasopharyngeal RT-PCR, fecal RT-PCR, tracheal swab, and serology (Chemiluminescent Microplate Immunoassay-CMIA technique). A patient was considered to have a COVID-19 infection if any of these tests were positive.

Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous data were expressed as median and interquartile range [IQR] values. Categorical data were expressed as proportions.

Results

Patient Characteristics

Over a period from March 22nd to April 30th, 2020, 35 patients fulfilling the inclusion criteria with febrile cardiogenic shock or left ventricular dysfunction and inflammatory state were included in the study. Demographic data and clinical features are summarized in Tables 1 and 2. Median age was 10 years. None had underlying cardiac disease. Co-morbidities were limited, and 17% of them were overweight.

SARS-Cov-2 infection

SARS-Cov-2 infection was confirmed in 31/35 patients (88.5%). Nasopharyngeal swab polymerase chain reaction (PCR) was positive in 12 patients (34%), and fecal PCR in 2 patients (6%). Thirty out of thirty-five (86%) patients had positive antibody assays: 23 had IgA and IgG, 3 had IgG, 2 had IgG and IgM, and 2 had IgA only. In addition, two patients were negative for SARS-CoV-2 PCR, but had typical lung CT features of COVID pneumonia. Results are missing in five patients. A history of recent contact with family members displaying viral-like symptoms was reported in 13/35 patients.

Presenting clinical symptoms

All children presented with fever (>38.5°C) and asthenia. Gastrointestinal symptoms were common, with abdominal pain, vomiting or diarrhea present in 80% of patients. Two children underwent emergency operation for suspected appendicitis that was ultimately diagnosed as mesenteric adenolymphitis. Clinical signs suggestive of Kawasaki disease - skin rash, cheilitis, cervical adenopathy, meningism - were frequent, but none of the patients met criteria for a classical form of this disease. Only 6 patients complained of chest pain. The electrocardiogram was not specific, with ST segment elevation in only one patient. The median delay between the first clinical symptoms and symptoms of heart failure was 6 days (IQR, 4.5-6 days). The majority (29/35) were admitted directly to the intensive care unit (ICU). Six patients were initially admitted to the regular pediatric ward but deteriorated within the first 24 hours (median 14 hours after admission in hospital) and were transferred into the ICU.

At admission to the ICU, 80% of patients were in cardiogenic shock requiring the use of intravenous inotropic drugs. Ten/35 patients (28%) required mechanical circulatory assistance with veno-arterial extracorporeal membrane oxygenation (V-A ECMO) that was

successfully weaned and removed in all. Two-thirds had respiratory distress requiring invasive mechanical ventilatory support.

Biology

All patients presented with a severe inflammatory state evidenced by elevated C-reactive protein and D-dimer. Interleukin 6 (n=13) was also elevated (Table 3).

Troponin I elevation was constant but mild to moderate. NT-proBNP or BNP elevation was present in all children.

Cardiac imaging

Echocardiography at admission revealed depressed left ventricular systolic function with an ejection fraction below 30% in 10/35 of patients, and between 30 and 50% in 25/35 patients. The Z-score of left ventricular dimensions was normal at admission in 29/35 patients. Left ventricular hypokinesis was global in 31/35 of patients. Three patients manifested segmental wall hypokinesis. One patient manifested a Takotsubo syndrome presentation with akinesis of the apical segment. Right ventricular function was normal in all patients. Pericardial effusion was present in three cases.

Dilatation of the coronary arteries (Z-score >2 adjusted for body temperature) was found in 6 patients (17%) including five patients with dilatation of the left main stem and one with dilatation the right coronary artery (4). No coronary aneurysm has been observed to date but follow-up has been planned to detect this potential complication.

Treatment

The majority of the patients received intravenous (28/35) inotropic support. First line treatment was intravenous immune globulin in 25/35 of patients. One patient was treated with repeated intravenous immune globulin due to persistent fever 48 hours after first infusion. Twelve patients received intravenous steroids having been considered high-risk patients with symptoms similar to an incomplete form of Kawasaki disease. Finally, three children received

treatment with an interleukin 1 receptor antagonist (anakinra) because of persistent severe inflammatory state. In addition, 23/35 patients were treated with therapeutic dose heparin.

Outcome

Clinical evolution has been favorable thus far for 28/35 patients, with 7/35 either still in the hospital or with residual left ventricular dysfunction (Table 4). At time of submission, all patients but one who was on ECMO had left the hospital after a median hospital stay of 8 days. Complete recovery of left ventricular function was observed in 71% of patients at a median delay of 2 days after admission. Five patients had residual mild to moderate left ventricular systolic dysfunction with a left ventricular ejection fraction >45% at last follow-up (median 12 days). None had a thrombotic or embolic event. Median ICU stay was 7 days (IQR 3.7-10 days) and median hospital stay was 10 days (IQR 8-14 days).

Discussion

We report a cluster of admissions for severe heart failure associated with multisystem inflammatory state in children (MIS-C). These findings contrast with prior reports in children in which the impact of COVID-19 in the pediatric population has been reported to be mild (1). Indeed, among the reported cases of COVID-19, the proportion of patients aged <18 years was 1.7% with relatively few being hospitalized. Further, the number of children admitted to a PICU was 0.6%-2.0% confirming that COVID-19 often has a mild course in children (1,2). A recent alert has been raised by the Pediatric Intensive Care Society in the U.S. and by other groups around the world on the rise in the number of children presenting with this emerging condition (5). It has been observed that they manifested features overlapping with toxic shock syndrome and atypical Kawasaki disease together with cardiac inflammation (MIS-C).

Acute myocardial injury/myocarditis associated with SARS-CoV-2 infection has been described in the adult population from the start of the pandemic (6,7). Further, myocardial

injury has been reported in up to 10-20% of patients infected with SARS-CoV-2 manifesting either as fulminant myocarditis, an ejection fraction decline or myocardial enzyme elevation (8,9). In the present series, the rapid resolution of systolic dysfunction together with mild to moderate troponin elevation suggests that the mechanism of heart failure is not consistent with myocardial damage as seen in adults associated with acute infection with SARS-CoV-2.

Clinical presentation

In the present series, abdominal and gastrointestinal symptoms rather than chest pain were prominent features. All children presented with spiking and remittent fever (>39°C to 40°C) with profound asthenia lasting approximately two days. In a large proportion of patients, the hemodynamic presentation at admission to the PICU was shock with low systemic blood pressure. The association with respiratory distress or reduced consciousness led to rapid initiation of ventilatory support. Pediatric intensivists are accustomed to suspect Kawasaki disease in children presenting with febrile shock particularly in older children and adolescents (10). As some patients manifested signs suggestive of atypical or incomplete Kawasaki disease, these patients were initially managed as severe forms of this disease. Indeed, it is well known that Kawasaki disease signs can be overlooked in this part of the pediatric population. Kawasaki disease shock syndrome manifests mainly with low systolic blood pressure or clinical signs of poor perfusion (11,12). Left ventricular systolic dysfunction is seen only a third of the patients but long-lasting diastolic dysfunction is a prominent finding in this syndrome (11). The syndrome that we present here (MIS-C) may share some aspects of the physiology of Kawasaki shock syndrome, but left ventricular systolic dysfunction was present in all patients in association with low systolic blood pressure. Heart failure was an inclusion criterion in our series but MIS-C can also be observed without overt heart failure (5). Resistance to immune globulin treatment or subsequent development of coronary artery aneurysms may be associated with this new syndrome.

Similarities and differences with Kawasaki disease

Some aspects of this emerging pediatric disease (MIS-C) are similar to those of Kawasaki disease: prolonged fever, multisystem inflammation with skin rash, lymphadenopathy, diarrhea, meningism and high levels of inflammatory biomarkers. But differences are important and raise the question as to whether this syndrome is Kawasaki disease with SARS-CoV-2 as the triggering agent, or represents a different syndrome (MIS-C). Kawasaki disease predominantly affects young children <5 years, whereas the median age in our series is 10 years. Incomplete forms of Kawasaki disease occur in infants who may have fever as the sole clinical finding, whereas older patients are more prone to exhibit the complete form. Left ventricular dysfunction was the main cardiac feature in this series, with a limited number of patients having coronary artery dilatation (Table 2). Myocardial inflammation can be documented in a high proportion of patients with Kawasaki disease and it usually precedes coronary artery abnormalities (13). In Kawasaki disease, myocardial edema is the main finding without ischemic damage and with limited cell necrosis as evidenced by the mild to moderate elevation of troponin I (14). Left ventricular systolic dysfunction improved rapidly in our patients as it does in Kawasaki disease concomitant with a decline in the inflammatory process (15). The high levels of brain natriuretic peptide in our series suggest a mechanism of myocardial edema or stunning. In addition, elevated interleukin-6 levels might also be due to stretched cardiomyocytes and cardiac fibroblasts together with macrophage activation, as these immune cells are the principal producer of interleukin-6 (16). Interleukin-6 levels were very high when measured in our patients, and this might partly explain why some were vasoplegic.

The overlapping features between the condition presented here (MIS-C) and Kawasaki disease may be due to similar pathophysiology. The etiologic agent of Kawasaki disease is unknown but likely to be ubiquitous, causing asymptomatic childhood infection but triggering

the immunologic cascade of Kawasaki disease in genetically susceptible individuals. Please note that infection with a novel RNA virus that enters through the upper respiratory tract has been proposed to be the cause of the disease (17,18).

Relation to SARS-CoV-2

Among the proposed mechanisms for myocardial and lung injury caused by SARS-CoV-2, "cytokine storm" triggered by an imbalanced response by proinflammatory and regulatory T cells has been proposed (19). In our series, almost 90% of patients tested positive for SARS-CoV-2 infection. Besides the low sensitivity of PCR, it is possible that the virus has already been cleared from the upper respiratory tract in our patients, as those who had positive serologic test already had IgG type antibodies (20). This suggests that they had been in contact with the virus more than three weeks before admission. The delay between the pandemic in the general population and the recent emergence of this illness in children is surprising. Yet, this is consistent with the usual sequence of a canonical response to a conventional antigen. There are indeed conflicting data regarding peripheral blood T cell activation during acute Kawasaki disease (21). We successfully used intravenous immune globulin in these patients with adjunctive therapy in some of them. The exact mechanism of action of the immune globulin in Kawasaki disease is unclear, but there is clearly an anti-inflammatory action on monocytes/macrophages and consequently on the amount of circulating inflammatory molecules.

Early diagnosis of this SARS-CoV-2 associated multisystem disease complicated by heart failure (MIS-C) is certainly useful in the present period in identifying children who require treatment and in preventing left ventricular dysfunction and acute heart failure. Since the recent alert in France and other countries, we proposed a simple algorithm in the emergency room for children with prolonged and unexplained fever, including rapid NT-proBNP for urgent specialized evaluation for those with elevated NT-proBNP levels, and

more classical management for those without evidence of early cardiac involvement. Since the start of this protocol three weeks ago, we observed an increase in the number of patients with less severe forms of the disease without heart failure and a stable number of admissions for heart failure with none requiring mechanical assistance.

In our series, the majority of patients received intravenous immune globulin treatment with and without steroids. The use of anakinra was rarely indicated (22). Blocking the cytokine storm that obviously plays a role in this condition might be an alternative treatment in resistant forms that have not been yet encountered in our series. Targeting the interleukin-6 receptor or depleting cytokines by other means represent potential approaches available at this time.

In conclusion, the pediatric and cardiology communities should be acutely aware of this new disease probably related to SARS-CoV-2 infection (MIS-C), that shares similarities with Kawasaki disease but has specificities in its presentation. Early diagnosis and management appear to lead to favorable outcome using classical therapies. Elucidating the immune mechanisms of this disease will afford further insights for treatment and potential global prevention of severe forms. Identifying the genetic bases of individual susceptibility is also key to tailored prevention.

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None.

Disclosures

None.

Authors

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Table 1. Clinical signs and symptoms

	Value
Age	
Median	10
Distribution, n	
<1yr	0
1-5 years	1
6-10 years	15
11-16 years	19
Sex, n (%)	
Male	18 (51)
Female	17 (49)
Comorbidity, n (%)	10 (28)
Asthma	3 (8.5)
Lupus	1 (3)
Overweight (BMI > 25)	6 (17)
Signs and symptoms, n (%)	
Asthenia	35 (100)
Fever	35 (100)
Gastrointestinal symptoms	29 (83)
Respiratory distress	23 (65)
Rhinorrhea	15 (43)
Adenopathy	21 (60)
Skin rash	20 (57)
Meningism	11 (31)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 2. Cardiac signs

	n (%)
Clinical signs	
Chest pain	6 (17)
Cardiogenic shock with collapse	28 (80)
Ventricular arrhythmia	1 (3)
Systolic blood pressure at admission (percentile (IQR))	1 (1-10)
Coronary artery dilatation Z-score > +2 Aneurysms at day 10 (echography only)	6 (17) 0 (0)
Left ventricular ejection fraction at baseline, n (%)	
<30%	10 (28)
30-50%	25 (72)
Evolution of LVEF (median±SD)	
Baseline (35 patients)	32±9
Day 3 (23 patients)	52±10
Day 7 (34 patients)	60±6
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Time to full recovery, days (median and range)	2 (2-5)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 3. Laboratory findings

	Baseline	Peak value (Day) (n patients)	Nadir value (Day) (n patients)	Normal values
High sensitive troponin I (ng/L) (n=35)	347 (186-1267)	408 (258-679) Day 1 (n=16)	28 (18-53) Day 10 (n=16)	<26 ng/ml
Creatinine kinase (U/L) (n=19)	174 (110-510)	-	-	<180 U/L
NT-proBNP (n=5)	41484 (35811 - 52475)	-	-	< 300 pg/mL
BNP (pg/mL) (n=28)	5743 (2648 - 11909)	4256 (2340-6503) Day 1 (n=11)	72 (56-140) Day 7 (n=12)	< 100 pg/mL
D-Dimer (ng/ml) (n=20)	5284 (4069-9095)	-	-	< 500 ng/mL
C-reactive protein, (mg/mL) (n=35)	241 (150-311)	-	-	< 6 mg/mL
Procalcitonin (ng/ml) (n=26)	36 (8-99)	-	-	< 2 ng/mL
White blood cell count, $x10^3$/L (n=35)	16 (12-23)	-	-	< $12x10^3$/L
Neutrophil count, x 10^3/L (n=34)	13 (8-19)	-	-	< $8.5x10^3$/L
Interleukin 6 (pg/mL) (n=13)	135 (87-175)	-	-	< 8.5 pg/mL

BNP Brain natriuretic peptide

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 4. Treatment and responses

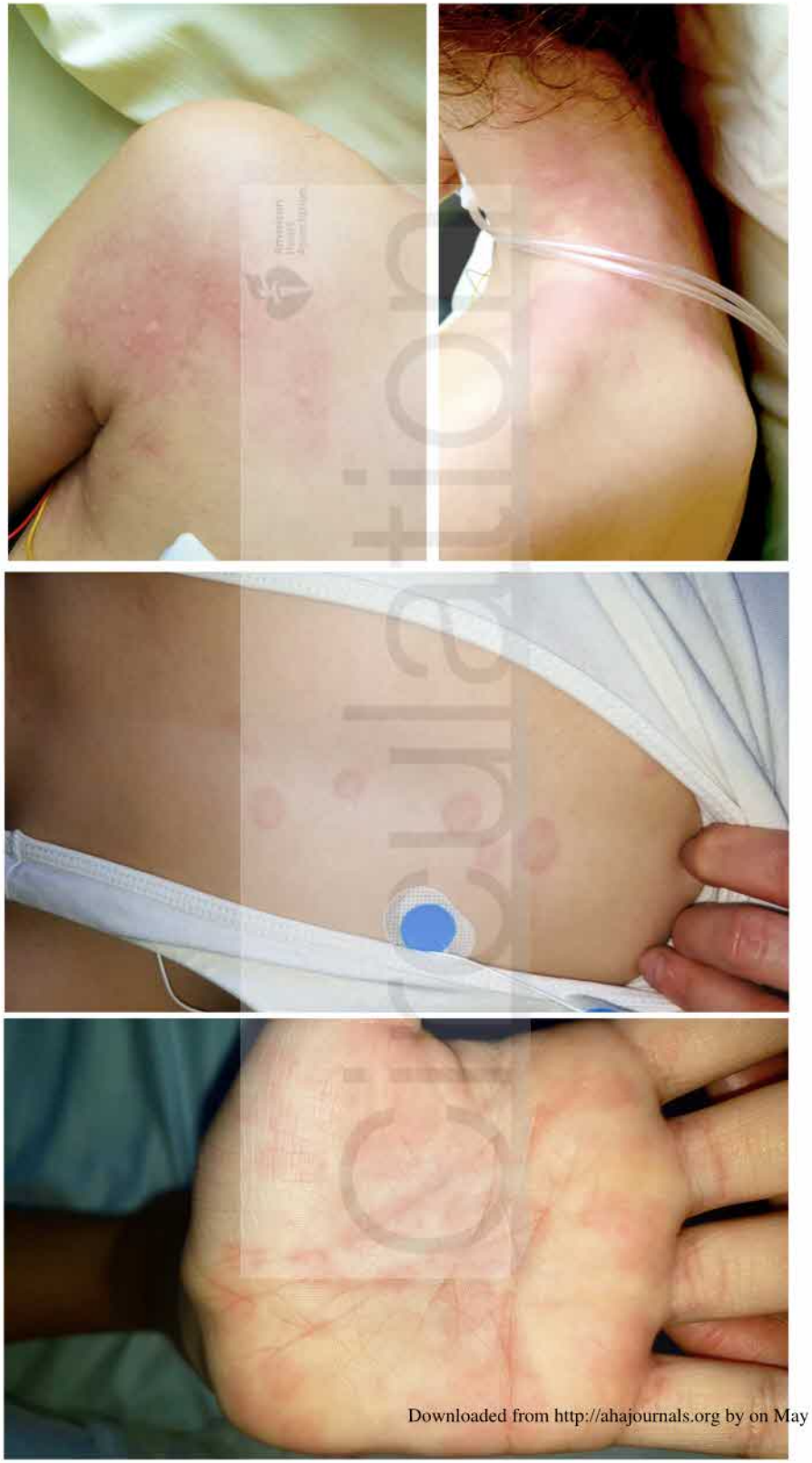
Treatment, n (%)	
Inotropic support	28 (80)
Immunoglobulin infusion	25 (71)
Intravenous corticosteroids	12 (34)
Interleukin 1 receptor antagonist	3 (8)
Anticoagulation with heparin	23 (65)
Respiratory support, n (%)	33 (94)
Invasive	22 (62)
Non invasive	11 (32)
VA-ECMO, n (%)	10 (28)
ECMO duration in days (range)	4.5 (3-6)
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Death, n (%)	0 (0)

VA ECMO: veno-arterial Extracorporeal membrane oxygenation.
Data are median (IQR) or n (%), where n is the total number of patients with available data.

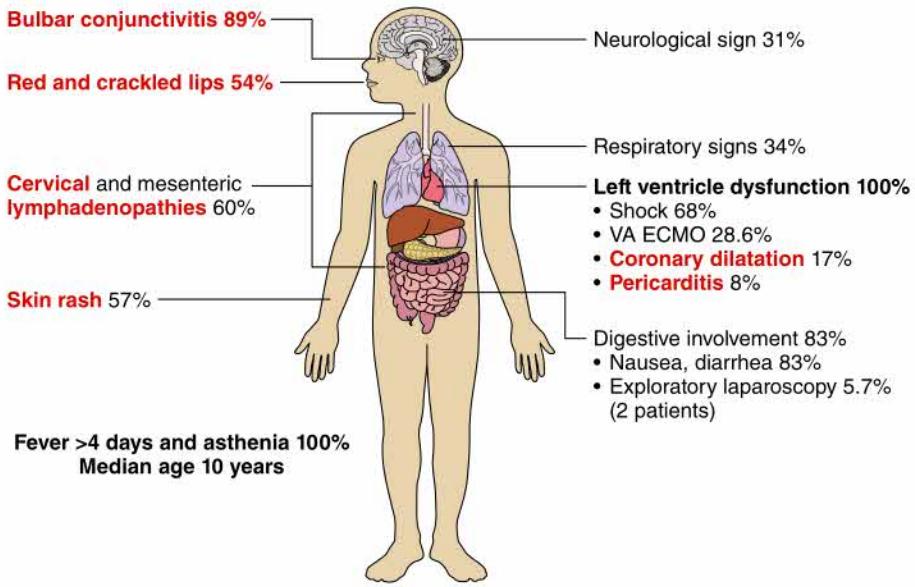
Figure Legends

Figure 1: Maculo-papular rash in a 12-year old girl.

Figure 2: Schematic representation of the clinical signs in severe forms of SARS-CoV-2 related multisystem inflammation. Red text indicates signs or symptoms consistent with Kawasaki disease. In black, signs that are rare in Kawasaki disease. Percentages are those present in the present series of patients.



SARS-COV-2 related multisystem inflammation



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From: Vacalis, Demetri (CDC/OCOO/OSSAM)
Sent: Tue, 19 May 2020 15:48:43 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Subject: Literature search on Pediatric Inflammatory Multisystem Syndrome (PIMS)
Attachments: UpToDate Coronavirus disease 2019 (COVID-19) Considerations in children.pdf, UpToDate Kawasaki disease Clinical features and diagnosis.pdf, UpToDate Kawasaki disease Initial treatment and prognosis.pdf, COVID-19 PMIS Articles 2020.rtf, COVID-19 PMIS Articles before 2020.rtf, Effectiveness of Intravenous Immunoglobulin for Children with Severe COVID-19 A Rapid Review.pdf, Kawasaki PIMS A1-B2.docx, 2nd input- Steve G.docx

Attached are the majority of articles found when searching for PIMS, keying on clinical topics of concern.

I hope this helps.

Best Regards,

Demetri

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OSSAM Office of Safety, Security, and Asset Management
Public Health Intelligence Office (PHIO)

Coronavirus disease 2019 (COVID-19): Considerations in children

Authors: Jaime G Deville, MD, Eunkyung Song, MD, Christopher P Ouellette, MD
Section Editor: Morven S Edwards, MD
Deputy Editor: Mary M Torchia, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

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Kawasaki disease: Clinical features and diagnosis

Author: Robert Sundel, MD
Section Editors: Marisa Klein-Gitelman, MD, MPH, Sheldon L Kaplan, MD
Deputy Editor: Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2020. | **This topic last updated:** Dec 06, 2019.

INTRODUCTION

Kawasaki disease (KD, previously called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood [1]. KD also occurs rarely in adults. It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy [2]. However, complications such as coronary artery (CA) aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality. (See "Cardiovascular sequelae of Kawasaki disease: Clinical features and evaluation".)

The clinical manifestations and diagnosis of KD are discussed in this review. The epidemiology, etiology, treatment, and complications of KD, including cardiac sequelae, are presented separately. Incomplete (atypical) KD and unique features in infants and adults are also reviewed separately. (See "Kawasaki disease: Epidemiology and etiology" and "Kawasaki disease: Initial treatment and prognosis" and "Cardiovascular sequelae of Kawasaki disease: Clinical features and evaluation" and "Incomplete (atypical) Kawasaki disease" and "Kawasaki disease: Complications".)

CLINICAL MANIFESTATIONS

The clinical features of KD reflect widespread inflammation of primarily medium-sized muscular arteries. Diagnosis is based upon evidence of systemic inflammation (eg, fever) in association with signs of mucocutaneous inflammation. The characteristic bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, rash, extremity changes, and cervical lymphadenopathy typically develop after a brief nonspecific prodrome of respiratory or gastrointestinal symptoms [3-8]

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Kawasaki disease: Initial treatment and prognosis

Author: Robert Sundel, MD
Section Editors: Marisa Klein-Gitelman, MD, MPH, Sheldon L Kaplan, MD
Deputy Editor: Elizabeth TePas, MD, MS

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2020. | **This topic last updated:** Jan 15, 2020.

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COVID-19 PMIS Articles 2020 3rd Literature Search.

2020 (431)

(2020). "Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020." Mmwr **Morbidity and mortality weekly report. 69**(14): 422-426.
As of April 2, 2020, the coronavirus disease 2019 (COVID-19) pandemic has resulted in >890,000 cases and >45,000 deaths worldwide, including 239,279 cases and 5,443 deaths in the United States (1,2). In the United States, 22% of the population is made up of infants, children, and adolescents aged <18 years (children) (3). Data from China suggest that pediatric COVID-19 cases might be less severe than cases in adults and that children might experience different symptoms than do adults (4,5); however, disease characteristics among pediatric patients in the United States have not been described. Data from 149,760 laboratory-confirmed COVID-19 cases in the United States occurring during February 12-April 2, 2020 were analyzed. Among 149,082 (99.6%) reported cases for which age was known, 2,572 (1.7%) were among children aged <18 years. Data were available for a small proportion of patients on many important variables, including symptoms (9.4%), underlying conditions (13%), and hospitalization status (33%). Among those with available information, 73% of pediatric patients had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18-64 years during the same period; 5.7% of all pediatric patients, or 20% of those for whom hospitalization status was known, were hospitalized, lower than the percentages hospitalized among all adults aged 18-64 years (10%) or those with known hospitalization status (33%). Three deaths were reported among the pediatric cases included in this analysis. These data support previous findings that children with COVID-19 might not have reported fever or cough as often as do adults (4). Whereas most COVID-19 cases in children are not severe, serious COVID-19 illness resulting in hospitalization still occurs in this age group. Social distancing and everyday preventive behaviors remain important for all age groups as patients with less serious illness and those without symptoms likely play an important role in disease transmission (6,7).

(2020). "Recommendations on the identification and transfer of children with critical diabetes during the COVID-19 outbreak. [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(4): 285-289.
Coronavirus disease 2019 (COVID-19) is the most serious public health problem in China. Children with diabetes are also among the population susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Traffic problems caused by epidemic prevention and control increase the difficulty in the management of children with severe diabetes. In order to control the spread of epidemic, children with mild diabetes are advised to be managed at home and in the community. However, how to treat children with severe diabetes effectively and safely during the outbreak of COVID-19 brings great challenges to primary doctors. The Subspecialty Group of Endocrinology and Metabolism, Society of Pediatrics, Chinese Medical Association and the Subspecialty Group of Endocrinology and Metabolism, Society of Pediatrics, Chinese Medical Doctor Association have developed the recommendations on the identification and transfer of children with critical diabetes during the COVID-19 outbreak, which provide a reference for primary doctors to quickly assess the severity of patient's condition and treat the illness accordingly, thus reducing the risk of referral infection and improving clinical prognosis.

(2020). "Response plan in the neonatal intensive care unit during epidemic of SARS-CoV-2 infection (2nd Edition). [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(3): 205-210.
Since December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread from China to other countries. In order to effectively respond

to possible neonatal SARS-CoV-2 infection, neonatologists from the Medical Association of Chinese People's Liberation Army and the Editorial Committee of Chinese Journal of Contemporary Pediatrics proposed the response plan in the neonatal intensive care unit during epidemic of SARS-CoV-2 infection (1st edition) at the end of January of 2020. Based on the further knowledge and experience on SARS-CoV-2 infection, the neonatologists updated the plan according to the current evidence, so as to provide a better guide for clinical medical staff to deal with the SARS-CoV-2 infection in the NICU.

(2020). "Standardized management guideline for pediatric wards of hematology and oncology during the epidemic of coronavirus disease 2019. [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(3): 177-182.
With the spread of coronavirus disease 2019 (COVID-19) and growing knowledge of its diagnosis and treatment, it has been clear that children are also susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The children with hematological tumors are a special population with immunosuppression and special therapeutic characteristics. Here the management guideline for pediatric wards of hematology and oncology during COVID-19 epidemic is established based on the features of children with hematological tumors.

(2020). "Summary of recommendations regarding COVID-19 in children with diabetes: Keep Calm and Mind your Diabetes Care and Public Health Advice." Pediatric diabetes **21**(3): 413-414.

Abduljalil, J. M. and B. M. Abduljalil (2020). "Epidemiology, genome, and clinical features of the pandemic SARS-CoV-2: a recent view." New Microbes and New Infections **35 (no pagination)**(100672).
Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, the number of globally confirmed cases according to World Health Organization statistics reached 292 124 in 189 countries by 22 March 2020. The number of deaths reached 12 784, with estimated case-fatality rates ranging from 0.5% to 5.7%. Children population seems to be the least affected by the disease, while the highest rate of death is among the elderly and people with comorbidities. Most infected individuals are asymptomatic or only exhibit mild symptoms. After the incubation period, the most common symptoms are fever, cough and fatigue. Asymptomatic carrier state is of paramount importance because of carriers' ability to spread the infection and to shed the virus into the air and surroundings. Although much is still unknown about SARS-CoV-2, the scientific research is moving at an unprecedented pace towards understanding the nature, effective control, prevention and treatment of SARS-CoV-2. Various reports have suggested an in vivo evolution of the virus, which may explain the rapid spread and changing epidemiology of SARS-CoV-2, but further evidence is needed. Unfortunately, no effective treatment or therapeutic drug is available for the disease; only supportive treatment and classical intervention measures are available for confronting the SARS-CoV-2 pandemic.

Alonso Diaz, C., et al. (2020). "[First case of neonatal infection due to SARS-CoV-2 in Spain]." Anales de Pediatria **92**(4): 237-238.

Al-Romaihi, H. E., et al. (2020). "Molecular epidemiology of influenza, RSV, and other respiratory infections among children in Qatar: A six years report (2012-2017)." International Journal of Infectious Diseases **95**: 133-141.
Background: Studies on the etiology of respiratory infections among children in Qatar and surrounding countries are limited. Objective(s): To describe the prevalence and seasonality of RSV, influenza, and other respiratory pathogens among children in Qatar. Method(s): We retrospectively collected and analyzed data of 33,404 children (<15 years) presented with influenza-like illness from 2012 to 2017. Result(s): At least one respiratory pathogen was detected in 26,138 (78%) of patients. Together, human rhinoviruses (HRV), respiratory syncytial virus (RSV), and influenza viruses comprised nearly two-thirds of all cases, affecting 24%,

19.7%, and 18.5%, respectively. A prevalence of 5-10% was recorded for adenovirus, parainfluenza viruses (PIVs), human bocavirus (HboV), and human coronaviruses (HCoVs). Human metapneumovirus (HMPV), enteroviruses, M. pneumonia, and parechovirus had prevalences below 5%. While RSV, influenza, and HMPV exhibited strong seasonal activity in the winter, HRV was active during low RSV and influenza circulation. The burden of RSV exceeds that of influenza among young age groups, whereas influenza correlated positively with age. Further, HRV, adenovirus, influenza, and RSV infection rates varied significantly between male and females. Conclusion(s): This comprehensive multi-year study provides insights into the etiology of ILI among children in Qatar, which represents the Gulf region. Our results reinforce the significance of active surveillance of respiratory pathogens to improve infection prevention and control strategies, particularly among children. Copyright © 2020 The Author(s)

Altena, E., et al. (2020). "Dealing with sleep problems during home confinement due to the COVID-19 outbreak: practical recommendations from a task force of the European CBT-I Academy." Journal of sleep research. **04**.
In the current global home confinement situation due to the COVID-19 outbreak, most individuals are exposed to an unprecedented stressful situation of unknown duration. This may not only increase daytime stress, anxiety and depression levels but also disrupt sleep. Importantly, because of the fundamental role that sleep plays in emotion regulation, sleep disturbance can have direct consequences upon next day emotional functioning. In this paper we summarize what is known about the stress-sleep link and confinement as well as effective insomnia treatment. We discuss those effects of the current home confinement situation that can disrupt sleep but also those that could benefit sleep quality. We suggest adaptions of cognitive behavioral therapy elements that are feasible to implement for those facing changed work schedules and requirements, those with health anxiety and those handling childcare and homeschooling, whilst also recognizing the general limitations imposed on physical exercise and social interaction. Managing sleep problems as best as possible during home confinement can limit stress and possibly prevent disruptions of social relationships. Copyright This article is protected by copyright. All rights reserved.

Alviggi, C., et al. (2020). "COVID-19 and assisted reproductive technology services: repercussions for patients and proposal for individualized clinical management." Reproductive Biology & Endocrinology **18**(1): 45.
The prolonged lockdown of health services providing high-complexity fertility treatments -as currently recommended by many reproductive medicine entities- is detrimental for society as a whole, and infertility patients in particular. Globally, approximately 0.3% of all infants born every year are conceived using assisted reproductive technology (ART) treatments. By contrast, the total number of COVID-19 deaths reported so far represents approximately 1.0% of the total deaths expected to occur worldwide over the first three months of the current year. It seems, therefore, that the number of infants expected to be conceived and born -but who will not be so due to the lockdown of infertility services- might be as significant as the total number of deaths attributed to the COVID-19 pandemic. We herein propose remedies that include a prognostic-stratification of more vulnerable infertility cases in order to plan a progressive restart of worldwide fertility treatments. At a time when preventing complications and limiting burdens for national health systems represent relevant issues, our viewpoint might help competent authorities and health care providers to identify patients who should be prioritized for the continuation of fertility care in a safe environment.

Andina, D., et al. (2020). "Chilblains in children in the setting of COVID-19 pandemic." Pediatric dermatology. **09**.
BACKGROUND: Different skin manifestations of COVID-19 are being reported. Acral lesions on the hands and feet, closely resembling chilblains, have been recognized during the peak incidence of the COVID-19 pandemic MATERIAL AND METHODS: A retrospective review of 22

children and adolescents with chilblain-like lesions seen over a short period of time in the Emergency Department of a children's hospital during the peak incidence of COVID-19 in Madrid, Spain. RESULT(S): All patients had lesions clinically consistent with chilblains of the toes or feet, with 3 also having lesions of the fingers. Pruritus and mild pain were the only skin symptoms elicited, and only 10 had mild respiratory and/or GI symptoms. None had fever. Coagulation tests, hemogram, serum chemistry and lupus anticoagulant were normal in all patients tested. One out of 16 tested cases had elevated D-dimer results, but without systemic symptoms or other lab anomalies. SARS-CoV-2 PCR tested in 19 cases was positive in just 1 case. Skin biopsies obtained in 6 patients were consistent with chilblains. On follow-up, all cases showed spontaneous marked improvement or complete healing. CONCLUSION(S): Acute chilblains were observed during COVID-19 pandemic in children and teenagers. It is a mildly symptomatic condition with an excellent prognosis, usually requiring no therapy. Etiopathogenesis remains unknown. Copyright This article is protected by copyright. All rights reserved.

Ang, L., et al. (2020). "Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines." Complementary Therapies in Clinical Practice **39**: 101174.
This review aimed to summarize and analyze the pattern identification (PI), herbal formulae, and composition of herbs provided by recent guidelines for the treatment of pediatric COVID-19. Seven data sources were reviewed until March 25, 2020. We analyzed the herbal formulae included in the guidelines and performed a network analysis to identify the frequency of herbs recommended in the herbal formulae. All 3 guidelines were provincial guidelines from China. Our results showed that there were 4 stages, 12 PIs, and 13 herbal formulae recommended by the provincial guidelines. These herbal formulae included a total of 56 herbs. Based on our network analysis, Scutellariae Radix was paired with Artemisiae Annuae Herba in one cluster. In another cluster, Armeniacae Semen was paired with Coicis Semen and Ephedrae Herba was paired with Gypsum Fibrosum. This review serves as a reference for the use of traditional medicine in the treatment of pediatric COVID-19.

Angeletti, A., et al. (2020). "Risk of COVID-19 in young kidney transplant recipients. Results from a single-center observational study." Clinical Transplantation **12**: 12.
Coronavirus Disease 2019 (COVID-19) represents a global public health emergency, recently taken on pandemic proportions, with over 2.7 million confirmed cases worldwide(1). Children/young adults seem to have a less severe clinical manifestation of COVID-19 (2), but data on disease susceptibility in pediatric transplant recipients on chronic immunosuppressive therapy are limited (3, 4). This poses major uncertainties regarding pediatric transplant activity and management of anti-rejection therapy.

Anonymous (2020). "Covid-19 and pregnancy." BMJ (Clinical research ed.) **369**: m1672.
Guideline: Coronavirus (COVID-19) Infection in pregnancyPublished by the Royal College of Obstetricians and Gynaecologists (RCOG), with input from the Royal College of Midwives, the Royal College of Paediatrics and Child Health (RCPH), the Royal College of Anaesthetists, and the Obstetric Anaesthetists' Association.This summary is based on version 8 of the guideline, published on 17 April 2020 (https://www.rcog.org.uk/globalassets/documents/guidelines/2020-04-17-coronavirus-covid-19-infection-in-pregnancy.pdf). Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.

Anzai, F., et al. (2020). "Crucial role of NLRP3 inflammasome in a murine model of Kawasaki disease." Journal of Molecular and Cellular Cardiology **138**: 185-196.
Kawasaki disease (KD) is a systemic febrile syndrome during childhood that is characterized by coronary arteritis. The etiopathogenesis of KD remains to be elucidated. NLRP3 inflammasome is a large multiprotein complex that plays a key role in IL-1beta-driven sterile inflammatory

diseases. In the present study, we investigated the role of NLRP3 inflammasome in a murine model of KD induced by Candida albicans water-soluble fraction (CAWS) and found that NLRP3 inflammasome is required for the development of CAWS-induced vasculitis. CAWS administration induced IL-1beta production, caspase-1 activation, leukocyte infiltration, and fibrotic changes in the aortic root and coronary arteries, which were significantly inhibited by a deficiency of IL-1beta, NLRP3, and ASC. In vitro experiments showed that among cardiac resident cells, macrophages, but not endothelial cells or fibroblasts, expressed Dectin-2, but did not produce IL-1beta in response to CAWS. In contrast, CAWS induced caspase-1 activation and IL-1beta production in bone marrow-derived dendritic cells (BMDCs), which were inhibited by a specific caspase-1 inhibitor and a deficiency of NLRP3, ASC, and caspase-1. CAWS induced NLRP3 and pro-IL-1beta expression through a Dectin-2/Syk/JNK/NF-kappaB pathway, and caspase-1 activation and cleavage of pro-IL-1beta through Dectin-2/Syk/JNK-mediated mitochondrial ROS generation, indicating that CAWS induces the priming and activation of NLRP3 inflammasome in BMDCs. These findings provide new insights into the pathogenesis of KD vasculitis, and suggest that NLRP3 inflammasome may be a potential therapeutic target for KD.

Arvind, B., et al. (2020). "Aetiological agents for pulmonary exacerbations in children with cystic fibrosis: An observational study from a tertiary care centre in northern India." Indian Journal of Medical Research **151**(1): 65-70.

Background & objectives: Pulmonary disease is the main cause of morbidity and mortality in cystic fibrosis (CF). The infection occurs with a unique spectrum of bacterial pathogens that are usually acquired in an age-dependent fashion. The objective of this study was to find out the aetiological agents in respiratory specimens from children with CF during pulmonary exacerbation and relate with demographic variables.

Methods: In this observational study, airway secretions from children (n=104) with CF presenting with pulmonary exacerbations were collected and tested for bacteria, fungi, mycobacteria and viral pathogens using appropriate laboratory techniques. The frequencies of isolation of various organisms were calculated and associated with various demographic profiles.

Results: Bacteria were isolated in 37 (35.5%) and viral RNA in 27 (29.3%) children. Pseudomonas was the most common bacteria grown in 31 (29.8%) followed by Burkholderia cepacia complex (Bcc) in three (2.8%) patients. Among viruses, Rhinovirus was the most common, identified in 16 (17.4%) samples followed by coronavirus in four (4.3%). Fungi and mycobacteria were isolated from 23 (22.1%) and four (3.8%) children, respectively. Aspergillus flavus was the most common fungus isolated in 13 (12.5%) children.

Interpretation & conclusions: Pseudomonas was the most common organism isolated during exacerbation. Non-tuberculous mycobacteria were not isolated, whereas infection with Bcc and Mycobacterium tuberculosis was observed, which could probably have a role in CF morbidity. Polymicrobial infections were associated with severe exacerbations.

Awad, S., et al. (2020). "Viral Surveillance of Children with Acute Respiratory Infection in Two Main Hospitals in Northern Jordan, Irbid, during Winter of 2016." Journal of Pediatric Infectious Diseases **15**(1): 001-010.

Acute lower respiratory infection (ALRI) is a major cause of morbidity and mortality worldwide. Data regarding the etiology of acute respiratory infection (ARI) is scarce in developing countries. The aim of this study was to identify the viral etiology of ARI/ALRI in hospitalized children and factors associated with increased length of stay (LoS) and severe disease presentation in Northern Jordan. This was a prospective viral surveillance study using real-time reverse transcriptase-polymerase chain reaction in children younger than 5 years admitted with ARI to two main hospitals in Northern Jordan during the winter of 2016. Nasopharyngeal swabs were obtained and tested for respiratory syncytial virus (RSV) and other viruses. Demographic and clinical characteristics of RSV-positive patients were compared with those of RSV-negative patients. There were 479 patients hospitalized with ARI. Their mean age (standard deviation)

was 10.4 (11.6) months. 53.9% tested positive for at least one virus, with RSV being the most commonly detected virus (34%). Compared with RSV-negative patients, RSV-positive patients were younger, more likely to have chronic lung disease, and more likely to present with cough, rhinorrhea, difficulty in breathing, retraction, flaring, grunting, wheezing, and a higher respiratory rate. Prematurity, presence of a chronic illness, oxygen saturation < 90%, and atelectasis and consolidation on chest X-rays were significantly associated with an increased mean LoS. Patients with a history of prematurity had higher risk of severe disease (odds ratio = 2.6; 95% confidence interval: 1.5, 4.7; p = 0.001). Compared with patients 6 months old and younger, patients aged 6.1 to 12 months were less likely to have severe disease. Human metapneumovirus (HMPV)-positive ALRI was associated with increased odds of severe disease. Viruses are recognized as etiological agent of ARI/ALRI-associated morbidity in developing countries that need more attention and implementation of targeted strategies for prevention and detection. HMPV can be a cause of severe ALRI.

Baergen, R. N. and D. S. Heller (2020). "Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings." Pediatric & Developmental Pathology **23**(3): 177-180.
This study describes the pathology and clinical information on 20 placentas whose mother tested positive for the novel Coronovirus (2019-nCoV) cases. Ten of the 20 cases showed some evidence of fetal vascular malperfusion or fetal vascular thrombosis. The significance of these findings is unclear and needs further study.

Bai, K., et al. (2020). "Clinical Analysis of 25 Novel Coronavirus Infections in Children." Pediatric Infectious Disease Journal **12**: 12.
BACKGROUND: To describe the characteristics of clinical manifestations of children with 2019 novel coronavirus (2019-nCoV) infection in Chongqing.
METHODS: All 25 children with laboratory-confirmed 2019-nCoV infection by real-time reverse transcription-PCR (RNA-PCR) were admitted from the 4 designated treatment hospitals of 2019-nCoV in Chongqing from January 19 to March 12, 2020. Clinical data and epidemiological history of these patients were retrospectively collected and analyzed.
RESULTS: The diagnosis was confirmed through RNA-PCR testing. Among the 25 cases, 14 were males and 11 were females. The median age was 11.0 (6.3-14.5) years (range 0.6-17.0 years). All children were related to a family cluster outbreak, and 7 children (28%) with a travel or residence history in Hubei Province. These patients could be categorized into different clinical types, including 8 (32%) asymptomatic, 4 (16%) very mild cases and 13 (52%) common cases. No severe or critical cases were identified. The most common symptoms were cough (13 cases, 52%) and fever (6 cases, 24%). The duration time of clinical symptoms was 13.0 (8.0-25.0) days. In the 25 cases, on admission, 21 cases (84%) had normal white blood cell counts, while only 2 cases (8%) more than 10 x 10/L and 2 cases (8%) less than 4 x 10/L, respectively; 22 cases(88%) had normal CD4+ T lymphocyte counts, while in the remaining 3 cases(8%) this increased mildly; 23 cases had normal CD8+ T lymphocyte counts, while in the remaining 2 cases (8%) CD8+ T lymphocyte counts were mildly increased as well. All Lymphocyte counts were normal. There were no statistical differences of lab results between the groups of asymptomatic cases, mild cases and common cases. There were only 13 cases with abnormal CT imaging, most of which were located in the subpleural area of the bottom of the lung. All patients were treated with interferon, 6 cases combined with Ribavirin, and 12 cases combined with lopinavir or ritonavir. The days from onset to RNA turning negative was 15.20 +/- 6.54 days. There was no significant difference of RNA turning negative between the groups of interferon, interferon plus ribavirin and interferon plus lopinavir or ritonavir treatment. All the cases recovered and were discharged from hospital.
CONCLUSIONS: The morbidity of 2019-nCoV infection in children is lower than in adults and the clinical manifestations and inflammatory biomarkers in children are nonspecific and milder than that in adults. RNA-PCR test is still the most reliable diagnostic method, especially for asymptomatic

patients.

Bajema, K. L., et al. (2020). "Persons Evaluated for 2019 Novel Coronavirus - United States, January 2020." MMWR - Morbidity & Mortality Weekly Report **69**(6): 166-170.
In December 2019, a cluster of cases of pneumonia emerged in Wuhan City in central China's Hubei Province. Genetic sequencing of isolates obtained from patients with pneumonia identified a novel coronavirus (2019-nCoV) as the etiology (1). As of February 4, 2020, approximately 20,000 confirmed cases had been identified in China and an additional 159 confirmed cases in 23 other countries, including 11 in the United States (2,3). On January 17, CDC and the U.S. Department of Homeland Security's Customs and Border Protection began health screenings at U.S. airports to identify ill travelers returning from Wuhan City (4). CDC activated its Emergency Operations Center on January 21 and formalized a process for inquiries regarding persons suspected of having 2019-nCoV infection (2). As of January 31, 2020, CDC had responded to clinical inquiries from public health officials and health care providers to assist in evaluating approximately 650 persons thought to be at risk for 2019-nCoV infection. Guided by CDC criteria for the evaluation of persons under investigation (PUIs) (5), 210 symptomatic persons were tested for 2019-nCoV; among these persons, 148 (70%) had travel-related risk only, 42 (20%) had close contact with an ill laboratory-confirmed 2019-nCoV patient or PUI, and 18 (9%) had both travel- and contact-related risks. Eleven of these persons had laboratory-confirmed 2019-nCoV infection. Recognizing persons at risk for 2019-nCoV is critical to identifying cases and preventing further transmission. Health care providers should remain vigilant and adhere to recommended infection prevention and control practices when evaluating patients for possible 2019-nCoV infection (6). Providers should consult with their local and state health departments when assessing not only ill travelers from 2019-nCoV-affected countries but also ill persons who have been in close contact with patients with laboratory-confirmed 2019-nCoV infection in the United States.

Balasubramanian, S., et al. (2020). "Coronavirus Disease (COVID-19) in Children - What We Know So Far and What We Do Not?" Indian pediatrics. **09**.
Pediatric coronavirus disease - 19 (COVID-19) infection is relatively mild when compared to adults, and children are reported to have a better prognosis. Mortality in children appears rare. Clinical features of COVID-19 in children include fever and cough, but a large proportion of infected children appears to be asymptomatic and may contribute to transmission. It remains unclear why children and young adults are less severely affected than older individuals, but this might involve differences in immune system function in the elderly and/or differences in the expression/function of the cellular receptor for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) - Angiotensin converting enzyme 2 (ACE2). Laboratory findings and chest imaging may not be specific in children with COVID-19. Diagnosis is by Reverse transcriptase-Polymerase chain reaction (RT-PCR) testing of upper or lower respiratory tract secretions. This review additionally considers COVID-19 in immunosuppressed children, and also suggests a management algorithm for the few children who appear to present with life threatening infection, including the potential use of antiviral and immunomodulatory treatment. The most significant threat to global child health from SARS-CoV-2 is unlikely to be related to COVID 19 in children, but rather the socio-economic consequences of a prolonged pandemic.

Balevic, S. J., et al. (2020). "Hydroxychloroquine in Patients with Rheumatic Disease Complicated by COVID-19: Clarifying Target Exposures and the Need for Clinical Trials." Journal of Rheumatology **11**: 11.
OBJECTIVE: To characterize hydroxychloroquine exposure in patients with rheumatic disease receiving long-term hydroxychloroquine compared to target concentrations with reported antiviral activity against the 2019 coronavirus SARS-CoV-2.
METHODS: We evaluated total hydroxychloroquine concentrations in serum and plasma from published literature values, frozen serum samples from a pediatric lupus trial, and simulated concentrations

using a published pharmacokinetic model during pregnancy. For each source, we compared observed or predicted hydroxychloroquine concentrations to target concentrations with reported antiviral activity against SARS-CoV-2.
RESULTS: The average total serum/plasma hydroxychloroquine concentrations were below the lowest SARS-CoV-2 target of 0.48 mg/L in all studies. Assuming the highest antiviral target exposure (total plasma concentration of 4.1 mg/L), all studies had approximately one-tenth the necessary concentration for in-vitro viral inhibition. Pharmacokinetic model simulations confirmed that pregnant adults receiving common dosing for rheumatic diseases did not achieve target exposures; however, the models predict that a dosage of 600 mg once a day during pregnancy would obtain the lowest median target exposure for most patients after the first dose.
CONCLUSION: We found that the average patient receiving treatment with hydroxychloroquine for rheumatic diseases, including children and non-pregnant/pregnant adults, are unlikely to achieve total serum or plasma concentrations shown to inhibit SARS-CoV-2 in-vitro. Nevertheless, patients receiving hydroxychloroquine long-term may have tissue concentrations far exceeding that of serum/plasma. Because the therapeutic window for hydroxychloroquine in the setting of SARS-CoV-2 is unknown, well-designed clinical trials that include patients with rheumatic disease are urgently needed to characterize the efficacy, safety, and target exposures for hydroxychloroquine.

Bann, D. V., et al. (2020). "Best Practice Recommendations for Pediatric Otolaryngology during the COVID-19 Pandemic." Otolaryngology - Head & Neck Surgery: 194599820921393.
OBJECTIVE: To review the impact of coronavirus disease 2019 (COVID-19) on pediatric otolaryngology and provide recommendations for the management of children during the COVID-19 pandemic.
DATA SOURCES: Clinical data were derived from peer-reviewed primary literature and published guidelines from national or international medical organizations. Preprint manuscripts and popular media articles provided background information and illustrative examples.
METHODS: Included manuscripts were identified via searches using PubMed, MEDLINE, and Google Scholar, while organizational guidelines and popular media articles were identified using Google search queries. Practice guidelines were developed via consensus among all authors based on peer-reviewed manuscripts and national or international health care association guidelines. Strict objective criteria for inclusion were not used due to the rapidly changing environment surrounding the COVID-19 pandemic and a paucity of rigorous empirical evidence.
CONCLUSIONS: In the face of the COVID-19 pandemic, medical care must be judiciously allocated to treat the most severe conditions while minimizing the risk of long-term sequelae and ensuring patient, physician, and health care worker safety.
IMPLICATIONS FOR PRACTICE: The COVID-19 pandemic will have a profound short- and long-term impact on health care worldwide. Although the full repercussions of this disease have yet to be realized, the outlined recommendations will guide otolaryngologists in the treatment of pediatric patients in the face of an unprecedented global health crisis.

Barral-Arca, R., et al. (2020). "A Meta-Analysis of Multiple Whole Blood Gene Expression Data Unveils a Diagnostic Host-Response Transcript Signature for Respiratory Syncytial Virus." International Journal of Molecular Sciences **21**(5): 06.
Respiratory syncytial virus (RSV) is one of the major causes of acute lower respiratory tract infection worldwide. The absence of a commercial vaccine and the limited success of current therapeutic strategies against RSV make further research necessary. We used a multi-cohort analysis approach to investigate host transcriptomic biomarkers and shed further light on the molecular mechanism underlying RSV-host interactions. We meta-analyzed seven transcriptome microarray studies from the public Gene Expression Omnibus (GEO) repository containing a total of 922 samples, including RSV, healthy controls, coronaviruses, enteroviruses, influenzas, rhinoviruses, and coinfections, from both adult and pediatric patients. We identified > 1500 genes differentially expressed when comparing the transcriptomes of RSV-infected patients

against healthy controls. Functional enrichment analysis showed several pathways significantly altered, including immunologic response mediated by RSV infection, pattern recognition receptors, cell cycle, and olfactory signaling. In addition, we identified a minimal 17-transcript host signature specific for RSV infection by comparing transcriptomic profiles against other respiratory viruses. These multi-genic signatures might help to investigate future drug targets against RSV infection.

Baruchel, A., et al. (2020). "COVID-19 and acute lymphoblastic leukemias of children and adolescents: First recommendations of the Leukemia committee of the French Society for the fight against Cancers and Leukemias in children and adolescents (SFCE)." Bulletin du Cancer **30**: 30. Since the emergence of the SARS-CoV-2 infection, many recommendations have been made. However, the very nature of acute lymphoblastic leukemias and their treatment in children and adolescents led the Leukemia Committee of the French Society for the fight against cancers and leukemias in children and adolescents (SFCE) to propose more specific recommendations, even if data for this population are still scarce. They may have to evolve according to the rapid evolution of knowledge on COVID-19.

Bayham, J. and E. P. Fenichel (2020). "Impact of school closures for COVID-19 on the US health-care workforce and net mortality: a modelling study." The Lancet Public Health **5**(5): e271-e278. Background: The coronavirus disease 2019 (COVID-19) pandemic is leading to social (physical) distancing policies worldwide, including in the USA. Some of the first actions taken by governments are the closing of schools. The evidence that mandatory school closures reduce the number of cases and, ultimately, mortality comes from experience with influenza or from models that do not include the effect of school closure on the health-care labour force. The potential benefits from school closures need to be weighed against costs of health-care worker absenteeism associated with additional child-care obligations. In this study, we aimed to measure child-care obligations for US health-care workers arising from school closures when these are used as a social distancing measure. We then assessed how important the contribution of health-care workers would have to be in reducing mortality for their absenteeism due to child-care obligations to undo the benefits of school closures in reducing the number of cases. Method(s): For this modelling analysis, we used data from the monthly releases of the US Current Population Survey to characterise the family structure and probable within-household child-care options of US health-care workers. We accounted for the occupation within the health-care sector, state, and household structure to identify the segments of the health-care workforce that are most exposed to child-care obligations from school closures. We used these estimates to identify the critical level at which the importance of health-care labour supply in increasing the survival probability of a patient with COVID-19 would undo the benefits of school closures and ultimately increase cumulative mortality. Finding(s): Between January, 2018, and January, 2020, the US Current Population Survey included information on more than 3.1 million individuals across 1.3 million households. We found that the US health-care sector has some of the highest child-care obligations in the USA, with 28.8% (95% CI 28.5-29.1) of the health-care workforce needing to provide care for children aged 3-12 years. Assuming non-working adults or a sibling aged 13 years or older can provide child care, 15.0% (14.8-15.2) of the health-care workforce would still be in need of child care during a school closure. We observed substantial variation within the health-care system. We estimated that, combined with reasonable parameters for COVID-19 such as a 15.0% case reduction from school closings and 2.0% baseline mortality rate, a 15.0% decrease in the health-care labour force would need to decrease the survival probability per percent health-care worker lost by 17.6% for a school closure to increase cumulative mortality. Our model estimates that if the infection mortality rate of COVID-19 increases from 2.00% to 2.35% when the health-care workforce declines by 15.0%, school closures could lead to a greater number of deaths than they prevent. Interpretation(s): School closures come with many trade-offs, and can create unintended child-care obligations. Our results suggest that the potential contagion prevention from school closures needs to be

carefully weighted with the potential loss of health-care workers from the standpoint of reducing cumulative mortality due to COVID-19, in the absence of mitigating measures. Funding(s): None. Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license

Bi, Q., et al. (2020). "Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study." The Lancet Infectious Diseases.
Background: Rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, prompted heightened surveillance in Shenzhen, China. The resulting data provide a rare opportunity to measure key metrics of disease course, transmission, and the impact of control measures. Method(s): From Jan 14 to Feb 12, 2020, the Shenzhen Center for Disease Control and Prevention identified 391 SARS-CoV-2 cases and 1286 close contacts. We compared cases identified through symptomatic surveillance and contact tracing, and estimated the time from symptom onset to confirmation, isolation, and admission to hospital. We estimated metrics of disease transmission and analysed factors influencing transmission risk. Finding(s): Cases were older than the general population (mean age 45 years) and balanced between males (n=187) and females (n=204). 356 (91%) of 391 cases had mild or moderate clinical severity at initial assessment. As of Feb 22, 2020, three cases had died and 225 had recovered (median time to recovery 21 days; 95% CI 20-22). Cases were isolated on average 4.6 days (95% CI 4.1-5.0) after developing symptoms; contact tracing reduced this by 1.9 days (95% CI 1.1-2.7). Household contacts and those travelling with a case were at higher risk of infection (odds ratio 6.27 [95% CI 1.49-26.33] for household contacts and 7.06 [1.43-34.91] for those travelling with a case) than other close contacts. The household secondary attack rate was 11.2% (95% CI 9.1-13.8), and children were as likely to be infected as adults (infection rate 7.4% in children <10 years vs population average of 6.6%). The observed reproductive number (R) was 0.4 (95% CI 0.3-0.5), with a mean serial interval of 6.3 days (95% CI 5.2-7.6). Interpretation(s): Our data on cases as well as their infected and uninfected close contacts provide key insights into the epidemiology of SARS-CoV-2. This analysis shows that isolation and contact tracing reduce the time during which cases are infectious in the community, thereby reducing the R. The overall impact of isolation and contact tracing, however, is uncertain and highly dependent on the number of asymptomatic cases. Moreover, children are at a similar risk of infection to the general population, although less likely to have severe symptoms; hence they should be considered in analyses of transmission and control. Funding(s): Emergency Response Program of Harbin Institute of Technology, Emergency Response Program of Peng Cheng Laboratory, US Centers for Disease Control and Prevention. Copyright © 2020 Elsevier Ltd

Brogan, P., et al. (2020). "Lifetime cardiovascular management of patients with previous Kawasaki disease." Heart **106**(6): 411-420.
Kawasaki disease (KD) is an inflammatory disorder of young children, associated with vasculitis of the coronary arteries with subsequent aneurysm formation in up to one-third of untreated patients. Those who develop aneurysms are at life-long risk of coronary thrombosis or the development of stenotic lesions, which may lead to myocardial ischaemia, infarction or death. The incidence of KD is increasing worldwide, and in more economically developed countries, KD is now the most common cause of acquired heart disease in children. However, many clinicians in the UK are unaware of the disorder and its long-term cardiac complications, potentially leading to late diagnosis, delayed treatment and poorer outcomes. Increasing numbers of patients who suffered KD in childhood are transitioning to the care of adult services where there is significantly less awareness and experience of the condition than in paediatric services. The aim of this document is to provide guidance on the long-term management of patients who have vascular complications of KD and guidance on the emergency management of acute coronary complications. Guidance on the management of acute KD is published elsewhere. Copyright © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Brough, H. A., et al. (2020). "Managing childhood allergies and immunodeficiencies during respiratory virus epidemics - the 2020 COVID-19 pandemic." Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. **22**.
While the world is facing an unprecedented pandemic with COVID-19, patients with chronic diseases need special attention and if warranted adaptation of their regular treatment plan. In children, allergy and asthma are among the most prevalent non-communicable chronic diseases, and health care providers taking care of these patients need guidance. At the current stage of knowledge, children have less severe symptoms of COVID-19, and severe asthma and immunodeficiency are classified as risk factors. In addition, there is no evidence that currently available asthma and allergy treatments, including antihistamines, corticosteroids, bronchodilators increase the risk of severe disease from COVID-19. Most countries affected by COVID-19 have opted for nationwide confinement, which means that communication with the primary clinician is often performed by telemedicine. Optimal disease control of allergic, asthmatic and immunodeficient children should be sought according to usual treatment guidelines. This statement of the EAACI Section on Pediatrics puts forward six recommendations for the management of childhood allergies and immunodeficiencies based on six underlying facts and existing evidence. Copyright This article is protected by copyright. All rights reserved.

Bush, R., et al. (2020). "Mild COVID-19 in a pediatric renal transplant recipient." American Journal of Transplantation **13**: 13.
As of mid-April 2020, the coronavirus disease of 2019 (COVID-19) pandemic has affected more than 2 million people and caused 135,000 deaths worldwide. Not much is known about the effect of this disease in immunosuppressed children with renal transplantation (RT). Here we report a 13-year-old child with multiple comorbidities who acquired COVID-19 five years post-RT in the United States. Maintenance immunosuppression (IS) consisted of sirolimus and mycophenolate. There was no history of travel or exposure to sick contacts. The presenting features were fever, cough, rhinorrhea and hypoxemia. Diarrhea was the only extra pulmonary manifestation. Chest x-ray was normal. He did not require intensive care unit care or ventilation. There was a transient rise in his serum creatinine without change in urine output; dialysis was not required. Slight reduction in IS was done. He had an excellent clinical recovery within four days and was able to be discharged home. His respiratory symptoms resolved but the diarrhea persisted during a 4 week follow-up period. This report provides a brief perspective on the short-term COVID-19 clinical course in an immunosuppressed child. More reports will add valuable information on the potential variety of spectrum of the illness in this subset of children.

Cai, J., et al. (2020). "A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **28**.
We first described the 2019 novel coronavirus infection in 10 children occurring in areas other than Wuhan. The coronavirus diseases in children are usually mild and epidemiological exposure is a key clue to recognize pediatric case. Prolonged virus shedding is observed in respiratory tract and feces at the convalescent stage. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Cai, J. H., et al. (2020). "First case of 2019 novel coronavirus infection in children in Shanghai. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**(2): 86-87.

Cai, J. H., et al. (2020). "[First case of 2019 novel coronavirus infection in children in Shanghai]." Zhonghua Erke Zazhi **58**(2): 86-87.

Calvo, C., et al. (2020). "[Recommendations on the clinical management of the COVID-19 infection by the

<<new coronavirus>> SARS-CoV2. Spanish Paediatric Association working group]." Anales de Pediatria **92**(4): 241.e241-241.e211.
On 31 December 2019, the Wuhan Municipal Committee of Health and Healthcare (Hubei Province, China) reported that there were 27 cases of pneumonia of unknown origin with symptoms starting on the 8 December. There were 7 serious cases with common exposure in market with shellfish, fish, and live animals, in the city of Wuhan. On 7 January 2020, the Chinese authorities identified that the agent causing the outbreak was a new type of virus of the Coronaviridae family, temporarily called <<new coronavirus>>, 2019-nCoV. On January 30th, 2020, the World Health Organisation (WHO) declared the outbreak an International Emergency. On 11 February 2020 the WHO assigned it the name of SARS-CoV2 and COVID-19 (SARS-CoV2 and COVID-19). The Ministry of Health summoned the Specialties Societies to prepare a clinical protocol for the management of COVID-19. The Spanish Paediatric Association appointed a Working Group of the Societies of Paediatric Infectious Diseases and Paediatric Intensive Care to prepare the present recommendations with the evidence available at the time of preparing them.

Calvo, C., et al. (2020). "[Epidemiological update on SARS-CoV-2 infection in Spain. Comments on the management of infection in pediatrics]." Anales de Pediatria **92**(4): 239-240.

Canarutto, D., et al. (2020). "COVID-19 infection in a paucisymptomatic infant: Raising the index of suspicion in epidemic settings." Pediatric Pulmonology **55**(6): E4-E5.
Few children have been reported to have been affected by novel coronavirus disease 2019 (COVID-19); it is unclear whether children are less likely to be infected or rather display fewer symptoms. We present the case of a 32-day-old boy infected by COVID-19 that presented with an upper air way infection which resolved spontaneously and did not require any therapy. We argue that in epidemic settings children presenting with any mild symptom potentially attributable to COVID-19 should be considered contagious until proven otherwise, and that management must be guided by clinical conditions.

Canova, V., et al. (2020). "Transmission risk of SARS-CoV-2 to healthcare workers -observational results of a primary care hospital contact tracing." Swiss Medical Weekly **150**: w20257.
BACKGROUND: The coronavirus disease (COVID)-19 epidemic is evolving rapidly. Healthcare workers are at increased risk for infection, and specific requirements for their protection are advisable to ensure the functioning of the basic healthcare system, including the availability of general practitioners (GPs). Understanding the transmission risk is particularly important for guiding evidence-based protective measures in the primary healthcare setting.
METHODS: Healthcare worker contacts of an initially undiagnosed COVID-19 case, who were without personal protective equipment, in particular not wearing facemasks, were screened with nasopharyngeal swabs and polymerase chain reaction tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), irrespective of respiratory symptoms or fever seven days after initial contact. The details of exposure to the index case were obtained during routine contact investigation after unintentional pathogen exposure.
RESULTS: Twenty-one healthcare workers reported contacts with the index case. Three healthcare workers reported respiratory symptoms (cough) or low-grade fever within 4 days. None of them tested positive for SARS-CoV-2 at the time of symptom onset. All 21 healthcare workers tested SARS-CoV-2 negative 7 days after initial index case contact, including the three healthcare workers with previous symptoms. Ten of the 21 healthcare workers reported a cumulative exposure time of >15 minutes. Longer cumulative contact times were associated with more individual contacts, reduced contact time per contact and activities with physical patient contact. The closest relative of the index patient tested SARS-CoV-2 positive 2 days after the index case presented at the hospital emergency department.
CONCLUSION: We found a low risk of SARS-CoV-2 transmission in a primary care setting. These findings are compatible with previous reports of the highest transmission probability in household settings with prolonged close contacts. The current protective measures for healthcare workers, including

strict adherence to basic standard hygiene and facemasks, offer considerable protection during short periods of contact with symptomatic COVID-19 cases by diminishing the risk of direct and indirect transmission.

Cao, D., et al. (2020). "Clinical analysis of ten pregnant women with COVID-19 in Wuhan, China: A retrospective study." International Journal of Infectious Diseases **95**: 294-300.
Background: COVID-19 is spreading globally. This study aims to evaluate the clinical characteristics and outcomes of pregnant women confirmed with COVID-19 to provide reference for clinical work. Method(s): The clinical features and outcomes of 10 pregnant women confirmed with COVID-19 at Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, a tertiary- care teaching hospital in Hubei province, Wuhan, China from January 23 to February 23, 2020 were retrospectively analyzed. Result(s): All the 10 observed pregnant women including 9 singletons and 1 twin were native people in Wuhan. All of them were diagnosed mild COVID-19, and none of the patients developed severe COVID-19 or died. Among the 10 patients, two patients underwent vaginal delivery, two patients underwent intrapartum cesarean section, and the remaining six patients underwent elective cesarean section. All of 10 patients showed lung abnormalities by pulmonary CT images after delivery. Their eleven newborns were recorded and no neonatal asphyxia was observed. Conclusion(s): Pulmonary CT screening on admission may be necessary to reduce the risk of nosocomial transmission of COVID-19 during the outbreak period. And COVID-19 is not an indication of cesarean section. Copyright © 2020 The Authors

Cao, Q., et al. (2020). "SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics." Journal of the Formosan Medical Association **119**(3): 670-673.

Caparros-Gonzalez, R. A. (2020). "[Maternal and neonatal consequences of coronavirus COVID-19 infection during pregnancy: a scoping review]." Revista Espanola de Salud Publica **94**: 17.
BACKGROUND: Coronavirus disease 2019 (COVID-19) is a new pathology, declared a public health emergency by the World Health Organization, which can have negative consequences for pregnant women and their newborns. The aim of this study was to explore the available knowledge on the consequences of developing COVI-19 in pregnant women and their neonates.
METHODS: Scoping Review, in which the search for articles was conducted using DeCS ("pregnancy", "coronavirus", "health") and MeSH ("pregnan*", "pregnant women", "coronavirus"), linking the terms with the Boolean AND operator. Databases used were Web of Science, Scopus, BVS, Scielo and CUIDEN. In addition, the PRISMA methodology was applied.
RESULTS: Ten studies were identified that assessed maternal and neonatal health after maternal COVID-19 infection. Pregnant women seem to had no serious symptoms. Neonates appeared to be affected to a greater extent. A death was reported in a premature newborn whose mother had COVID-19 pneumonia. There did not appear to be vertical transmission from mother to child. Nevertheless, this information was not conclusive.
CONCLUSIONS: COVID-19 appears to be more benign with pregnant women than with their neonates.

Carlotti, A., et al. (2020). "COVID-19 Diagnostic and Management Protocol for Pediatric Patients." Clinics (Sao Paulo, Brazil) **75**: e1894.
This review aims to verify the main epidemiologic, clinical, laboratory-related, and therapeutic aspects of coronavirus disease 2019 (COVID-19) in critically ill pediatric patients. An extensive review of the medical literature on COVID-19 was performed, mainly focusing on the critical care of pediatric patients, considering expert opinions and recent reports related to this new disease. Experts from a large Brazilian public university analyzed all recently published material to produce a report aiming to standardize the care of critically ill children and adolescents. The report emphasizes on the clinical presentations of the disease and ventilatory support in pediatric patients with COVID-19. It establishes a flowchart to guide health practitioners on triaging critical cases. COVID-19 is essentially an unknown clinical condition for the majority of pediatric

intensive care professionals. Guidelines developed by experts can help all practitioners standardize their attitudes and improve the treatment of COVID-19.

Carrabba, G., et al. (2020). "Neurosurgery in an infant with COVID-19." The Lancet **395**(10234): e76.

Castagnoli, R., et al. (2020). "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review." JAMA Pediatrics.
Importance: The current rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection justifies the global effort to identify effective preventive strategies and optimal medical management. While data are available for adult patients with coronavirus disease 2019 (COVID-19), limited reports have analyzed pediatric patients infected with SARS-CoV-2. Objective(s): To evaluate currently reported pediatric cases of SARS-CoV-2 infection. Evidence Review: An extensive search strategy was designed to retrieve all articles published from December 1, 2019, to March 3, 2020, by combining the terms coronavirus and coronavirus infection in several electronic databases (PubMed, Cochrane Library, and CINAHL), and following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Retrospective cross-sectional and case-control studies, case series and case reports, bulletins, and national reports about the pediatric SARS-CoV-2 infection were included. The risk of bias for eligible observational studies was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. Finding(s): A total of 815 articles were identified. Eighteen studies with 1065 participants (444 patients were younger than 10 years, and 553 were aged 10 to 19 years) with confirmed SARS-CoV-2 infection were included in the final analysis. All articles reflected research performed in China, except for 1 clinical case in Singapore. Children at any age were mostly reported to have mild respiratory symptoms, namely fever, dry cough, and fatigue, or were asymptomatic. Bronchial thickening and ground-glass opacities were the main radiologic features, and these findings were also reported in asymptomatic patients. Among the included articles, there was only 1 case of severe COVID-19 infection, which occurred in a 13-month-old infant. No deaths were reported in children aged 0 to 9 years. Available data about therapies were limited. Conclusions and Relevance: To our knowledge, this is the first systematic review that assesses and summarizes clinical features and management of children with SARS-CoV-2 infection. The rapid spread of COVID-19 across the globe and the lack of European and US data on pediatric patients require further epidemiologic and clinical studies to identify possible preventive and therapeutic strategies. Copyright © 2020 American Medical Association. All rights reserved.

Castelnovo, L., et al. (2020). "Symmetric cutaneous vasculitis in COVID-19 pneumonia." Journal of the European Academy of Dermatology and Venereology : JEADV. **07**.
Fever, cough, breathing difficulties, digestive issues and loss of smell and taste are the most common symptoms of novel SARS-CoV2 infection but cutaneous manifestations have been highlighted by several dermatologists. We found reports (1-3) to be very interesting because it was underlined how the COVID19 infection can also give cutaneous manifestations vasculitis - like. It has already been described how purple in children, when accompanied by fever, can be a rare but possible manifestation of novel SARs-CoV2 infection(4). Copyright This article is protected by copyright. All rights reserved.

Chakraborty, C., et al. (2020). "SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options." European Review for Medical & Pharmacological Sciences **24**(7): 4016-4026.
SARS-CoV-2 is responsible for the outbreak of severe respiratory illness (COVID-19) in Wuhan City, China and is now spreading rapidly throughout the world. The prompt outbreak of COVID-19 and its quick spread without any controllable measure defines the severity of the situation. In this crisis, a collective pool of knowledge about the advancement of clinical diagnostic and management for COVID-19 is a prerequisite. Here, we summarize all the available

updates on the multidisciplinary approaches for the advancement of diagnosis and proposed therapeutic strategies for COVID-19. Moreover, the review discusses different aspects of the COVID-19, including its epidemiology; incubation period; the general clinical features of patients; the clinical features of intensive care unit (ICU) patients; SARS-CoV-2 infection in the presence of co-morbid diseases and the clinical features of pediatric patients infected with the SARS-CoV-2. Advances in various diagnostic approaches, such as the use of real-time polymerase chain reaction (RT-PCR), chest radiography, and computed tomography (CT) imaging; and other modern diagnostic methods, for this infection have been highlighted. However, due to the unavailability of adequate evidence, presently there are no officially approved drugs or vaccines available against SARS-CoV-2. Additionally, we have discussed various therapeutic strategies for COVID-19 under different categories, like the possible treatment plans with drug (antiviral drugs and anti-cytokines) therapy for disease prevention. Lastly, potentials candidates for the vaccines against SARS-CoV-2 infection have been described. Collectively, the review provides an overview of the SARS-CoV-2 infection outbreak along with the recent advancements and strategies for diagnosis and therapy of COVID-19.

Chan, J. F. W., et al. (2020). "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster." The Lancet **395**(10223): 514-523.

Background: An ongoing outbreak of pneumonia associated with a novel coronavirus was reported in Wuhan city, Hubei province, China. Affected patients were geographically linked with a local wet market as a potential source. No data on person-to-person or nosocomial transmission have been published to date. Method(s): In this study, we report the epidemiological, clinical, laboratory, radiological, and microbiological findings of five patients in a family cluster who presented with unexplained pneumonia after returning to Shenzhen, Guangdong province, China, after a visit to Wuhan, and an additional family member who did not travel to Wuhan. Phylogenetic analysis of genetic sequences from these patients were done. Finding(s): From Jan 10, 2020, we enrolled a family of six patients who travelled to Wuhan from Shenzhen between Dec 29, 2019 and Jan 4, 2020. Of six family members who travelled to Wuhan, five were identified as infected with the novel coronavirus. Additionally, one family member, who did not travel to Wuhan, became infected with the virus after several days of contact with four of the family members. None of the family members had contacts with Wuhan markets or animals, although two had visited a Wuhan hospital. Five family members (aged 36-66 years) presented with fever, upper or lower respiratory tract symptoms, or diarrhoea, or a combination of these 3-6 days after exposure. They presented to our hospital (The University of Hong Kong-Shenzhen Hospital, Shenzhen) 6-10 days after symptom onset. They and one asymptomatic child (aged 10 years) had radiological ground-glass lung opacities. Older patients (aged >60 years) had more systemic symptoms, extensive radiological ground-glass lung changes, lymphopenia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels. The nasopharyngeal or throat swabs of these six patients were negative for known respiratory microbes by point-of-care multiplex RT-PCR, but five patients (four adults and the child) were RT-PCR positive for genes encoding the internal RNA-dependent RNA polymerase and surface Spike protein of this novel coronavirus, which were confirmed by Sanger sequencing. Phylogenetic analysis of these five patients' RT-PCR amplicons and two full genomes by next-generation sequencing showed that this is a novel coronavirus, which is closest to the bat severe acute respiatory syndrome (SARS)-related coronaviruses found in Chinese horseshoe bats. Interpretation(s): Our findings are consistent with person-to-person transmission of this novel coronavirus in hospital and family settings, and the reports of infected travellers in other geographical regions. Funding(s): The Shaw Foundation Hong Kong, Michael Seak-Kan Tong, Respiratory Viral Research Foundation Limited, Hui Ming, Hui Hoy and Chow Sin Lan Charity Fund Limited, Marina Man-Wai Lee, the Hong Kong Hainan Commercial Association South China Microbiology Research Fund, Sanming Project of Medicine (Shenzhen), and High Level-Hospital Program (Guangdong Health Commission). Copyright © 2020 Elsevier Ltd

Chandrasekharan, P., et al. (2020). "Neonatal Resuscitation and Postresuscitation Care of Infants Born to Mothers with Suspected or Confirmed SARS-CoV-2 Infection." American journal of perinatology. **08**.
The first case of novel coronavirus disease of 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was reported in November2019. The rapid progression to a global pandemic of COVID-19 has had profound medical, social, and economic consequences. Pregnant women and newborns represent a vulnerable population. However, the precise impact of this novel virus on the fetus and neonate remains uncertain. Appropriate protection of health care workers and newly born infants during and after delivery by a COVID-19 mother is essential. There is some disagreement among expert organizations on an optimal approach based on resource availability, surge volume, and potential risk of transmission. The manuscript outlines the precautions and steps to be taken before, during, and after resuscitation of a newborn born to a COVID-19 mother, including three optional variations of current standards involving shared-decision making with parents for perinatal management, resuscitation of the newborn, disposition, nutrition, and postdischarge care. The availability of resources may also drive the application of these guidelines. More evidence and research are needed to assess the risk of vertical and horizontal transmission of SARS-CoV-2 and its impact on fetal and neonatal outcomes. . The risk of vertical transmission is unclear; transmission from family members/providers to neonates is possible.. . Optimal personal-protective-equipment (airborne vs. droplet/contact precautions) for providers is crucial to prevent transmission.. . Parents should be engaged in shared decision-making with options for rooming in, skin-to-skin contact, and breastfeeding.. Copyright Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

Chang, L. S. and H. C. Kuo (2020). "The role of corticosteroids in the treatment of Kawasaki disease." Expert Review of Anti-Infective Therapy **18**(2): 155-164.
Introduction: Kawasaki disease (KD) is a form of systemic vasculitis that can lead to complications of coronary artery lesions (CAL). Diagnosis without delay and treatment with intravenous immunoglobulin (IVIG) are vital for a better prognosis. Anti-inflammatory drugs are generally used empirically in pediatric patients as off label. Corticosteroids are effective with anti-inflammatory effects applied in vasculitis. Areas covered: The timing of corticosteroid treatment in KD has been widely discussed by scholars. Some corticosteroids may still be effective which could be useful for such specific populations as high-risk patients. In this narrative review, we searched clinical studies, meta-analyzes, and systemic reviews using the PubMed database to summarize the available evidence on corticosteroid usage in KD through October 2019 and then discussed the relevant issues. Expert opinion: Today, the available evidence is more powerful to recommend corticosteroids for KD, moving from an unproven therapy to an effective adjunctive treatment. We suggest using methylprednisolone pulse therapy as an alternative rescue therapy for immunoglobulin-resistant KD, as well as identifying high-risk patients who need initial corticosteroid with IVIG treatment with an adequate route, dose, and duration. In the future, studies that evaluate the precision role of corticosteroids for individualized KD patients with CAL are warranted. Copyright © 2020, © 2020 Informa UK Limited, trading as Taylor & Francis Group.

Chang, T. H., et al. (2020). "Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis." Journal of the Formosan Medical Association **119**(5): 982-989.
BACKGROUND/PURPOSE: Current studies on pediatric coronavirus disease 2019 (COVID-19) are rare. The clinical characteristics and spectrum are still unknown. Facing this unknown and emerging pathogen, we aimed to collect current evidence about COVID-19 in children.
METHODS: We performed a systematic review in PubMed and Embase to find relevant case series. Because some reports were published in Chinese journals, the journals and publications of the

Chinese Medical Association related to COVID-19 were completely reviewed. A random effects model was used to pool clinical data in the meta-analysis.
RESULTS: Nine case series were included. In the pooled data, most of patients (75%) had a household contact history. The disease severity was mainly mild to moderate (98%). Only 2 children (2%) received intensive care. Fever occurred in 59% of the patients, while cough in 46%. Gastrointestinal symptoms (12%) were uncommon. There are 26% children are asymptomatic. The most common radiographic finding was ground glass opacities (48%). Currently, there is no evidence of vertical transmission to neonates born to mothers with COVID-19. Compared with the most relevant virus, SARS-CoV, SARS-CoV-2 causes less severe disease.
CONCLUSION: COVID-19 has distinct features in children. The disease severity is mild. Current diagnosis is based mainly on typical ground glass opacities on chest CT, epidemiological suspicion and contact tracing.

Chao, J. Y., et al. (2020). "Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City." Journal of Pediatrics **11**: 11.
OBJECTIVE: To describe the clinical profiles and risk factors for critical illness in hospitalized children and adolescents with COVID-19.
STUDY DESIGN: Children 1 month to 21 years with COVID-19 from a single tertiary care children's hospital between March 15-April 13, 2020 were included. Demographic and clinical data were collected.
RESULTS: 67 children tested positive for COVID-19; 21 (31.3%) were managed as outpatients. Of 46 admitted patients, 33 (72%) were admitted to the general pediatric medical unit and 13 (28%) to the pediatric intensive care unit (PICU). Obesity and asthma were highly prevalent but not significantly associated with PICU admission ($p=0.99$). Admission to the PICU was significantly associated with higher C-reactive protein, procalcitonin, and pro-B type natriuretic peptide levels and platelet counts ($p<0.05$ for all). Patients in the PICU were more likely to require high-flow nasal cannula ($p=0.0001$) and were more likely to have received Remdesivir through compassionate release ($p<0.05$). Severe sepsis and septic shock syndromes were observed in 7 (53.8%) PICU patients. Acute respiratory distress syndrome (ARDS) was observed in 10 (77%) PICU patients, 6 of whom (46.2%) required invasive mechanical ventilation for a median of 9 days. Of the 13 patients in the PICU, 8 (61.5%) were discharged home, and 4 (30.7%) patients remain hospitalized on ventilatory support at day 14. One patient died after withdrawal of life-sustaining therapy because of metastatic cancer.
CONCLUSIONS: We describe a higher than previously recognized rate of severe disease requiring PICU admission in pediatric patients admitted to the hospital with COVID-19.

Chen, F., et al. (2020). "First case of severe childhood novel coronavirus pneumonia in China. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**(3): 179-182.

Chen, F., et al. (2020). "[First case of severe childhood novel coronavirus pneumonia in China]." Zhonghua Erke Zazhi **58**(3): 179-182.

Chen, H., et al. (2020). "Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records." Lancet **395**(10226): 809-815.
BACKGROUND: Previous studies on the pneumonia outbreak caused by the 2019 novel coronavirus disease (COVID-19) were based on information from the general population. Limited data are available for pregnant women with COVID-19 pneumonia. This study aimed to evaluate the clinical characteristics of COVID-19 in pregnancy and the intrauterine vertical transmission potential of COVID-19 infection.
METHODS: Clinical records, laboratory results, and chest CT scans were retrospectively reviewed for nine pregnant women with laboratory-confirmed COVID-19 pneumonia (ie, with maternal throat swab

samples that were positive for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) who were admitted to Zhongnan Hospital of Wuhan University, Wuhan, China, from Jan 20 to Jan 31, 2020. Evidence of intrauterine vertical transmission was assessed by testing for the presence of SARS-CoV-2 in amniotic fluid, cord blood, and neonatal throat swab samples. Breastmilk samples were also collected and tested from patients after the first lactation.

FINDINGS: All nine patients had a caesarean section in their third trimester. Seven patients presented with a fever. Other symptoms, including cough (in four of nine patients), myalgia (in three), sore throat (in two), and malaise (in two), were also observed. Fetal distress was monitored in two cases. Five of nine patients had lymphopenia (<1.0 x 109 cells per L). Three patients had increased aminotransferase concentrations. None of the patients developed severe COVID-19 pneumonia or died, as of Feb 4, 2020. Nine livebirths were recorded. No neonatal asphyxia was observed in newborn babies. All nine livebirths had a 1-min Apgar score of 8-9 and a 5-min Apgar score of 9-10. Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus.

INTERPRETATION: The clinical characteristics of COVID-19 pneumonia in pregnant women were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia. Findings from this small group of cases suggest that there is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy.

FUNDING: Hubei Science and Technology Plan, Wuhan University Medical Development Plan.

Chen, H. R., et al. (2020). "A Case of Childhood Covid-19 Infection with Pleural Effusion Complicated by Possible Secondary Mycoplasma Pneumoniae Infection." The Pediatric infectious disease journal. **05**.

We report a case of childhood coronavirus disease 2019 infection with pleural effusion complicated by possible secondary Mycoplasma pneumoniae infection. Fever and pulmonary lesions on computed tomography were the early clinical manifestations, and the patient developed nonproductive cough later. The hydrothorax in this coronavirus disease 2019 case was exudative, showing predominantly mature lymphocytes.

Chen, J., et al. (2020). "The clinical and immunological features of pediatric COVID-19 patients in China." Genes and Diseases.

In December 2019, the corona virus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) emerged in Wuhan, China and rapidly spread worldwide. Few information on clinical features and immunological profile of COVID-19 in paediatrics. The clinical features and treatment outcomes of twelve paediatric patients confirmed as COVID-19 were analyzed. The immunological features of children patients was investigated and compared with twenty adult patients. The median age was 14.5-years (range from 0.64 to 17), and six of the patients were male. The average incubation period was 8 days. Clinically, cough (9/12, 75%) and fever (7/12, 58.3%) were the most common symptoms. Four patients (33.3%) had diarrhea during the disease. As to the immune profile, children had higher amount of total T cell, CD8+ T cell and B cell but lower CRP levels than adults ($P < 0.05$). Ground-glass opacity (GGO) and local patchy shadowing were the typical radiological findings on chest CT scan. All patients received antiviral and symptomatic treatment and the symptom relieved in 3-4 days after admitted to hospital. The paediatric patients showed mild symptom but with longer incubation period. Children infected with SARS-CoV-2 had different immune profile with higher T cell amount and low inflammatory factors level, which might ascribed to the mild clinical symptom. We advise that nucleic acid test or examination of serum IgM/IgG antibodies against SARS-CoV-2 should be taken for children with exposure history regardless of clinical symptom.

Chen, S. (2020). "An online solution focused brief therapy for adolescent anxiety during the novel coronavirus disease (COVID-19) pandemic: a structured summary of a study protocol for a

randomised controlled trial." Trials [Electronic Resource] **21**(1): 402.
OBJECTIVES: This study aims to assess the effectiveness of delivering Solution Focused Brief Therapy (SFBT) through telecommunication with a group of adolescents who present anxiety symptoms during the COVID-19 outbreak. We hypothesize that participants who are randomly assigned to receive 2-4 sessions of Solution Focused Brief Therapy would have better clinical outcomes than participants who are in the waitlist group. We additionally hypothesized that using SFBT can also change participants' depression levels and their coping strategies in dealing with distress during the COVID-19 pandemic.
TRIAL DESIGN: This study employs a randomized delayed crossover open label controlled trial in adolescents who are presenting anxiety symptoms during the COVID-19 outbreak. Participants who meet the enrollment criteria stated below will be invited to participate in this study through telecommunication. Those accepting will be randomly allocated to the intervention group or waitlist group.

Chen, S., et al. (2020). "[Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases]." Chung-Hua Ping Li Hsueh Tsa Chih - Chinese Journal of Pathology **49**(0): E005.
Objective: To investigate the clinical characteristics and placental pathology of 2019-nCoV infection in pregnancy, and to evaluate intrauterine vertical transmission potential of 2019-nCoV infection.

Chen, S., et al. (2020). "Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia." Journal of Medical Virology.
The aim is to evaluate pregnant women infected with coronavirus disease 2019 (COVID-19) and provide help for clinical prevention and treatment. All five cases of pregnant women confirmed COVID-19 were collected among patients who admitted to the Maternal and Child Hospital of Hubei Province between January 20 and February 10, 2020. All patients, aging from 25 to 31 years old, had the gestational week from 38th weeks to 41st weeks. All pregnant women did not have an antepartum fever but developed a low-grade fever (37.5-38.5) within 24 hours after delivery. All patients had normal liver and renal function, two patients had elevated plasma levels of the myocardial enzyme. Unusual chest imaging manifestations, featured with ground-grass opacity, were frequently observed in bilateral (three cases) or unilateral lobe (two cases) by computed tomography (CT) scan. All labors smoothly processed, the Apgar scores were 10 points 1 and 5 minutes after delivery, no complications were observed in the newborn. Pregnancy and perinatal outcomes of patients with COVID-19 should receive more attention. It is probable that pregnant women diagnosed with COVID-19 have no fever before delivery. Their primary initial manifestations were merely low-grade postpartum fever or mild respiratory symptoms. Therefore, the protective measures are necessary on admission; the instant CT scan and real-time reverse-transcriptase polymerase-chain-reaction assay should be helpful in early diagnosis and avoid cross-infection on the occasion that patients have fever and other respiratory signs. Copyright © 2020 Wiley Periodicals, Inc.

Chen, X. B., et al. (2020). "Retrospective Analysis of 61 Cases of Children Died of Viral Pneumonia." Fa i Hsueh Tsa Chih Journal of Forensic Medicine **36**(2): 25.
Abstract: Objective To retrospectively analyze the forensic and pathological postmortem examination and clinical data of children who died of viral pneumonia in identification of cause of death cases and to discuss the clinical characteristics and pathological features of viral pneumonia in children, in order to provide reference to pathological diagnosis of viral pneumonia in children caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Methods In this study, postmortem examination data from the institute of 61 cases of children whose cause of death were identified as viral pneumonia in recent years were collected. The gender, age, clinical symptoms and pathological features were comparatively analyzed. Results Among the 61 cases of children who died of viral pneumonia, most were within 2 years old

(83.61%), and a large proportion died within 2 weeks after the onset of the disease (91.80%). General changes in postmortem examination included respiratory mucosal hyperemia, pleural effusion, pulmonary swelling, variegated pulmonary pleura and serosa, focal hemorrhage and edema of the cut surface of the lung. A large proportion of children had enlarged mesenteric lymph nodes (83.61%), and 21.31% of children had thymic dysplasia. Histopathological changes included pulmonary alveoli and interstitial edema, pulmonary hemorrhage, alveolar epithelial shedding, serous and (or) fibrous exudation in the alveoli, formation of viral inclusions, formation of transparent membranes, infiltration of inflammatory cells that mainly consisted of macrophages and lymphocytes in interstitial substance and alveoli. Viral infections often affected the heart and gastrointestinal tract. Conclusion The clinical symptoms of children with viral pneumonia are difficult to notice, and because their immune system is not fully developed and they have poor autoimmunity, they can easily get into a critical condition and even die. Through analysis of the characteristics of forensic autopsy and histopathological changes, this study could provide reference for pathological diagnosis of viral pneumonia.

Chen, Y., et al. (2020). "[The network investigation on knowledge, attitude and practice about COVID-19 of the residents in Anhui Province]." Chung-Hua Yu Fang i Hsueh Tsa Chih [Chinese Journal of Preventive Medicine] **54**(4): 367-373.
Objective: To analyze the current situation of the knowledge, attitudes and practice about COVID-19 of the residents in Anhui Province.

Chen, Y., et al. (2020). "Infants Born to Mothers With a New Coronavirus (COVID-19)." Frontiers in Pediatrics **8 (no pagination)**(104).
A novel viral respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for an epidemic of the coronavirus disease 2019 (COVID-19) in cases in China and worldwide. Four full-term, singleton infants were born to pregnant women who tested positive for COVID-19 in the city of Wuhan, the capital of Hubei province, China, where the disease was first identified. Of the three infants, for who consent to be diagnostically tested was provided, none tested positive for the virus. None of the infants developed serious clinical symptoms such as fever, cough, diarrhea, or abnormal radiologic or hematologic evidence, and all four infants were alive at the time of hospital discharge. Two infants had rashes of unknown etiology at birth, and one had facial ulcerations. One infant had tachypnea and was supported by non-invasive mechanical ventilation for 3 days. One had rashes at birth but was discharged without parental consent for a diagnostic test. This case report describes the clinical course of four live born infants, born to pregnant women with the COVID-19 infection.

Chen, Y., et al. (2020). "Prevalence of self-reported depression and anxiety among pediatric medical staff members during the COVID-19 outbreak in Guiyang, China." Psychiatry Research **288 (no pagination)**(113005).

Chen, Z., et al. (2020). "[Diagnosis and treatment recommendation for pediatric coronavirus disease-19]." Zhejiang da Xue Xue Bao. Yi Xue Ban/Journal of Zhejiang University. Medical Sciences **49**(1): 1-8.

Chen, Z., et al. (2020). "Diagnosis and treatment recommendation for pediatric COVID-19 (the second edition). [Chinese]." Zhejiang da xue xue bao **Yi xue ban = Journal of Zhejiang University. Medical sciences. 49**(2): 139-146.
The coronavirus disease 2019 (COVID-19) has caused a global pandemic. All people including children are generally susceptible to COVID-19, but the condition is relatively mild for children. The diagnosis of COVID-19 is largely based on the epidemiological evidence and clinical manifestations, and confirmed by positive detection of virus nucleic acid in respiratory samples. The main symptoms of COVID-19 in children are fever and cough; the total number of white

blood cell count is usually normal or decreased; the chest imaging is characterized by interstitial pneumonia, which is similar to other respiratory virus infections and Mycoplasma pneumoniae infections. Early identification, early isolation, early diagnosis and early treatment are important for clinical management. The treatment of mild or moderate type of child COVID-19 is mainly symptomatic. For severe and critical ill cases, the oxygen therapy, antiviral drugs, antibacterial drugs, glucocorticoids, mechanical ventilation or even extracorporeal membrane oxygenation (ECMO) may be adopted, and the treatment plan should be adjusted timely through multi-disciplinary cooperation.

Chen, Z., et al. (2020). "COVID-19 with post-chemotherapy agranulocytosis in childhood acute leukemia: a case report. [Chinese]." Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi **41**: E004.

Chen, Z. M., et al. (2020). "Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus." World Journal of Pediatrics **05**: 05.
Since December 2019, an epidemic caused by novel coronavirus (2019-nCoV) infection has occurred unexpectedly in China. As of 8 pm, 31 January 2020, more than 20 pediatric cases have been reported in China. Of these cases, ten patients were identified in Zhejiang Province, with an age of onset ranging from 112 days to 17 years. Following the latest National recommendations for diagnosis and treatment of pneumonia caused by 2019-nCoV (the 4th edition) and current status of clinical practice in Zhejiang Province, recommendations for the diagnosis and treatment of respiratory infection caused by 2019-nCoV for children were drafted by the National Clinical Research Center for Child Health, the National Children's Regional Medical Center, Children's Hospital, Zhejiang University School of Medicine to further standardize the protocol for diagnosis and treatment of respiratory infection in children caused by 2019-nCoV.

Chidini, G., et al. (2020). "SARS-CoV-2 Infection in a Pediatric Department in Milan: A Logistic Rather Than a Clinical Emergency." The Pediatric infectious disease journal. **25**.

Chiotos, K., et al. (2020). "Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2." Journal of the Pediatric Infectious Diseases Societ **22**: 22.
BACKGROUND: Although Coronavirus Disease 2019 (COVID-19) is mild in nearly all children, a small proportion of pediatric patients develops severe or critical illness. Guidance is therefore needed regarding use of agents with potential activity against severe acute respiratory syndrome coronavirus 2 in pediatrics.
METHODS: A panel of pediatric infectious diseases physicians and pharmacists from 18 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a set of guidance statements was developed and refined based on review of best available evidence and expert opinion.
RESULTS: Given the typically mild course of pediatric COVID-19, supportive care alone is suggested for the overwhelming majority of cases. The panel suggests a decision-making framework for antiviral therapy that weighs risks and benefits based on disease severity as indicated by respiratory support needs, with consideration on a case-by-case basis of potential pediatric risk factors for disease progression. If an antiviral is used, the panel suggests remdesivir as the preferred agent. Hydroxychloroquine could be considered for patients who are not candidates for remdesivir or when remdesivir is not available. Antivirals should preferably be used as part of a clinical trial if available.
CONCLUSIONS: Antiviral therapy for COVID-19 is not necessary for the great majority of pediatric patients. For those rare children who develop severe or critical disease, this guidance offer an approach for decision-making regarding antivirals, informed by available data. As evidence continues to evolve rapidly, the need for updates to the guidance is anticipated.

Choi, S. H., et al. (2020). "Epidemiology and clinical features of coronavirus disease 2019 in children." Korean Journal of Pediatrics **63**(4): 125-132.

Coronavirus disease-2019 (COVID-19), which started in Wuhan, China, in December 2019 and declared a worldwide pandemic on March 11, 2020, is a novel infectious disease that causes respiratory illness and death. Pediatric COVID-19 accounts for a small percentage of patients and is often milder than that in adults; however, it can progress to severe disease in some cases. Even neonates can suffer from COVID-19, and children may spread the disease in the community. This review summarizes what is currently known about COVID-19 in children and adolescents. Copyright © 2020 by The Korean Pediatric Society.

Ciaglia, E., et al. (2020). "COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children." Frontiers in Pediatrics **8 (no pagination)**(206).

Cindy, H., et al. (2020). "Caring for Pediatric Patients with Diabetes amidst the COVID-19 Storm." The Journal of pediatrics. **05**.

Colonna, C., et al. (2020). "Chilblains-like lesions in children following suspected Covid-19 infection." Pediatric dermatology. **06**.
During the COVID-19 pandemic, chilblains-like lesions have been reported in mildly symptomatic children and adolescents. We present four children investigated for suspected COVID-19 infection with who presented with acral skin findings and mild systemic symptoms. Histology from one case showed signs of vasculitis with evident fibrin thrombus. Copyright This article is protected by copyright. All rights reserved.

Coronado Munoz, A., et al. (2020). "Late-Onset Neonatal Sepsis in a Patient with Covid-19." New England Journal of Medicine **382**(19): e49.

Cowling, B. J., et al. (2020). "Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study." The Lancet Public Health **5**(5): e279-e288.
Background: A range of public health measures have been implemented to suppress local transmission of coronavirus disease 2019 (COVID-19) in Hong Kong. We examined the effect of these interventions and behavioural changes of the public on the incidence of COVID-19, as well as on influenza virus infections, which might share some aspects of transmission dynamics with COVID-19. Method(s): We analysed data on laboratory-confirmed COVID-19 cases, influenza surveillance data in outpatients of all ages, and influenza hospitalisations in children. We estimated the daily effective reproduction number (R<inf>t</inf>) for COVID-19 and influenza A H1N1 to estimate changes in transmissibility over time. Attitudes towards COVID-19 and changes in population behaviours were reviewed through three telephone surveys done on Jan 20-23, Feb 11-14, and March 10-13, 2020. Finding(s): COVID-19 transmissibility measured by R<inf>t</inf> has remained at approximately 1 for 8 weeks in Hong Kong. Influenza transmission declined substantially after the implementation of social distancing measures and changes in population behaviours in late January, with a 44% (95% CI 34-53%) reduction in transmissibility in the community, from an estimated R<inf>t</inf> of 1.28 (95% CI 1.26-1.30) before the start of the school closures to 0.72 (0.70-0.74) during the closure weeks. Similarly, a 33% (24-43%) reduction in transmissibility was seen based on paediatric hospitalisation rates, from an R<inf>t</inf> of 1.10 (1.06-1.12) before the start of the school closures to 0.73 (0.68-0.77) after school closures. Among respondents to the surveys, 74.5%, 97.5%, and 98.8% reported wearing masks when going out, and 61.3%, 90.2%, and 85.1% reported avoiding crowded places in surveys 1 (n=1008), 2 (n=1000), and 3 (n=1005), respectively. Interpretation(s): Our study shows that non-pharmaceutical interventions (including border restrictions, quarantine and isolation, distancing, and changes in population behaviour) were associated with reduced transmission of COVID-19 in Hong Kong, and are also likely to have substantially reduced influenza transmission in early February, 2020. Funding(s): Health and Medical Research Fund, Hong Kong. Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access

Cron, R. Q. and W. W. Chatham (2020). "The Question of Whether to Remain on Therapy for Chronic Rheumatic Diseases in the Setting of the Covid-19 Pandemic." The Journal of rheumatology. **25**.
We appreciate our Italian colleagues' interest in our editorial denoting the rheumatologist's role in helping to diagnose and treat cytokine storm syndrome (CSS) in the setting of the Covid-19 panemic (1). It is encouraging that none of the 123 pediatric rheumatology patients (primarily juvenile idiopathic arthritis) on background biological disease modifying anti-rheumatic drug (bDMARD) therapies in Milan, Italy surveyed over a 7-week period from February 25 through April 14, 2020 (during which time Covid-19 was hyper-endemic there) had either confirmed or suspected Covid-19 (2).

Cui, Y., et al. (2020). "A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting With Pneumonia, Liver Injury, and Heart Damage." Journal of Infectious Diseases **221**(11): 1775-1781.
BACKGROUND: Previous studies on the pneumonia outbreak caused by the 2019 novel coronavirus disease (COVID-19) were mainly based on information from adult populations. Limited data are available for children with COVID-19, especially for infected infants.
METHODS: We report a 55-day-old case with COVID-19 confirmed in China and describe the identification, diagnosis, clinical course, and treatment of the patient, including the disease progression from day 7 to day 11 of illness.
RESULTS: This case highlights that children with COVID-19 can also present with multiple organ damage and rapid disease changes.
CONCLUSIONS: When managing such infant patients with COVID-19, frequent and careful clinical monitoring is essential.

Cui, Y., et al. (2020). "A 55-Day-Old Female Infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage." The Journal of infectious diseases. **17**.
Previous studies on the pneumonia outbreak caused by the 2019 novel coronavirus disease (COVID-19) were mainly based on information from adult populations. Limited data are available for children with COVID-19, especially for infected infants. We report a 55-day-old case with COVID-19 confirmed in China and describe the identification, diagnosis, clinical course, and treatment of the patient, including the disease progression from day 7 to day 11 of illness. This case highlights that children with COVID-19 can also present with multiple organ damage and rapid disease changes. When managing such patients, frequent and careful clinical monitoring is essential. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Damle, B., et al. (2020). "Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19." Clinical Pharmacology & Therapeutics **17**: 17.
Azithromycin (AZ) is a broad-spectrum macrolide antibiotic with a long half-life and a large volume of distribution. It is primarily used for the treatment of respiratory, enteric, and genitourinary bacterial infections. AZ is not approved for the treatment of viral infections, and there is no well-controlled, prospective, randomized clinical evidence to support AZ therapy in coronavirus disease 2019 (COVID-19). Nevertheless, there are anecdotal reports that some hospitals have begun to include AZ in combination with hydroxychloroquine or chloroquine (CQ) for treatment of COVID-19. It is essential that the clinical pharmacology (CP) characteristics of AZ be considered in planning and conducting clinical trials of AZ alone or in combination with other agents, to ensure safe study conduct and to increase the probability of achieving definitive answers regarding efficacy of AZ in the treatment of COVID-19. The safety profile of AZ used as an antibacterial agent is well established.¹ This work assesses published in vitro and clinical evidence for AZ as an agent with antiviral properties. It also provides basic CP

information relevant for planning and initiating COVID-19 clinical studies with AZ, summarizes safety data from healthy volunteer studies, and safety and efficacy data from phase II and phase II/III studies in patients with uncomplicated malaria, including a phase II/III study in pediatric patients following administration of AZ and CQ in combination. This paper may also serve to facilitate the consideration and use of a priori-defined control groups for future research.

Davenne, E., et al. (2020). "[Coronavirus and COVID-19 : focus on a galopping pandemic]." Revue Medicale de Liege **75**(4): 218-225.
The international community is currently facing a pandemic of acute respiratory syndrome caused by a new coronavirus, SARS-CoV-2. This syndrome has been named COVID-19 for CoronaVIrus Disease 2019 by the World Health Organization. The starting point of the epidemic is the city of Wuhan (China), where the virus is said to have been transmitted from animals to humans before inter-human transmission. This is the third epidemic caused by a coronavirus after those of severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) started in 2012. COVID-19 has rapidly spread to China and is currently spreading all over the world. The infection mainly affects patients over 40 years of age and mortality is increased in the presence of comorbidities. Children are pauci- or asymptomatic. The diagnosis is most often based on the detection of the viral genome in the nasopharynx by molecular biology methods. In the absence of specific anti-viral molecules, treatment is currently mainly symptomatic. It is clear that the COVID-19 pandemic is more difficult to control than what the first data suggested. The key strategy to SARS-CoV-2 is to limit its transmission. Preventive measures are mainly based on the application of adequate hand hygiene measures and disinfection of the environment, as well as measures of social distance aimed at limiting contacts in the population and protecting populations at risk.

D'Cruz, M. (2020). "The ICMR bulletin on targeted hydroxychloroquine prophylaxis for Covid-19: Need to interpret with caution." Indian Journal of Medical Ethics **V**(2): 100-102.
The National Task Force for Covid-19 of the Indian Council of Medical Research (ICMR) in a bulletin dated March 21, 2020 recommended the use of hydroxychloroquine for prophylaxis in asymptomatic health care workers caring for suspected or confirmed patients and household contacts of confirmed patients. This is cause for concern with regard to bioethics and good clinical practice. The evidence for the efficacy of chloroquine and hydroxychloroquine is currently derived from open label trials and cell culture studies with no conclusive evidence available from randomised clinical trials. Hydroxychloroquine also carries contraindications in the case of conditions such as maculopathy, retinopathy and QTc prolongation and should be used with caution in vulnerable populations such as children, pregnancy, lactation and the elderly. Despite this, there has been a rush to procure and self-medicate with hydroxychloroquine, which has been addressed by the National Task Force. The WHO and the FDA have not found adequate evidence to recommend any specific medication for the treatment of Covid-19. While further evidence is awaited, including from trials registered with the FDA and the ICMR, it is recommended that the administration of hydroxychloroquine for chemo-prophylaxis be considered on a case by case basis with monitoring by a registered medical practitioner including electrocardiography (ECG). The potential for retinal and cardiac toxicity must also be borne in mind. It is further recommended that a public advisory regarding the need for caution in chemo-prophylaxis be made available in the public domain. Keywords: Coronavirus, Covid-19, SARS-CoV-2, hydroxychloroquine, chloroquine, chemoprophylaxis, bioethics, evidence- based medicine.

de Niet, A., et al. (2020). "The role of children in the transmission of mild SARS-CoV-2 infection." Acta Paediatrica, International Journal of Paediatrics.
We thank dr. Ludvigsson (1) on his effort to improve knowledge on SARS-CoV-2 infection in children. In trying to understand the spread of the disease, one of the most notable features is that only a small number of severe SARS-CoV-2 infections have involved children. The huge age

disparity in disease severity might be one of the most stringent fundamental knowledge gaps. Copyright This article is protected by copyright. All rights reserved.

De Rose, D. U., et al. (2020). "Novel Coronavirus disease (COVID-19) in newborns and infants: what we know so far." Italian Journal of Pediatrics **46**(1): 56.
Recently, an outbreak of viral pneumonitis in Wuhan, Hubei, China successively spread as a global pandemia, led to the identification of a novel betacoronavirus species, the 2019 novel coronavirus, successively designated 2019-nCoV then SARS-CoV-2). The SARS-CoV-2 causes a clinical syndrome designated coronavirus disease 2019 (COVID19) with a spectrum of manifestations ranging from mild upper respiratory tract infection to severe pneumonitis, acute respiratory distress syndrome (ARDS) and death. Few cases have been observed in children and adolescents who seem to have a more favorable clinical course than other age groups, and even fewer in newborn babies. This review provides an overview of the knowledge on SARS-CoV-2 epidemiology, transmission, the associated clinical presentation and outcomes in newborns and infants up to 6 months of life.

de Vries, A. P. J., et al. (2020). "Immediate impact of COVID-19 on transplant activity in the Netherlands." Transplant Immunology **61 (no pagination)**(101304).
The rapid emergence of the COVID-19 pandemic is unprecedented and poses an unparalleled obstacle in the sixty-five year history of organ transplantation. Worldwide, the delivery of transplant care is severely challenged by matters concerning - but not limited to - organ procurement, risk of SARS-CoV-2 transmission, screening strategies of donors and recipients, decisions to postpone or proceed with transplantation, the attributable risk of immunosuppression for COVID-19 and entrenched health care resources and capacity. The transplant community is faced with choosing a lesser of two evils: initiating immunosuppression and potentially accepting detrimental outcome when transplant recipients develop COVID-19 versus postponing transplantation and accepting associated waitlist mortality. Notably, prioritization of health care services for COVID-19 care raises concerns about allocation of resources to deliver care for transplant patients who might otherwise have excellent 1-year and 10-year survival rates. Children and young adults with end-stage organ disease in particular seem more disadvantaged by withholding transplantation because of capacity issues than from medical consequences of SARS-CoV-2. This report details the nationwide response of the Dutch transplant community to these issues and the immediate consequences for transplant activity. Worrisome, there was a significant decrease in organ donation numbers affecting all organ transplant services. In addition, there was a detrimental effect on transplantation numbers in children with end-organ failure. Ongoing efforts focus on mitigation of not only primary but also secondary harm of the pandemic and to find right definitions and momentum to restore the transplant programs. Copyright © 2020 Elsevier B.V.

DeBaun, M. R. (2020). "Initiating adjunct low dose-hydroxyurea therapy for stroke prevention in children with SCA during the COVID-19 pandemic." Blood **13**: 13.

DeBiasi, R. L., et al. (2020). "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region." Journal of Pediatrics **13**: 13.

Dhochak, N., et al. (2020). "Pathophysiology of COVID-19: Why Children Fare Better than Adults?" Indian Journal of Pediatrics: 1-10.
The world is facing Coronavirus Disease-2019 (COVID-19) pandemic, which is causing a large number of deaths and burden on intensive care facilities. It is caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) originating in Wuhan, China. It has been seen that fewer children contract COVID-19 and among infected, children have less severe disease. Insights in pathophysiological mechanisms of less severity in children could be important for devising therapeutics for high-risk adults and elderly. Early closing of schools and day-care

centers led to less frequent exposure and hence, lower infection rate in children. The expression of primary target receptor for SARS-CoV-2, i.e. angiotensin converting enzyme-2 (ACE-2), decreases with age. ACE-2 has lung protective effects by limiting angiotensin-2 mediated pulmonary capillary leak and inflammation. Severe COVID-19 disease is associated with high and persistent viral loads in adults. Children have strong innate immune response due to trained immunity (secondary to live-vaccines and frequent viral infections), leading to probably early control of infection at the site of entry. Adult patients show suppressed adaptive immunity and dysfunctional over-active innate immune response in severe infections, which is not seen in children. These could be related to immune-senescence in elderly. Excellent regeneration capacity of pediatric alveolar epithelium may be contributing to early recovery from COVID-19. Children, less frequently, have risk factors such as co-morbidities, smoking, and obesity. But young infants and children with pre-existing illnesses could be high risk groups and need careful monitoring. Studies describing immune-pathogenesis in COVID-19 are lacking in children and need urgent attention.

Dipasquale, V., et al. (2020). "Challenges in paediatric inflammatory bowel diseases in the COVID-19 time." Digestive & Liver Disease **52**(5): 593-594.

Dona, D., et al. (2020). "Fecal-Oral Transmission of Sars-Cov-2 in Children: Is It Time to Change Our Approach?" The Pediatric infectious disease journal. **16**.
Starting from 2 pediatric cases of COVID-19, with confirmation at nasopharyngeal and rectal swabs, we considered the lesson learnt from previous Coronavirus epidemics and reviewed evidence on the current outbreak. Surveillance with rectal swabs might be extended to infants and children, for the implications for household contacts and isolation timing.

Donders, F., et al. (2020). "ISIDOG recommendations concerning COVID-19 and pregnancy." Diagnostics **10 (4) (no pagination)**(243).
Providing guidelines to health care workers during a period of rapidly evolving viral pandemic infections is not an easy task, but it is extremely necessary in order to coordinate appropriate action so that all patients will get the best possible care given the circumstances they are in. With these International Society of Infectious Disease in Obstetrics and Gynecology (ISIDOG) guidelines we aim to provide detailed information on how to diagnose and manage pregnant women living in a pandemic of COVID-19. Pregnant women need to be considered as a high-risk population for COVID-19 infection, and if suspected or proven to be infected with the virus, they require special care in order to improve their survival rate and the well-being of their babies. Both protection of healthcare workers in such specific care situations and maximal protection of mother and child are envisioned. Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland.

Dong, Y., et al. (2020). "Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China." Pediatrics. **16**.

Dong, Y., et al. (2020). "Epidemiology of COVID-19 Among Children in China." e20200702.
OBJECTIVE: To identify the epidemiological characteristics and transmission patterns of pediatric patients with the 2019 novel coronavirus disease (COVID-19) in China.METHODS: Nationwide case series of 2135 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16, 2020, to February 8, 2020, were included. The epidemic curves were constructed by key dates of disease onset and case diagnosis. Onset-to-diagnosis curves were constructed by fitting a log-normal distribution to data on both onset and diagnosis dates.RESULTS: There were 728 (34.1%) laboratory-confirmed cases and 1407 (65.9%) suspected cases. The median age of all patients was 7 years (interquartile range: 2–13 years), and 1208 case patients (56.6%) were boys. More than 90% of all patients had asymptomatic, mild, or moderate cases. The median time from illness onset to diagnoses was 2 days (range:

0–42 days). There was a rapid increase of disease at the early stage of the epidemic, and then there was a gradual and steady decrease. The disease rapidly spread from Hubei province to surrounding provinces over time. More children were infected in Hubei province than any other province.CONCLUSIONS: Children of all ages appeared susceptible to COVID-19, and there was no significant sex difference. Although clinical manifestations of children's COVID-19 cases were generally less severe than those of adult patients, young children, particularly infants, were vulnerable to infection. The distribution of children's COVID-19 cases varied with time and space, and most of the cases were concentrated in Hubei province and surrounding areas. Furthermore, this study provides strong evidence of human-to-human transmission.

Dong, Y., et al. (2020). "Infectious diseases in children and adolescents in China: Analysis of national surveillance data from 2008 to 2017." The BMJ **369 (no pagination)**(m1043).
Objectives To outline which infectious diseases in the pre-covid-19 era persist in children and adolescents in China and to describe recent trends and variations by age, sex, season, and province. Design National surveillance studies, 2008-17. Setting 31 provinces in mainland China. Participants 4 959 790 Chinese students aged 6 to 22 years with a diagnosis of any of 44 notifiable infectious diseases. The diseases were categorised into seven groups: quarantinable; vaccine preventable; gastrointestinal and enteroviral; vectorborne; zoonotic; bacterial; and sexually transmitted and bloodborne. Main outcome measures Diagnosis of, and deaths from, 44 notifiable infectious diseases. Results From 2008 to 2017, 44 notifiable infectious diseases were diagnosed in 4 959 790 participants (3 045 905 males, 1 913 885 females) and there were 2532 deaths (1663 males, 869 females). The leading causes of death among infectious diseases shifted from rabies and tuberculosis to HIV/AIDS, particularly in males. Mortality from infectious diseases decreased steadily from 0.21 per 100 000 population in 2008 to 0.07 per 100 000 in 2017. Quarantinable conditions with high mortality have effectively disappeared. The incidence of notifiable infectious diseases in children and adolescents decreased from 280 per 100 000 in 2008 to 162 per 100 000 in 2015, but rose again to 242 per 100 000 in 2017, largely related to mumps and seasonal influenza. Excluding mumps and influenza, the incidence of vaccine preventable diseases fell from 96 per 100 000 in 2008 to 7 per 100 000 in 2017. The incidence of gastrointestinal and enterovirus diseases remained constant, but typhoid, paratyphoid, and dysentery continued to decline. Vectorborne diseases all declined, with a particularly noticeable reduction in malaria. Zoonotic infections remained at low incidence, but there were still unpredictable outbreaks, such as pandemic A/H1N1 2009 influenza. Tuberculosis remained the most common bacterial infection, although cases of scarlet fever doubled between 2008 and 2017. Sexually transmitted diseases and bloodborne infections increased significantly, particularly from 2011 to 2017, among which HIV/AIDS increased fivefold, particularly in males. Difference was noticeable between regions, with children and adolescents in western China continuing to carry a disproportionate burden from infectious diseases. Conclusions China's success in infectious disease control in the pre-covid-19 era was notable, with deaths due to infectious diseases in children and adolescents aged 6-22 years becoming rare. Many challenges remain around reducing regional inequalities, scaling-up of vaccination, prevention of further escalation of HIV/AIDS, renewed efforts for persisting diseases, and undertaking early and effective response to highly transmissible seasonal and unpredictable diseases such as that caused by the novel SARS-CoV-2 virus. Copyright © © Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Du, W., et al. (2020). "Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China." Infection.
Aims and background: The COVID-19 outbreak spread in China and is a threat to the world. We reported on the epidemiological, clinical, laboratory, and radiological characteristics of children cases to help health workers better understand and provide timely diagnosis and treatment. Method(s): Retrospectively, two research centers' case series of 67 consecutive hospitalized cases including 53 adult and 14 children cases with COVID-19 between 23 Jan 2020 and 15 Feb

2020 from Jinan and Rizhao were enrolled in this study. Epidemiological, clinical, laboratory, and radiological characteristics of children and adults were analyzed and compared. Result(s): Most cases in children were mild (21.4%) and conventional cases (78.6%), with mild clinical signs and symptoms, and all cases were of family clusters. Fever (35.7%) and dry cough (21.4%) were described as clinical manifestations in children cases. Dry cough and phlegm were not the most common symptoms in children compared with adults (p = 0.03). In the early stages of the disease, lymphocyte counts did not significantly decline but neutrophils count did in children compared with adults (p = 0.02). There was a lower level of CRP (p = 0.00) in children compared with adults. There were 8 (57.1%) asymptomatic cases and 6 (42.9%) symptomatic cases among the 14 children cases. The age of asymptomatic patients was younger than that of symptomatic patients (p = 0.03). Even among asymptomatic patients, 5 (62.5%) cases had lung injuries including 3 (60%) cases with bilateral involvement, which was not different compared with that of symptomatic cases (p = 0.58, p = 0.74). Conclusion(s): The clinical symptoms of children are mild, there is substantial lung injury even among children, but that there is less clinical disease, perhaps because of a less pronounced inflammatory response, and that the occurrence of this pattern appears to inversely correlate with age. Copyright © 2020, Springer-Verlag GmbH Germany, part of Springer Nature.

Ebrahimi, S. A. (2020). "Noscapine, a possible drug candidate for attenuation of cytokine release associated with SARS-CoV-2." Drug Development Research.
Successful treatment of viral infections has proven to be huge challenge for modern medicine with the most effective approach being prior vaccination. The problem with vaccination is the time it takes to develop an effective vaccine, validate its safety and manufacture it in large quantities. Facing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), we simply do not have the time to develop the vaccine before thousands of people die. Therefore, any treatment which can decrease the severe symptoms due to lung damage may help attenuate mortality rates. Inactivation of ACE2 during virus fusion into the host cell may be one of the underlying reasons for intense immunological reaction seen in the lung tissue. This overreaction is probably mediated through the bradykinin receptor activation. Noscapine, a medication used for the treatment of cough, has been shown to inhibit bradykinin enhanced cough response in man. As it is already marketed in a number of countries as a cough medicine, even for children, a suitable formulation with all the required licenses is available that can be rapidly utilized in preliminary trials. Copyright © 2020 Wiley Periodicals, Inc.

Elakabawi, K., et al. (2020). "Kawasaki Disease: Global Burden and Genetic Background." Cardiology Research **11**(1): 9-14.
Kawasaki disease (KD) is a childhood vasculitides associated with serious coronary artery lesions. It is the most common cause of pediatric acquired heart disease in developed countries, and is increasingly reported from many rapidly industrializing developing countries. The incidence varies widely among different nations and is highest in North-East Asian countries, where almost 1 in 100 children in Japan having the disease by age of 5, where the lowest incidence reported in sub-Saharan Africa. The etiology of KD is still uncertain; interaction between a genetic predisposition and several environmental and immunological factors has been hypothesized. Several susceptibility genes were identified to be associated with the development of KD and increased risk of coronary artery lesions. Gene-gene associations and alteration of deoxyribonucleic acid (DNA) methylation are also found to play key roles in the pathogenesis and prognosis of KD. This article will focus on the global epidemiological patterns of KD, and the currently known genetic predisposition.

Elenga, N. (2020). "The Imperative of Early Treatment for Children with COVID-19 Infection." Indian Pediatrics **30**: 30.

Elshafeey, F., et al. (2020). "A systematic scoping review of COVID-19 during pregnancy and childbirth."

International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. **24**.
BACKGROUND: Clinical presentation and outcomes of COVID-19 infection during pregnancy remain limited and fragmented. OBJECTIVE(S): To summarize the existing literature on COVID-19 infection during pregnancy and childbirth, particularly concerning clinical presentation and outcomes. SEARCH STRATEGY: A systematic search of LitCovid, EBSCO MEDLINE, CENTRAL, CINAHL, Web of Science, and Scopus electronic databases. The references of relevant studies were also searched. SELECTION CRITERIA: Identified titles and abstracts were screened to select original reports and cross-checked for overlap of cases. DATA COLLECTION AND ANALYSIS: A descriptive summary organized by aspects of clinical presentations (symptoms, imaging, and laboratory) and outcomes (maternal and perinatal). MAIN RESULTS: We identified 33 studies reporting 385 pregnant women with COVID-19 infection: 368 (95.6%) mild; 14 (3.6%) severe; and 3 (0.8%) critical. Seventeen women were admitted to intensive care, including six who were mechanically ventilated and one maternal mortality. A total of 252 women gave birth, comprising 175 (69.4%) cesarean and 77 (30.6%) vaginal births. Outcomes for 256 newborns included four RT-PCR positive neonates, two stillbirths, and one neonatal death. CONCLUSION(S): COVID-19 infection during pregnancy probably has a clinical presentation and severity resembling that in non-pregnant adults. It is probably not associated with poor maternal or perinatal outcomes. Copyright This article is protected by copyright. All rights reserved.

Eroglu-Ertugrul, N. G., et al. (2020). "The value of flexible bronchoscopy in pulmonary infections of immunosuppressed children." Clinical Respiratory Journal **14**(2): 78-84.
Objectives: To demonstrate the value of flexible bronchoscopy (FB) and bronchoalveolar lavage (BAL) when determining causes of lung infection in immunocompromised children; to investigate differences in causes and radiological features of lung infections following bone marrow transplantation (BMT) compared to other immunosuppressive conditions; to evaluate the reliability of radiological findings when predicting the pathogen. Method(s): We retrospectively evaluated 132 immunosuppressed children who underwent FB and BAL because pulmonary complications between January 1999 and May 2014 at the Hacettepe University Hospital Pediatric Pulmonology Unit. Two groups, Group I (n = 106) and Group II (n = 26), consisted of patients who had primary or secondary immunodeficiency and those who were immunosuppressed because BMT, respectively. Radiological findings before FB and macroscopic and microscopic findings of the procedure were evaluated. Result(s): FB and BAL were diagnostic in 86/132 patients (65.1%) and the antimicrobial treatment changed for 75/132 patients (56.8%). The most common pathogen was bacteria (Streptococcus pneumoniae was the leading one). Bacteria were more frequent in Group I than Group II (P =.008). No significant difference in radiological findings between Groups I and II was found. Considering all patients, a significant association was detected between viral pathogens and radiologically interstitial infiltration and a ground-glass appearance (P =.003). However, no significant association was detected between bacterial and fungal pathogens and the radiological findings. Conclusion(s): In immunosuppressed patients, FB and BAL should be evaluated early for clarifying the causative agents. Then, appropriate treatments can be utilised and the side effects and high cost of unnecessary treatment may be mitigated. Copyright © 2019 John Wiley & Sons Ltd

Espinoza, J., et al. (2020). "A Guide to Chatbots for COVID-19 Screening at Pediatric Health Care Facilities." JMIR Public Health and Surveillance **6**(2): e18808.
The coronavirus disease 2019 (COVID-19) outbreak has required institutions to rapidly adapt to changing public health circumstances. The Centers for Disease Control and Prevention has encouraged health care facilities to explore novel health care delivery modes. However, many institutions may not be prepared to begin offering digital health and telehealth services. Chatbots are one digital health tool that can help evolve triage and screening processes in a scalable manner. Here, we present a decision-making and implementation framework for deploying COVID-19 screening chatbots at pediatric health care facilities.

Fan, Q., et al. (2020). "Anal swab findings in an infant with COVID-19." Pediatric Investigation **4**(1): 48-50.
Introduction: The transmission pathways of coronavirus disease 2019 (COVID-19) remain not completely clear. In this case study the test for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in pharyngeal swab and anal swab were compared. Case presentation: A 3-month-old girl was admitted to our hospital with COVID-19. Her parents had both been diagnosed with COVID-19. The results of pharyngeal swab and anal swab of the little girl were recorded and compared during the course of the disease. The oropharyngeal specimen showed negative result for SARS-CoV-2 on the 14th day after onset of the illness. However, the anal swab was still positive for SARS-CoV-2 on the 28th day after the onset of the illness. Conclusion(s): The possibility of fecal-oral transmission of COVID-19 should be assessed. Personal hygiene during home quarantine merits considerable attention. Copyright © 2020 Chinese Medical Association. Pediatric Investigation published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development

Fang, F. and X. P. Luo (2020). "Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**(2): 81-85.

Farrell, S., et al. (2020). "Recommendations for the Care of Pediatric Orthopedic Patients During the COVID Pandemic." Journal of the American Academy of Orthopaedic Surgeons **14**: 14.
The COVID pandemic has necessitated modifications to pediatric orthopaedic practice to protect patients, families and healthcare workers, and to minimize viral transmission. It is critical to balance benefits of alterations to current practice to reduce chances of COVID infection, with the potential long-term impact on patients. Early experiences of the pandemic from orthopaedic surgeons in China, Singapore and Italy have provided opportunity to take proactive and preventive measures to protect all involved in pediatric orthopaedic care. These guidelines, based on expert opinion and best available evidence, provide a framework for management of pediatric orthopaedic patients during the COVID pandemic. General principles include limiting procedures to urgent cases such as traumatic injuries, and deferring outpatient visits during the acute phase of the pandemic. Non-operative methods should be considered where possible. For patients with developmental or chronic orthopaedic conditions, it may be possible to delay treatment for 2 to 4 months without substantial detrimental long-term impact.

Fegert, J. M. and U. M. E. Schulze (2020). "Covid-19 and its impact on child and adolescent psychiatry - a German and personal perspective." Irish Journal of Psychological Medicine: 1-8.
As in other European countries, the current Covid-19 pandemic has not only massively restricted normal life in Germany, it is also having a significant effect on medical treatment, particularly in the areas of child and adolescent psychiatric care, as well as on university teaching. The federal structure of Germany and epidemiological differences between individual federal states has had a crucial impact on the regulations issued and their success. During the last number of weeks, tele-child-psychiatry and psychotherapy have increased, and outpatient services have been used cautiously and sparingly. Medical staff numbers will be augmented by doctors and nurses returning from retirement and also by medical students on a voluntary basis. The federal government has warned that discrepancies in education will increase due to the closure of schools. Questions of child protection are currently of particular importance in the context of such closures and the non-availability of day-care centres.

Feng, K., et al. (2020). "Analysis of CT features of 15 Children with 2019 novel coronavirus infection. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**: E007.
Objective: To explore imaging characteristics of children with 2019 novel coronavirus (2019-nCoV) infection. Method(s): A retrospective analysis was performed on clinical data and chest CT images of 15 children diagnosed with 2019-nCoV. They were admitted to the third

people's Hospital of Shenzhen from January 16 to February 6, 2020. The distribution and morphology of pulmonary lesions on chest CT images were analyzed. Result(s): Among the 15 children, there were 5 males and 10 females, aged from 4 to 14 years old. Five of the 15 children were febrile and 10 were asymptomatic on first visit. The first nasal or pharyngeal swab samples in all the 15 cases were positive for 2019-nCoV nucleic acid. For their first chest CT images, 6 patients had no lesions, while 9 patients had pulmonary inflammation lesions. Seven cases of small nodular ground glass opacities and 2 cases of speckled ground glass opacities were found. After 3 to 5 days of treatment, 2019-nCoV nucleic acid in a second respiratory sample turned negative in 6 cases. Among them, chest CT images showed less lesions in 2 cases, no lesion in 3 cases, and no improvement in 1 case. Other 9 cases were still positive in a second nucleic acid test. Six patients showed similar chest CT inflammation, while 3 patients had new lesions, which were all small nodular ground glass opacities. Conclusion(s): The early chest CT images of children with 2019-nCoV infection are mostly small nodular ground glass opacities. The clinical symptoms of children with 2019-nCoV infection are nonspecific. Dynamic reexamination of chest CT and nucleic acid are important.

Feng, K., et al. (2020). "[Analysis of CT features of 15 children with 2019 novel coronavirus infection]." Zhonghua Erke Zazhi **58**(4): 275-278.
Objective: To explore imaging characteristics of children with 2019 novel coronavirus (2019-nCoV) infection.

Filocamo, G., et al. (2020). "Absence of severe complications from SARS-CoV-2 infection in children with rheumatic diseases treated with biologic drugs." The Journal of rheumatology. **25**.
We read with interest the Editorial by Cron and Chatam (1) suggesting a cytokine storm syndrome (CSS) occurring in response to SARS-CoV-2 infection and, consequently, a possible role for targeted approaches to blocking inflammatory cytokines.

Francom, C. R., et al. (2020). "Pediatric laryngoscopy and bronchoscopy during the COVID-19 pandemic: A four-center collaborative protocol to improve safety with perioperative management strategies and creation of a surgical tent with disposable drapes." International Journal of Pediatric Otorhinolaryngology **134**: 110059.
Aerosolization procedures during the COVID-19 pandemic place all operating room personnel at risk for exposure. We offer detailed perioperative management strategies and present a specific protocol designed to improve safety during pediatric laryngoscopy and bronchoscopy. Several methods of using disposable drapes for various procedures are described, with the goal of constructing a tent around the patient to decrease widespread contamination of dispersed droplets and generated aerosol. The concepts presented herein are translatable to future situations where aerosol generating procedures increase risk for any pathogenic exposure. This protocol is a collaborative effort based on knowledge gleaned from clinical and simulation experience from Children's Hospital Colorado, Children's Hospital of Philadelphia, The Hospital for Sick Children in Toronto, and Boston Children's Hospital.

Frauenfelder, C., et al. (2020). "Practical insights for paediatric otolaryngology surgical cases and performing microlaryngobronchoscopy during the COVID-19 pandemic." International Journal of Pediatric Otorhinolaryngology **134 (no pagination)**(110030).
Paediatric otolaryngology practice involves examining and operating in anatomical locations with high levels of aerosol generation and transmission of COVID-19 to treating clinicians, especially from the asymptomatic patient populations including children. During the COVID-19 pandemic all emergent otolaryngological conditions affecting the airway, oral, and nasal cavities should be managed medically where possible and any operating deferred. We present guidelines for operating on paediatric otolaryngological patients when necessary during the COVID-19 pandemic, and incorporate experience gathered during microlaryngobronchoscopy on a COVID-19 positive infant at our institution.

Frieden, I. J., et al. (2020). "Management of Infantile Hemangiomas during the COVID Pandemic." Pediatric Dermatology **16**: 16.
The COVID-19 pandemic has caused significant shifts in patient care including a steep decline in ambulatory visits and a marked increase in the use of telemedicine. Infantile hemangiomas can require urgent evaluation and risk stratification to determine which infants need treatment and which can be managed with continued observation. For those requiring treatment, prompt initiation decreases morbidity and improves long-term outcomes. The Hemangioma Investigator Group has created consensus recommendations for management of infantile hemangiomas via telemedicine. FDA/EMA approved monitoring guidelines, clinical practice guidelines and relevant, up-to-date publications regarding initiation and monitoring of beta-blocker therapy were used to inform the recommendations. Clinical decision-making guidelines about when telehealth is an appropriate alternative to in-office visits, including medication initiation, dosage changes, and ongoing evaluation are included. The importance of communication with caregivers in the context of telemedicine is discussed and online resources for both hemangioma education and for propranolol therapy provided.

Garazzino, S., et al. (2020). "Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020." Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin **25**(18): 05.
Data on features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children and adolescents are scarce. We report preliminary results of an Italian multicentre study comprising 168 laboratory-confirmed paediatric cases (median: 2.3 years, range: 1 day-17.7 years, 55.9% males), of which 67.9% were hospitalised and 19.6% had comorbidities. Fever was the most common symptom, gastrointestinal manifestations were frequent; two children required intensive care, five had seizures, 49 received experimental treatments and all recovered.

Garg, S. K., et al. (2020). "Managing New-Onset Type 1 Diabetes During the COVID-19 Pandemic: Challenges and Opportunities." Diabetes technology & therapeutics. **17**.
Background: The current COVID-19 pandemic provides an incentive to expand considerably the use of telemedicine for high-risk patients with diabetes, and especially for the management of type 1 diabetes (T1D). Telemedicine and digital medicine also offer critically important approaches to improve access, efficacy, efficiency, and cost-effectiveness of medical care for people with diabetes. Method(s): Two case reports are presented where telemedicine was used effectively and safely after day 1 in person patient education. These aspects of the management of new-onset T1D patients (adult and pediatric) included ongoing diabetes education of the patient and family digitally. The patients used continuous glucose monitoring with commercially available analysis software (Dexcom Clarity and Glooko) to generate ambulatory glucose profiles and interpretive summary reports. The adult subject used multiple daily insulin injections; the pediatric patient used an insulin pump. The subjects were managed using a combination of e-mail, Internet via Zoom, and telephone calls. Result(s): These two cases show the feasibility and effectiveness of use of telemedicine in applications in which we had not used it previously: new-onset diabetes education and insulin dosage management. Conclusion(s): The present case reports illustrate how telemedicine can be used safely and effectively for new-onset T1D training and education for both pediatric and adult patients and their families. The COVID-19 pandemic has acutely stimulated the expansion of the use of telemedicine and digital medicine. We conclude that telemedicine is an effective approach for the management of patients with new-onset T1D.

Garrido, I., et al. (2020). ""Review article: COVID-19 and liver disease - what we know on 1st May 2020"." Alimentary Pharmacology & Therapeutics **13**: 13.
BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of coronavirus disease 2019 (COVID-19), became a global threat to human health.

Liver impairment has been frequently reported as a common manifestation, although its clinical significance is still unclear, particularly in patients with underlying chronic liver disease (CLD).
AIMS: To summarize the changes in liver function tests during SARS-CoV-2 infection and the impact of COVID-19 in patients with underlying CLD.
METHODS: A literature review using online database Pubmed was done using the search terms "SARS-CoV-2", "COVID-19", "liver", "cirrhosis" and "liver transplantation".
RESULTS: COVID-19 is frequently associated with different degrees of abnormal liver function tests, most notably transaminases, which are usually transitory and of mild degree. Available evidence suggests that liver injury may result from direct pathogenic effect by the virus, systemic inflammation or toxicity from commonly used drugs in this subset of patients. SARS-CoV-2 infection in children is associated with minimal or no increase in liver enzymes, thus the presence of abnormal liver function tests should trigger evaluation for underlying liver diseases. Although it seems that patients with CLD are not at greater risk for acquiring the infection, those with cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, autoimmune liver diseases or liver transplant may have a greater risk for severe COVID-19.
CONCLUSIONS: Abnormal liver function tests during the course of COVID-19 are common, though clinically significant liver injury is rare. Further research is needed focusing on the effect of existing liver-related comorbidities on treatment and outcome of COVID-19.

Gasparyan, A. Y., et al. (2020). "Perspectives of Immune Therapy in Coronavirus Disease 2019." Journal of Korean Medical Science **35**(18): e176.
The global fight against coronavirus disease 2019 (COVID-19) is largely based on strategies to boost immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and prevent its severe course and complications. The human defence may include antibodies which interact with SARS-CoV-2 and neutralize its aggressive actions on multiple organ systems. Protective cross-reactivity of antibodies against measles and other known viral infections has been postulated, primarily as a result of the initial observations of asymptomatic and mild COVID-19 in children. Uncontrolled case series have demonstrated virus-neutralizing effect of convalescent plasma, supporting its efficiency at early stages of contracting SARS-CoV-2. Given the variability of the virus structure, the utility of convalescent plasma is limited to the geographic area of its preparation, and for a short period of time. Intravenous immunoglobulin may also be protective in view of its nonspecific antiviral and immunomodulatory effects. Finally, human monoclonal antibodies may interact with some SARS-CoV-2 proteins, inhibiting the virus-receptor interaction and prevent tissue injury. The improved understanding of the host antiviral responses may help develop safe and effective immunotherapeutic strategies against COVID-19 in the foreseeable future.

Geldsetzer, P. (2020). "Use of Rapid Online Surveys to Assess People's Perceptions During Infectious Disease Outbreaks: A Cross-sectional Survey on COVID-19." Journal of medical Internet research **22**(4): e18790.
BACKGROUND: Given the extensive time needed to conduct a nationally representative household survey and the commonly low response rate of phone surveys, rapid online surveys may be a promising method to assess and track knowledge and perceptions among the general public during fast-moving infectious disease outbreaks. OBJECTIVE(S): This study aimed to apply rapid online surveying to determine knowledge and perceptions of coronavirus disease 2019 (COVID-19) among the general public in the United States and the United Kingdom. METHOD(S): An online questionnaire was administered to 3000 adults residing in the United States and 3000 adults residing in the United Kingdom who had registered with Prolific Academic to participate in online research. Prolific Academic established strata by age (18-27, 28-37, 38-47, 48-57, or >=58 years), sex (male or female), and ethnicity (white, black or African American, Asian or Asian Indian, mixed, or "other"), as well as all permutations of these strata. The number of participants who could enroll in each of these strata was calculated to reflect the distribution in the US and UK general population. Enrollment into the survey within each stratum was on a

first-come, first-served basis. Participants completed the questionnaire between February 23 and March 2, 2020. RESULT(S): A total of 2986 and 2988 adults residing in the United States and the United Kingdom, respectively, completed the questionnaire. Of those, 64.4% (1924/2986) of US participants and 51.5% (1540/2988) of UK participants had a tertiary education degree, 67.5% (2015/2986) of US participants had a total household income between US $20,000 and US $99,999, and 74.4% (2223/2988) of UK participants had a total household income between 15,000 and 74,999. US and UK participants' median estimate for the probability of a fatal disease course among those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was 5.0% (IQR 2.0%-15.0%) and 3.0% (IQR 2.0%-10.0%), respectively. Participants generally had good knowledge of the main mode of disease transmission and common symptoms of COVID-19. However, a substantial proportion of participants had misconceptions about how to prevent an infection and the recommended care-seeking behavior. For instance, 37.8% (95% CI 36.1%-39.6%) of US participants and 29.7% (95% CI 28.1%-31.4%) of UK participants thought that wearing a common surgical mask was "highly effective" in protecting them from acquiring COVID-19, and 25.6% (95% CI 24.1%-27.2%) of US participants and 29.6% (95% CI 28.0%-31.3%) of UK participants thought it was prudent to refrain from eating at Chinese restaurants. Around half (53.8%, 95% CI 52.1%-55.6%) of US participants and 39.1% (95% CI 37.4%-40.9%) of UK participants thought that children were at an especially high risk of death when infected with SARS-CoV-2. CONCLUSION(S): The distribution of participants by total household income and education followed approximately that of the US and UK general population. The findings from this online survey could guide information campaigns by public health authorities, clinicians, and the media. More broadly, rapid online surveys could be an important tool in tracking the public's knowledge and misperceptions during rapidly moving infectious disease outbreaks.

Ghandi, Y., et al. (2020). "Clinical characteristics of Kawasaki disease in Markazi province, Iran." Journal of Comprehensive Pediatrics **11 (1) (no pagination)**(e85695).

Background: Kawasaki disease (KD) is described as a life-threatening vasculitis, which mostly develops in children below five years of age and is diagnosed according to clinical criteria. It is also a common rheumatologic disorder in Iran. Objective(s): The present study aimed at determining the clinical and demographic characteristics of KD patients in Iran. Method(s): We retrospectively assessed 69 cases of KD in an Iranian pediatric population from March 2014 to March 2018. The Japanese Kawasaki Disease Research Committee guidelines were used as the diagnostic criteria for typical KD. Incomplete or atypical KD was diagnosed in patients with coronary artery changes, but without all the criteria for KD. Result(s): In this study, 69 patients were recruited, with a male-female ratio of 1:8. Overall, 64% (n, 44) and 36% of children met the criteria for typical and atypical KD, respectively. Also, echocardiographic abnormalities were reported in eight patients (12%). Coronary artery aneurysm was found in 2% of patients, while other cardiac abnormalities were found in 12% of patients. The male-female ratio of coronary artery anomalies and other cardiac abnormalities was 3:1. Polymorphic exanthema was the most common clinical manifestation. The erythrocyte sedimentation rate >= 40 mm/h was the most common laboratory finding, while skin desquamation was the most common complication in other organs. Conclusion(s): KD is not uncommon in Markazi Province, Iran. In this study, distribution of demographic characteristics was not similar to reports from other countries. Also, clinical findings, age and gender distribution, laboratory findings, and complications in other organs were not similar to previous reports. The incidence of typical and atypical KD was different in this region, especially in terms of complications, such as cardiac and gastrointestinal complications.

Giwa, A. L., et al. (2020). "Novel 2019 coronavirus SARS-CoV-2 (COVID-19): An updated overview for emergency clinicians." Emergency Medicine Practice **22**(5): 1-28.
The novel coronavirus, COVID-19, has quickly become a worldwide threat to health, travel, and commerce. This overview analyzes the best information from the early research, including epidemiologic and demographic features from SARS-CoV-1 and MERS-CoV viruses; lessons learned from the experience of an emergency physician in Northern Italy, where the outbreak has devastated the healthcare system; evidence on transmission and prevention through safe use of PPE; evidence and advice on SARS-CoV-2 testing and co-infection; management options; airway management options; steps for rapid sequence intubation in the ED and managing disaster ventilation; and information on managing pediatric and pregnant patients.

Goldman, R. D. (2020). "Coronavirus disease 2019 in children: Surprising findings in the midst of a global pandemic." Canadian Family Physician **66**(5): 332-334.
Question Coronavirus disease 2019 (COVID-19) is affecting millions of people worldwide. It seems that it affects mostly adults older than 40 years of age, and the death rate is highest for older individuals in the population. What should I tell parents worried about their children contracting the coronavirus (SARS-CoV-2) causing COVID-19, and what symptoms should I look for to determine if there is a need to test for the virus?Answer The COVID-19 global pandemic affects all ages. Severe respiratory manifestations have been the mainstay of illness in adults, with what seems to be rapid deterioration necessitating mechanical ventilation. Only 5% of those tested and found to have COVID-19 have been younger than 19 years, possibly owing to limited testing, as the symptoms in children are usually mild. Symptoms in children include fever, dry cough, rhinorrhea, sore throat, and fatigue, and in 10% diarrhea or vomiting. Rarely dyspnea or hypoxemia were also described. Blood tests and imaging have been shown to be of little value in children and should only be ordered for those in whom you would normally order these investigations for viral-like illness. No specific therapy is available and supportive care with rest, fluids, and antipyretics for children is the recommended approach. Ibuprofen or acetaminophen for fever and pain can be given. Antiviral and immunomodulatory treatment is not recommended at this time for otherwise healthy children, and corticosteroids should also not be used. Children with immunocompromised states should be isolated and avoid contact with others.

Groetch, M., et al. (2020). "Dietary Management of Food Protein-Induced Enterocolitis Syndrome during COVID-19 Pandemic." Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. **06**.
As communities struggle to adapt to life under the threat of the global pandemic, COVID-19, those living with Food Protein-Induced Enterocolitis Syndrome (FPIES) must adapt with additional difficulties. Social distancing and shelter-in-place strategies have been implemented, resulting in fewer supermarkets trips, stockpile-purchasing behaviors in up to 74.5% of those surveyed(1), and shortages of staple food items all with potential impact on the availability of foods for those on limited diets. Concern about allergic reactions make exploring alternative or new ingredients undesirable or untenable. Remaining safe at home is important to avoid trips to the emergency department where families may be exposed to the COVID-19 virus and medical attention can be limited due to the burden on global health systems. Parents of children with FPIES are also understandably concerned about meeting their child's nutritional needs during these times of sheltering-in-place. Now more than ever, advice on what foods to serve and when to serve them is critically important. Copyright © 2020. Published by Elsevier Inc.

Guan, C. S., et al. (2020). "Imaging Features of Coronavirus disease 2019 (COVID-19): Evaluation on Thin-Section CT." Academic Radiology **27**(5): 609-613.
RATIONALE AND OBJECTIVES: To retrospectively analyze the chest imaging findings in patients with coronavirus disease 2019 (COVID-19) on thin-section CT.

MATERIALS AND METHODS: Fifty-three patients with confirmed COVID-19 infection underwent thin-section CT examination. Two chest radiologists independently evaluated the imaging in terms of distribution, ground-glass opacity (GGO), consolidation, air bronchogram, stripe, enlarged mediastinal lymph node, and pleural effusion.

RESULTS: Fourty-seven cases (88.7%) had findings of COVID-19 infection, and the other six (11.3%) were normal. Among the 47 cases, 78.7% involved both lungs, and 93.6% had peripheral infiltrates distributed along the subpleural area. All cases showed GGO, 59.6% of which were round and 40.4% patchy. Other imaging features included "crazy-paving pattern" (89.4%), consolidation (63.8%), and air bronchogram (76.6%). Air bronchograms were observed within GGO (61.7%) and consolidation (70.3%). Neither enlarged mediastinal lymph nodes nor pleural effusion were present. Thirty-three patients (62.3%) were followed an average interval of 6.2 +/- 2.9 days. The lesions increased in 75.8% and resorbed in 24.2% of patients.

CONCLUSION: COVID-19 showed the pulmonary lesions in patients infected with COVID-19 were predominantly distributed peripherally in the subpleural area.

Guan, W. J., et al. (2020). "Clinical Characteristics of Coronavirus Disease 2019 in China." New England Journal of Medicine **382**(18): 1708-1720.

BACKGROUND: Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

METHODS: We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

RESULTS: The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission.

CONCLUSIONS: During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others.).

Guichard, K., et al. (2020). Medecine du Sommeil.

In addition to the psychological impact of quarantine, there are sleep disturbances that must be taken into account by implementing appropriate strategies in order to maintain good mental and general health. Quarantine can disrupt sleep first in impacting circadian rhythms by decreasing the intensity of zeitgebers, second can promote insomnia in this period of acute stress and third can be a source of sleep deprivation in those on the front line and managing the crisis. In addition, in children/adolescents, confinement can also destructure the days and thus have an impact on overall health. For this, it is important to put in place strategies to prevent these sleep disturbances in order to reduce the psychological, infectious impact and deal optimally with this situation that we are all experiencing.

Guiqing, H. E., et al. (2020). "Serial Computed Tomography Manifestations in a Child with Coronavirus

Disease (COVID-19) Pneumonia." Indian Pediatrics **09**: 09.
Computed tomography (CT) manifestations and treatment of children with COVID-19 are still unclear. We report serial CT findings of a child with COVID-19 pneumonia who recovered without any sequelae.

Gujski, M., et al. (2020). "Current State of Knowledge About SARS-CoV-2 and COVID-19 Disease in Pregnant Women." Medical Science Monitor **26**: e924725.
During any epidemic of infectious diseases, pregnant women constitute an extremely sensitive group due to altered physiology and immune functions, and thus altered susceptibility to infection. With regard to the management of pregnant COVID-19 patients, in addition to the treatment of the infection itself, which is not that different from generally accepted principles, it is interesting to consider which obstetric procedures should be used to minimize the adverse effects on mother and child. Questions arise concerning the continuation of pregnancy, how to terminate the pregnancy, the possibility of virus transmission through the placenta, isolation of the newborn after birth, and breastfeeding. The aim of this study was to review the current state of knowledge about SARS-CoV-2 infection and COVID-19 disease in pregnant women. Because the epidemic began in China, most of the available literature comes from studies conducted there. The studies used to prepare this review article are the first non-randomized studies containing small groups of examined women. They do not provide clear indications, but show that in an epidemic situation, special care should be taken in pregnancy management, making decisions about termination of pregnancy, and handling of the newborn baby to minimize the risk of subsequent health consequences. Further analysis is needed on the incidence of COVID-19 among pregnant women and its consequences. This will allow us to develop recommendations on how to deal with patients in the future in case of repeated epidemic emergencies.

Gupta, N., et al. (2020). "Laboratory preparedness for SARS-CoV-2 testing in India: Harnessing a network of Virus Research & Diagnostic Laboratories." Indian Journal of Medical Research **151**(2 & 3): 216-225.
Background & objectives: An outbreak of respiratory illness of unknown aetiology was reported from Hubei province of Wuhan, People's Republic of China, in December 2019. The outbreak was attributed to a novel coronavirus (CoV), named as severe acute respiratory syndrome (SARS)-CoV-2 and the disease as COVID-19. Within one month, cases were reported from 25 countries. In view of the novel viral strain with reported high morbidity, establishing early countrywide diagnosis to detect imported cases became critical. Here we describe the role of a countrywide network of VRDLs in early diagnosis of COVID-19.
Methods: The Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV), Pune, established screening as well as confirmatory assays for SARS-CoV-2. A total of 13 VRDLs were provided with the E gene screening real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay. VRDLs were selected on the basis of their presence near an international airport/seaport and their past performance. The case definition for testing included all individuals with travel history to Wuhan and symptomatic individuals with travel history to other parts of China. This was later expanded to include symptomatic individuals returning from Singapore, Japan, Hong Kong, Thailand and South Korea.
Results: Within a week of standardization of the test at NIV, all VRDLs could initiate testing for SARS-CoV-2. Till February 29, 2020, a total of 2,913 samples were tested. This included both 654 individuals quarantined in the two camps and others fitting within the case definition. The quarantined individuals were tested twice - at days 0 and 14. All tested negative on both occasions. Only three individuals belonging to different districts in Kerala were found to be positive.
Interpretation & conclusions: Sudden emergence of SARS-CoV-2 and its potential to cause a pandemic posed an unsurmountable challenge to the public health system of India. However, concerted efforts of various arms of the Government of India resulted in a well-coordinated action at each level. India has successfully demonstrated its ability to establish quick diagnosis of SARS-CoV-2 at

NIV, Pune, and the testing VRDLs.

Gupta, N., et al. (2020). "Severe acute respiratory illness surveillance for coronavirus disease 2019, India, 2020." Indian Journal of Medical Research **151**(2 & 3): 236-240.
Background & objectives: Sentinel surveillance among severe acute respiratory illness (SARI) patients can help identify the spread and extent of transmission of coronavirus disease 2019 (COVID-19). SARI surveillance was initiated in the early phase of the COVID-19 outbreak in India. We describe here the positivity for COVID-19 among SARI patients and their characteristics.
Methods: SARI patients admitted at 41 sentinel sites from February 15, 2020 onwards were tested for COVID-19 by real-time reverse transcription-polymerase chain reaction, targeting E and RdRp genes of SARS-CoV-2. Data were extracted from Virus Research and Diagnostic Laboratory Network for analysis.
Results: A total of 104 (1.8%) of the 5,911 SARI patients tested were positive for COVID-19. These cases were reported from 52 districts in 20 States/Union Territories. The COVID-19 positivity was higher among males and patients aged above 50 years. In all, 40 (39.2%) COVID-19 cases did not report any history of contact with a known case or international travel.
Interpretation & conclusions: COVID-19 containment activities need to be targeted in districts reporting COVID-19 cases among SARI patients. Intensifying sentinel surveillance for COVID-19 among SARI patients may be an efficient tool to effectively use resources towards containment and mitigation efforts.

Han, Y. and H. Yang (2020). "The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): A Chinese perspective." Journal of Medical Virology **06**: 06.
2019 novel coronavirus (SARS-CoV-2), which originated in Wuhan, China, has attracted the world's attention over the last month. The Chinese government has taken emergency measures to control the outbreak and has undertaken initial steps in the diagnosis and treatment of 2019 novel coronavirus infection disease (COVID-19). However, SARS-CoV-2 possesses powerful pathogenicity as well as transmissibility and still holds many mysteries that are yet to be solved, such as whether the virus can be transmitted by asymptomatic patients or by mothers to their infants. Our research presents selected available cases of COVID-19 in China to better understand the transmission and diagnosis regarding this infectious disease.

Han, Y. N., et al. (2020). "A comparative-descriptive analysis of clinical characteristics in 2019-coronavirus-infected children and adults." Journal of Medical Virology.
Acute respiratory disease caused by 2019 novel coronavirus (2019-nCoV) has rapidly spread throughout China. Children and adults show a different clinical course. The purpose of the current study is to comparatively analyze the clinical characteristics of 2019-nCoV infection in children and adults and to explore the possible causes for the discrepancies present. The medical records of 25 adults and 7 children confirmed cases of 2019-2019-nCoV acute respiratory diseases were reviewed retrospectively. All children were family clusters. The total adult patients were differentiated into the local residents of Wuhan, a history of travel to Wuhan and direct contact with people from Wuhan. The numbers were 14 (56%), 10 (40%), and 1 (4%), respectively. The median incubation period of children and adults was 5 days (ranged, 3-12 days) and 4 days (ranged, 2-12 days), respectively. Diarrhoea and/or vomiting (57.1%) were demic by World Health Organiza more common in children, whereas for adults it was myalgia or fatigue (52%). On admission, the percentage of children having pneumonia (5%, 71.4%) was roughly the same as adults (20%, 80%). A total of 20% of adults had leucopoenia, but leukocytosis was more frequently in children (28.6%, P=.014). A higher number of children had elevated creatine kinase isoenzyme (57.1% vs 4%, P=.004). Antiviral therapy was given to all adult patients but to none of the children. In summary, knowledge of these differences between children and adults will not only be helpful for the clinical diagnosis of 2019-nCoV disease, but also for a future discussion on age-specific coronavirus infection. Copyright © 2020 Wiley Periodicals, Inc.

Hasan, A., et al. (2020). "Coronavirus Disease (COVID-19) and Pediatric Patients: A Review of Epidemiology, Symptomatology, Laboratory and Imaging Results to Guide the Development of a Management Algorithm." Cureus **12**(3): e7485.
Coronavirus disease (COVID-19) has been declared a worldwide pandemic. Compared to adults, there has been a significantly smaller number of reported cases of COVID-19 in the pediatric population, although the incidence is increasing every day. This article looks to review specific epidemiological factors, symptomatology, laboratory and imaging workup, and other relevant metrics derived from the limited published literature that are specific to the pediatric population, to provide a review for the pediatric practitioner and guide, in part, the creation of a clinical algorithm for the management of COVID-19 in the pediatric population that can be utilized by pediatric institutions.

Haslak, F., et al. (2020). "Childhood Rheumatic Diseases and COVID-19 Pandemic: An Intriguing Linkage and a New Horizon." Balkan medical journal. **08**.
As it is known, we are all in a pandemic situation due to a novel coronavirus, officially named "Severe Acute Respiratory Syndrome Coronavirus 2" and the disease caused by the virus named "Coronavirus disease-2019". The virus seems to has propensity to infect older male individuals with underlying disease. The clinical features were on a large scale that varies from being an asymptomatic carrier to acute respiratory distress syndrome and multiorgan dysfunction. Fever, dry cough and fatigue are the most common symptoms. Not only, the disease seems to be rare and have a milder course in pediatric age but also respiratory failure, multiorgan dysfunction, and death are extremely rare. Although several comorbidities such as hypertension, diabetes and cardiovascular diseases are defined as a risk factor for developing the acute respiratory syndrome and need for intensive care; immune-compromised situations such as rheumatic disease which require immunosuppressive treatment strikingly are not found to be a risk factor for more severe disease course. However, there is a lack of data regarding the effects of "Coronavirus disease-2019" on pediatric patients with rheumatic diseases. Additionally, there are three controversial circumstances that patients with rheumatic diseases are believed to be more likely to have viral infections like "Severe Acute Respiratory Syndrome Coronavirus 2", on the other hand, antirheumatic drugs may have a protective and therapeutic role in Coronavirus disease-2019 and children are more unlikely to have serious disease course. Therefore, we aimed to have a contributor role for explaining this conundrum and present a bird's eye view regarding this equivocal issue in this review.

Hattoufi, K., et al. (2020). "Molecular Diagnosis of Pneumonia Using Multiplex Real-Time PCR Assay RespiFinder SMART 22 FAST in a Group of Moroccan Infants." Advances in Virology **2020 (no pagination)**(6212643).
Background. In Morocco, pediatric pneumonia remains a serious public health problem, as it constitutes the first cause of mortality due to infectious diseases. The etiological diagnosis of acute respiratory tract infections is difficult. Therefore, it is necessary to use Multiplex real-time polymerase chain reaction assay tests in a routine setting for exact and fast identification. Objectives. In this paper, we present the clinical results of pediatric pneumonia and describe their etiology by using molecular diagnosis. Study design: Tracheal secretion was collected from infants presenting respiratory distress isolated or associated with systemic signs, attending the unit of Neonatology between December 1, 2016, and Mai 31, 2018. Samples were tested with the multiplex RespiFinder SMART 22 FAST which potentially detects 18 viruses and 4 bacteria. Results. Of the 86 infants considered in this study (mean age 31 +/- 19 days) suspected of acute respiratory tract infections, 71 (83%) were positive for one or multiple viruses or/and bacteria. The majority of acute respiratory tract infections had a viral origin (95%): respiratory syncytial viruses (A and B) (49%), rhinovirus (21%), coronaviruses 229E (11%), humain metapneumovirus (5%), influenza A (3%), influenza H1N1 (1%), adenovirus (2%), and parainfluenza virus type 4 (2%). Among our patients, 6% had Mycoplasma pneumoniae.

Coinfections were not associated with severe respiratory symptoms. Conclusion. The clinical spectrum of respiratory infections is complex and often nonspecific. Thus, the early and fast detection of related causative agents is crucial. The use of multiplex real time polymerase chain reaction may help choose an accurate treatment, reduce the overall use of unnecessary antibiotics, preserve intestinal flora, and decrease nosocomial infection by reducing the length of hospitalization. Copyright © 2020 Kenza Hattoufi et al.

He, Y., et al. (2020). "Strategic plan for management of COVID-19 in paediatric haematology and oncology departments." The Lancet Haematology **7**(5): e359-e362.

Hedrich, C. M. (2020). "COVID-19 - Considerations for the paediatric rheumatologist." Clinical Immunology **214**: 108420.
The novel coronavirus SARS-CoV2 is a threat to the health and well-being of millions of lifes across the globe. A significant proportion of adult patients require hospitalisation and may develop severe life-threatening complications. Children, on the other hand, can carry and transmit the virus, but usually do not develop severe disease. Mortality in the paediatric age-group is relatively low. Differences in virus containment and clearance, as well as reduced inflammation-related tissue and organ damage may be caused by age-specific environmental and host factors. Since severe complications in adults are frequently caused by uncontrolled immune responses and a resulting "cytokine storm" that may be controlled by targeted blockade of cytokines, previously established treatment with immunosuppressive treatments may indeed protect children from complications.

Henderson, L. A. and R. Q. Cron (2020). "Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management." Pediatric Drugs **22**(1): 29-44.
Macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis, is a frequently fatal complication of a variety of pediatric inflammatory disorders. MAS has been most commonly associated with systemic juvenile idiopathic arthritis (sJIA), as approximately 10% of children with sJIA develop fulminant MAS, with another 30–40% exhibiting a more subclinical form of the disease. Children with other rheumatologic conditions such as systemic lupus erythematosus and Kawasaki disease are also at risk for MAS. Moreover, MAS also complicates various genetic autoinflammatory disorders such as gain of function mutations in the cytosolic inflammasome NLRC4, pediatric hematologic malignancies (e.g., T-cell lymphoma), and primary immunodeficiencies characterized by immune dysregulation. Disease-specific and broadly inclusive diagnostic criteria have been developed to facilitate the diagnosis of MAS. Recently, simple screening tools such as the serum ferritin to erythrocyte sedimentation rate ratio have been proposed. Early diagnosis and rapid initiation of immunosuppression are essential for the effective management of MAS. With a better understanding of the pathophysiology of MAS and the advent of novel therapeutics, a broad immunosuppressive approach to treatment is giving way to targeted anti-cytokine therapies. These treatments include agents that block interleukin-1 (IL-1), IL-6, IL-18, interferon-γ, as well as inhibitors of downstream targets of cytokine signaling (e.g., Janus kinases). Increased early recognition of MAS among pediatric inflammatory disorders combined with the use of effective and less toxic cytokine-targeted therapies should lower the mortality of this frequently fatal disorder. © 2019, Springer Nature Switzerland AG.

Hong, H., et al. (2020). "Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children." Pediatrics & Neonatology **61**(2): 131-132.

Hopkins, C., et al. (2020). "Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study." Journal of Otolaryngology: Head and Neck Surgery **49**(1): 26.
BACKGROUND: A rapidly evolving evidence suggests that smell and taste disturbance are

common symptoms in COVID-19 infection. As yet there are no reports on duration and recovery rates. We set out to characterise patients reporting new onset smell and taste disturbance during the COVID-19 pandemic and report on early recovery rates.
METHODS: Online Survey of patients reporting self-diagnosed new onset smell and taste disturbance during the COVID-19 pandemic, with 1 week follow-up.
RESULTS: Three hundred eighty-two patents completed bot an initial and follow-up survey. 86.4% reported complete anosmia and a further 11.5% a very severe loss of smell at the time of completing the first survey. At follow-up 1 week later, there is already significant improvement in self-rating of severity of olfactory loss. 80.1% report lower severity scores at follow-up, 17.6% are unchanged and 1.9% are worse. 11.5% already report compete resolution at follow up, while 17.3% report persistent complete loss of smell, with reported duration being 1 to over 4 weeks. This is reflected in the overall cumulative improvement rate of 79% patients overall in the interval between surveys.
CONCLUSIONS: A review of the growing evidence base supports the likelihood that out cohort have suffered olfactory loss as part of COVID-19 infection. While early recovery rates are encouraging, long term rates will need to be further investigated and there may be an increase in patients with persistent post-viral loss as a result of the pandemic. We further call for loss of sense of smell to be formerly recognised as a marker of COVID-19 infection.

Hrusak, O., et al. (2020). "Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment." European Journal of Cancer **132**: 11-16.
Introduction: Since the beginning of COVID-19 pandemic, it is known that the severe course of the disease occurs mostly among the elderly, whereas it is rare among children and young adults. Comorbidities, in particular, diabetes and hypertension, clearly associated with age, besides obesity and smoke, are strongly associated with the need for intensive treatment and a dismal outcome. A weaker immunity of the elderly has been proposed as a possible explanation of this uneven age distribution. Thus, there is concern that children treated for cancer may allso be at risk for an unfavourable course of infection. Along the same line, anecdotal information from Wuhan, China, mentioned a severe course of COVID-19 in a child treated for leukaemia. Aim and methods: We made a flash survey on COVID-19 incidence and severity among children on anticancer treatment. Respondents were asked by email to fill in a short Web-based survey. Result(s): We received reports from 25 countries, where approximately 10,000 patients at risk are followed up. At the time of the survey, more than 200 of these children were tested, nine of whom were positive for COVID-19. Eight of the nine cases had asymptomatic to mild disease, and one was just diagnosed with COVID-19. We also discuss preventive measures that are in place or should be taken and treatment options in immunocompromised children with COVID-19. Conclusion(s): Thus, even children receiving anticancer chemotherapy may have a mild or asymptomatic course of COVID-19. While we should not underestimate the risk of developing a more severe course of COVID-19 than that observed here, the intensity of preventive measures should not cause delays or obstructions in oncological treatment. Copyright © 2020

Hu, L. and C. Wang (2020). "Radiological role in the detection, diagnosis and monitoring for the coronavirus disease 2019 (COVID-19)." European Review for Medical & Pharmacological Sciences **24**(8): 4523-4528.
OBJECTIVE: Coronavirus disease 2019 (COVID-19) has officially been declared a pandemic by the World Health Organization (WHO). Radiological examinations, especially computed tomography (CT), play an important role in the fight against COVID-19. A comprehensive and timely review of radiological role in the fight against COVID-19 remains urgent and mandatory. Hence, the aim of this review is to summarize the radiological role in the fight against COVID-19. This review of current studies on COVID-19 provides insight into the radiological role in the detection, diagnosis, and monitoring for COVID-19. The typical radiological features of COVID-19 include bilateral, multifocal, and multilobar ground glass opacification with patchy consolidation, a peripheral/subpleural or posterior distribution (or both), mainly in the lower lobes. A combination

of chest CT and repeat Reverse Transcription-Polymerase Chain Reaction (RT-PCR) testing may be beneficial for the diagnosis of COVID-19 in the setting of strongly clinical suspicion. Chest CT may improve the sensitivity for COVID-19 diagnosis, but patients' exposure to radiation should be kept as low as possible especially for children and pregnant women patients.

Huang, J., et al. (2020). "Recommendation about the perioperative prevention of infection to healthcare workers and the anesthesia management of children with SARS-CoV-2 infection." World Journal of Pediatric Surgery **3 (1) (no pagination)**(e000126).
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread widely and persistently over 100 countries. New challenges have occurred in the perioperative management of airway and anesthesia in children diagnosed with SARS-CoV-2 infection. According to current publications and to our own experiences in anesthesia management for cases with SARS-CoV-2 suspected, we reviewed concerns about the perioperative prevention of SARS-CoV-2 to medical staff and the anesthesia strategy to the patient. Copyright © © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Huang, X., et al. (2020). "Epidemiology and Clinical Characteristics of COVID-19." Archives of Iranian Medicine **23**(4): 268-271.
Since December 2019, there has been an outbreak of a novel coronavirus (COVID-19) infection in Wuhan, China. Meanwhile, the outbreak also drew attention and concern from the World Health Organization (WHO). COVID-19 is another human infectious disease caused by coronavirus. The transmission of COVID-19 is potent and the infection rate is fast. Since there is no specific drug for COVID-19, the treatment is mainly symptomatic supportive therapy. In addition, it should be pointed out that patients with severe illness need more aggressive treatment and meticulous care. Recently, accurate RNA detection has been decisive for the diagnosis of COVID-19. The development of highly sensitive RT-PCR has facilitated epidemiological studies that provide insight into the prevalence, seasonality, clinical manifestations and course of COVID-19 infection. In this review, we summarize the epidemiology and characteristics of COVID-19.

Hwang, T. J., et al. (2020). "Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19)." JAMA Pediatrics **07**: 07.

Ibrahim, L. F., et al. (2020). "SARS-CoV-2 Testing and Outcomes in the First 30Days after the First Case of COVID-19 at an Australian Children's Hospital." Emergency medicine Australasia : EMA. **10**.
OBJECTIVE: International studies describing COVID-19 in children have shown low proportions of paediatric cases and generally a mild clinical course. We aimed to present early data on children tested for SARS-CoV-2 at a large Australian tertiary children's hospital according to the state health department guidelines, which varied over time. METHOD(S): We conducted a retrospective cohort study at The Royal Children's Hospital, Melbourne, Australia. It included all paediatric patients (aged 0-18years) who presented to the Emergency Department (ED) or the Respiratory Infection Clinic (RIC) and were tested for SARS-CoV-2. The 30-day study period commenced after the first confirmed positive case was detected at the hospital on 21st March 2020, until 19th April 2020. We recorded epidemiological and clinical data. RESULT(S): There were 433 patients in whom SARS-CoV-2 testing was performed in ED (331 (76%)) or RIC (102 (24%)). There were 4 (0.9%) who had positive SARS-CoV-2 detected, none of whom were admitted to hospital or developed severe disease. Of these SARS-CoV-2 positive patients, 1/4 (25%) had a comorbidity, which was asthma. Of the SARS-CoV-2 negative patients, 196/429 (46%) had comorbidities. Risk factors for COVID-19 were identified in 4/4 SARS-CoV-2 positive patients and 47/429 (11%) SARS-CoV-2 negative patients. CONCLUSION(S): Our study identified a very low rate of SARS-CoV-2 positive cases in children presenting to a tertiary ED or RIC, none of whom were admitted to hospital. A high proportion of patients who were SARS-CoV-2 negative had comorbidities. Copyright This article is protected by copyright. All rights reserved.

Ietto, G. (2020). "SARS - CoV-2: Reasons of epidemiology of severe ill disease cases and therapeutic approach using trivalent vaccine (tetanus, diphtheria and Bordetella pertussis)." Medical Hypotheses **141**: 109779.
The novel coronavirus Covid-19 follows transmission route and clinical presentation of all community-acquired coronaviruses. Instead, the rate of transmission is significative higher, with a faster spread of the virus responsible of the worldwide outbreak and a significative higher mortality rate due to the development of a severe lung injury. Most noteworthy is the distribution of death rate among age groups. Children and younger people are almost protected from severe clinical presentation. Possible explanation of this phenomenon could be the ability of past vaccinations (especially tetanic, diphtheria toxoids and inactivated bacteria as pertussis) to stimulate immune system and to generate a scattered immunity against non-self antigens in transit, as coronaviruses and other community-circulating viruses and make immune system readier to develop specific immunity against Covid-19. The first support to this hypothesis is the distribution of mortality rate during historical pandemics ("Spanish flu" 1918, "Asian flu" 1956 and "the Hong Kong flu" 1968) among age groups before and after the introduction of vaccines. The immunological support to the hypothesis derives from recent studies about immunotherapy for malignancies, which propose the use of oncolytic vaccines combined with toxoids in order to exploit CD4 + memory T cell recall in supporting the ongoing anti-tumour response. According to this hypothesis vaccine formulations (tetanus, diphtheria, Bordetella pertussis) could be re-administrate after the first contact with Covid-19, better before the development of respiratory severe illness and of course before full-blown ARDS (Acute Respiratory Distress Syndrome). The CD4 + memory exploiting could help immune system to recall immunity of already know antigens against coronaviruses, avoiding or limiting "lung crash" until virus specific immunity develops and making it faster and prolonged. Finally, this administration could be helpful not only in already infected patients, but also before infection. In fact, people could have an immune system more ready when the contact with the Covid-19 will occur.

Ishii, M., et al. (2020). "History and Future of Treatment for Acute Stage Kawasaki Disease." Sunhwangi **50**(2): 112-119.
Kawasaki disease is a form of vasculitis, mainly in small and medium arteries of unknown origin, occurring frequently in childhood. It is the leading form of childhood-onset acquired heart disease in developed countries and leads to complications of coronary artery aneurysms in approximately 25% of cases if left untreated. Although more than half a century has passed since Professor Tomisaku Kawasaki's first report in 1957, the cause is not yet clear. Currently, intravenous immunoglobulin therapy has been established as the standard treatment for Kawasaki disease. Various treatment strategies are still being studied under the slogan, "Ending powerful inflammation in the acute phase as early as possible and minimizing the incidence of coronary artery lesions," as the goal of acute phase treatments for Kawasaki disease. Currently, in addition to immunoglobulin therapy, steroid therapy, therapy using infliximab, biological products, suppression of elastase secretion inside and outside the neutrophils, inactivated ulinastatin therapy and cyclosporine therapy, plasma exchange, etc. are performed. This chapter outlines the history and transition of the acute phase treatment for Kawasaki disease.

Jamrozik, E. and M. J. Selgelid (2020). "Human infection challenge studies in endemic settings and/or low-income and middle-income countries: key points of ethical consensus and controversy." Journal of Medical Ethics **07**: 07.
Human infection challenge studies (HCS) involve intentionally infecting research participants with pathogens (or other micro-organisms). There have been recent calls for more HCS to be conducted in low-income and middle-income countries (LMICs), where many relevant diseases are endemic. HCS in general, and HCS in LMICs in particular, raise numerous ethical issues. This paper summarises the findings of a project that explored ethical and regulatory issues related to LMIC HCS via (i) a review of relevant literature and (ii) 45 qualitative interviews with scientists

and ethicists. Among other areas of consensus, we found that there was widespread agreement that LMIC HCS can be ethically acceptable, provided that they have a sound scientific rationale, are accepted by local communities and meet usual research ethics requirements. Unresolved issues include those related to (i) acceptable approaches to trade-offs between the scientific aim to produce generalisable results and the protection of participants, (iii) the sharing of benefits with LMIC populations, (iii) the acceptable limits to risks and burdens for participants, (iv) the potential for third-party risk and whether the degree of acceptable third-party risk is different in endemic settings, (v) the conditions under which (if any) it would be appropriate to recruit children for disease-causing HCS, (v) appropriate levels of payment to participants and (vi) appropriate governance of (LMIC) HCS. This paper provides preliminary analyses of these ethical considerations in order to (i) inform scientists and policymakers involved in the planning, conduct and/or governance of LMIC HCS and (ii) highlight areas warranting future research. Insofar as this article focuses on HCS in (endemic) settings where diseases are present and/or widespread, much of the analysis provided is relevant to HCS (in HICs or LMICs) involving pandemic diseases including COVID19.

Janssens, G. O., et al. (2020). "A rapid review of evidence and recommendations from the SIOPE radiation oncology working group to help mitigate for reduced paediatric radiotherapy capacity during the COVID-19 pandemic or other crises." Radiotherapy & Oncology **148**: 216-222.
OBJECTIVE: To derive evidence-based recommendations for the optimal utilisation of resources during unexpected shortage of radiotherapy capacity.
METHODS AND MATERIALS: We have undertaken a rapid review of published literature on the role of radiotherapy in the multimodality treatment of paediatric cancers governing the European practise of paediatric radiotherapy. The derived data has been discussed with expert paediatric radiation oncologists to derive a hierarchy of recommendations.
RESULTS: The general recommendations to mitigate the potential detriment of an unexpected shortage of radiotherapy facilities include: (1) maintain current standards of care as long as possible (2) refer to another specialist paediatric radiotherapy department with similar level of expertise (3) prioritise use of existing radiotherapy resources to treat patients with tumours where radiotherapy has the most effect on clinical outcome (4) use chemotherapy to defer the start of radiotherapy where timing of radiotherapy is not expected to be detrimental (5) active surveillance for low-grade tumours if appropriate and (6) consider iso-effective hypofractionated radiotherapy regimens only for selected patients with predicted poor prognosis. The effectiveness of radiotherapy and recommendations for prioritisation of its use for common and challenging paediatric tumours are discussed.
CONCLUSION: This review provides evidence-based treatment recommendations during unexpected shortage of paediatric radiotherapy facilities. It has wider applications for the optimal utilisation of facilities, to improve clinical outcome in low- and middle-income countries, where limited resources continue to be a challenge.

Ji, L. N., et al. (2020). "Clinical features of pediatric patients with COVID-19: a report of two family cluster cases." World Journal of Pediatrics.
Background: Coronovirus disease 2019 (COVID-19) has spread rapidly across the globe. People of all ages are susceptible to COVID-19. However, literature reports on pediatric patients are limited. Method(s): To improve the recognition of COVID-19 infection in children, we retrospectively reviewed two confirmed pediatric cases from two family clusters. Both clinical features and laboratory examination results of the children and their family members were described. Result(s): The two confirmed children only presented with mild respiratory or gastrointestinal symptoms. Both of them had normal chest CT images. After general and symptomatic treatments, both children recovered quickly. Both families had travel histories to Hubei Province. Conclusion(s): Pediatric patients with COVID-19 are mostly owing to family cluster or with a close contact history. Infected children have relatively milder clinical symptoms than infected adults. We should attach importance to early recognition, early diagnosis, and early

treatment of infected children. Copyright © 2020, Children's Hospital, Zhejiang University School of Medicine.

Ji, T., et al. (2020). "Lockdown contained the spread of 2019 novel coronavirus disease in Huangshi city, China: Early epidemiological findings." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **07**.
BACKGROUND: To control the spread of 2019 novel coronavirus disease (COVID-19), China sealed Wuhan on Jan 23, 2020 and soon expanded lockdown to other twelve cities in Hubei province. We aimed to describe the epidemiological characteristics in one of the cities and highlight the effect of current implemented lockdown and nonpharmaceutical interventions. METHOD(S): We retrieved data of reported cases in Huangshi and Wuhan from publicly available disease databases. Local epidemiological data on suspected or confirmed cases in Huangshi were collected through field investigation. Epidemic curves were constructed with data on reported and observed cases. RESULT(S): The accumulated confirmed COVID-19 cases and fatality in Huangshi were reported to be 1015 and 3.74% respectively, compared with 50006 and 5.08% in Wuhan till Mar 27, 2020. Right after Jan 24, the epidemic curve based on observed cases in Huangshi became flattened. Feb 1, 2020 was identified as the "turning point" as the epidemic in Huangshi faded soon afterwards. COVID-19 epidemic was characterized by mild cases in Huangshi, accounting for 82.66% of total cases. Moreover, 50 asymptomatic infections were identified in adults and children. Besides, we found confirmed cases in 19 familial clusters and 21 health care workers, supporting inter-human transmission. CONCLUSION(S): Our study reported the temporal dynamics and characteristics of the COVID-19 epidemic in Huangshi city, China, across the unprecedented intervention. Such new epidemiological inference might provide further guidance on current lockdown measures in high-risk cities and, subsequently, help improve public health intervention strategies against the pandemic on the country and global levels. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Jiang, S., et al. (2020). "Coinfection of SARS-CoV-2 and multiple respiratory pathogens in children." Clinical Chemistry & Laboratory Medicine **16**: 16.

Jin, R. M. (2020). "Recommendation for the diagnosis and treatment of novel coronavirus infection in children in Hubei (Trial version 1). [Chinese]." Chinese Journal of Contemporary Pediatrics **22**(2): 96-99.
Since December 2019, a cluster of patients have been diagnosed to be infected with 2019 novel coronavirus (2019-nCoV) in Wuhan, China. The epidemic has been spreading to other areas of the country and abroad. A few cases have progressed rapidly to acute respiratory distress syndrome and/or multiple organ function failure. The epidemiological survey has indicated that the general population is susceptible to 2019-nCoV. A total of 14 children (6 months to 14 years of age, including 5 cases in Wuhan) have been confirmed to be infected with 2019-nCoV in China so far. In order to further standardize and enhance the clinical management of 2019-nCoV infection in children, reduce the incidence, and decrease the number of severe cases, we have formulated this diagnosis and treatment recommendation according to the recent information at home and abroad. Copyright © 2020 Xiangya Hospital of CSU. All rights reserved.

Joob, B. and V. Wiwanitkit (2020). "Hemorrhagic Problem Among the Patients With COVID-19: Clinical Summary of 41 Thai Infected Patients." Clinical & Applied Thrombosis/Hemostasis **26**: 1076029620918308.

Jullien, S., et al. (2020). "Pneumonia in children admitted to the national referral hospital in Bhutan: A prospective cohort study." International Journal of Infectious Diseases **95**: 74-83.
Objectives: The study aim was to describe the etiological profile and clinical characteristics of pneumonia among children hospitalized in Thimphu, Bhutan. Method(s): This prospective study

enrolled children aged 2-59 months admitted to the Jigme Dorji Wangchuck National Referral Hospital with World Health Organization (WHO)-defined clinical pneumonia. Demographic and clinico-radiological data were collected through questionnaires, physical examination, and chest radiography. Blood samples and nasopharyngeal washing were collected for microbiological analysis including culture and molecular methods. Result(s): From July 2017 to June 2018, 189 children were enrolled, of which 53.4% were infants. Pneumonia-related admissions were less frequent over the winter. Chest radiographies were obtained in 149 children; endpoints included pneumonia in 39 cases (26.2%), other infiltrates in 31 (20.8%), and were normal in 79 children (53.0%). Non-contaminated bacterial growth was detected in 8/152 (5.3%) blood cultures, with only two cases of Streptococcus pneumoniae. Viral detection in upper respiratory secretions was common, with at least one virus detected in 103/115 (89.6%). The three most-commonly isolated viruses were respiratory syncytial virus (52/115; 45.2%), rhinovirus (42/115; 36.5%), and human parainfluenza virus (19/115; 16.5%). A third of patients with viral infections showed mixed infections. Case fatality rate was 3.2% (6/189). Conclusion(s): Respiratory viral infections predominated among this cohort of WHO-defined clinical pneumonia cases, whereas bacterial aetiologies were uncommon, highlighting the epidemiologic transition that Bhutan seems to have reached. Copyright © 2020 The Authors

Kam, K. Q., et al. (2020). "A Well Infant with Coronavirus Disease 2019 (COVID-19) with High Viral Load." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **28**.
A well 6-month-old infant with coronavirus disease 2019 (COVID-19) had persistently positive nasopharyngeal swabs to day 16 of admission. This case highlights the difficulties in establishing the true incidence of COVID-19 as asymptomatic individuals can excrete the virus. These patients may play important roles in human-to-human transmission in the community. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Kamali Aghdam, M., et al. (2020). "Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report." Infectious Diseases **52**(6): 427-429.
Introduction: Novel coronavirus or coronavirus disease (COVID-19) can affect all age groups. The clinical course of the disease in children and infants is milder than in adults. It should be noted that, although typical symptoms may be present in children, non-specific symptoms could be noted in the neonate. The disease is rare in the neonate, so, its suspicion in this group can help to make a quick diagnose. Case report: A 15-day-old neonate was admitted with fever, lethargy, cutaneous mottling, and respiratory distress without cough. His mother had symptoms of Novel coronavirus. So Reverse-Transcription Polymerase Chain Reaction (RT-PCR) assay was done for the neonate and showed to be positive. The newborn was isolated and subjected to supportive care. Antibiotic and antiviral treatment was initiated. Eventually, the baby was discharged in good general condition. Conclusion(s): When a newborn presents with non-specific symptoms of infection with an added history of COVID-19 in his/her parents, it indicates the need for PCR testing for Novel coronavirus. Copyright © 2020, © 2020 Society for Scandinavian Journal of Infectious Diseases.

Kan, M. J., et al. (2020). "Fever without a source in a young infant due to SARS-CoV-2." Journal of the Pediatric Infectious Diseases Society. **22**.
A 5-week-old infant admitted for fever without a source subsequently tested positive for SARS-CoV-2. She had a mild hospital course without respiratory distress. This unexpected presentation changed regional hospital screening for COVID-19 and personal protective equipment use by medical providers evaluating infants with fever without a source. Copyright © The Author(s) 2020. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Kang, X., et al. (2020). "Anesthesia management in cesarean section for a patient with coronavirus disease 2019. [Chinese]." Zhejiang da xue xue bao **Yi xue ban = Journal of Zhejiang University. Medical sciences. 49**(1): 0.
Since the corona virus disease 2019 (COVID-19) affects the cardio-pulmonary function of pregnant women, the anesthetic management in the cesarean section for the patients, as well as the protection for medical staff is significantly different from that in ordinary surgical operation. This paper reports a pregnant woman with COVID-19, for whom a cesarean section was successfully performed in our hospital on February 8, 2020. Anesthetic management, protection of medical staff and psychological intervention for the patients during the operation are discussed. Importance should be attached to the preoperative evaluation of pregnant women with COVID-19 and the implementation of anesthesia plan. For ordinary COVID-19 patients intraspinal anesthesia is preferred in cesarean section, and the influence on respiration and circulation in both maternal and infant should be reduced; while for severe or critically ill patients general anesthesia with endotracheal intubation should be adopted. The safety of medical environment should be ensured, and level-III standard protection should be taken for anesthetists. Special attention and support should be given to maternal psychology. It is important to give full explanation before operation to reduce anxiety; to relieve the discomfort during operation to reduce tension; to avoid the bad mood of patients due to pain after operation.

Kang, X., et al. (2020). "[Anesthesia management in cesarean section for a patient with coronavirus disease 2019]." Zhejiang da Xue Xue Bao. Yi Xue Ban/Journal of Zhejiang University. Medical Sciences **49**(1): 0.
Since the corona virus disease 2019 (COVID-19) affects the cardio-pulmonary function of pregnant women, the anesthetic management in the cesarean section for the patients, as well as the protection for medical staff is significantly different from that in ordinary surgical operation. This paper reports a pregnant woman with COVID-19, for whom a cesarean section was successfully performed in our hospital on February 8, 2020. Anesthetic management, protection of medical staff and psychological intervention for the patients during the operation are discussed. Importance should be attached to the preoperative evaluation of pregnant women with COVID-19 and the implementation of anesthesia plan. For ordinary COVID-19 patients intraspinal anesthesia is preferred in cesarean section, and the influence on respiration and circulation in both maternal and infant should be reduced; while for severe or critically ill patients general anesthesia with endotracheal intubation should be adopted. The safety of medical environment should be ensured, and level-III standard protection should be taken for anesthetists. Special attention and support should be given to maternal psychology. It is important to give full explanation before operation to reduce anxiety; to relieve the discomfort during operation to reduce tension; to avoid the bad mood of patients due to pain after operation.

Kang, X., et al. (2020). "Anesthesia management in cesarean section for patient with COVID-19: a case report. [Chinese]." Zhejiang da xue xue bao **Yi xue ban = Journal of Zhejiang University. Medical sciences. 49**(2): 249-252.
Since the coronavirus disease 2019 (COVID-19) affects the cardio-pulmonary function of pregnant women, the anesthetic management and protection of medical staff in the cesarean section is significantly different from that in ordinary surgical operation. This paper reports a case of cesarean section for a woman with COVID-19, which was successfully performed in the First Affiliated Hospital of Zhejiang University School of Medicine on February 8, 2020. Anesthetic management, protection of medical staff and psychological intervention for the pregnant woman during the operation were discussed. Importance has been attached to the preoperative evaluation of pregnant women with COVID-19 and the implementation of anesthesia plan. For moderate patients, intraspinal anesthesia is preferred in cesarean section, and try to reduce its

influence in respiration and circulation in both maternal and infant; general anesthesia with endotracheal intubation should be adopted for severe or critically ill patients. Ensure the safety of medical environment, and anesthetists should carry out level-III standard protection. Special attention and support should be paid to maternal psychology: fully explanation before operation to reduce anxiety; relieve the discomfort during operation, so as to reduce tension; avoid the bad mood due to pain after operation.

Kanne, J. P. (2020). "Chest CT Findings in 2019 Novel Coronavirus (2019-nCoV) Infections from Wuhan, China: Key Points for the Radiologist." Radiology **295**(1): 16-17.

Karimi-Sari, H. and M. S. Rezaee-Zavareh (2020). "COVID-19 and viral hepatitis elimination programs: Are we stepping backward?" Liver International **22**: 22.
As Mendlowitz and colleagues mentioned in a recent commentary, the World Health Organization set a goal for the elimination of viral hepatitis until 2030. This means that the number of newly infected persons and related mortality should be decreased by 90% and 65%, respectively. The elimination programs focus on different parts such as testing, treatment, immunization against hepatitis B virus (HBV), preventing mother to child transmission, blood safety, and harm reduction. Now, COVID-19 is spreading fast throughout the world and more than one million people have been affected by this virus so far. While all attentions are now on providing effective medicines and vaccines for COVID-19, we should not forget other viruses and diseases.

Khan, F., et al. (2020). "An Overview of Signal Processing Techniques for Remote Health Monitoring Using Impulse Radio UWB Transceiver." Sensors **20**(9): 27.
Non-invasive remote health monitoring plays a vital role in epidemiological situations such as SARS outbreak (2003), MERS (2015) and the recently ongoing outbreak of COVID-19 because it is extremely risky to get close to the patient due to the spread of contagious infections. Non-invasive monitoring is also extremely necessary in situations where it is difficult to use complicated wired connections, such as ECG monitoring for infants, burn victims or during rescue missions when people are buried during building collapses/earthquakes. Due to the unique characteristics such as higher penetration capabilities, extremely precise ranging, low power requirement, low cost, simple hardware and robustness to multipath interferences, Impulse Radio Ultra Wideband (IR-UWB) technology is appropriate for non-invasive medical applications. IR-UWB sensors detect the macro as well as micro movement inside the human body due to its fine range resolution. The two vital signs, i.e., respiration rate and heart rate, can be measured by IR-UWB radar by measuring the change in the magnitude of signal due to displacement caused by human lungs, heart during respiration and heart beating. This paper reviews recent advances in IR- UWB radar sensor design for healthcare, such as vital signs measurements of a stationary human, vitals of a non-stationary human, vital signs of people in a vehicle, through the wall vitals measurement, neonate's health monitoring, fall detection, sleep monitoring and medical imaging. Although we have covered many topics related to health monitoring using IR-UWB, this paper is mainly focused on signal processing techniques for measurement of vital signs, i.e., respiration and heart rate monitoring.

Kim, S., et al. (2020). "School Opening Delay Effect on Transmission Dynamics of Coronavirus Disease 2019 in Korea: Based on Mathematical Modeling and Simulation Study." Journal of Korean Medical Science **35**(13): e143.
BACKGROUND: Nonpharmaceutical intervention strategy is significantly important to mitigate the coronavirus disease 2019 (COVID-19) spread. One of the interventions implemented by the government is a school closure. The Ministry of Education decided to postpone the school opening from March 2 to April 6 to minimize epidemic size. We aimed to quantify the school closure effect on the COVID-19 epidemic. METHOD(S): The potential effects of school opening were measured using a mathematical model considering two age groups: children (aged 19 years and younger) and adults (aged over 19). Based on susceptible-exposed-infectious-recovered

model, isolation and behavior-changed susceptible individuals are additionally considered. The transmission parameters were estimated from the laboratory confirmed data reported by the Korea Centers for Disease Control and Prevention from February 16 to March 22. The model was extended with estimated parameters and estimated the expected number of confirmed cases as the transmission rate increased after school opening. RESULT(S): Assuming the transmission rate between children group would be increasing 10 fold after the schools open, approximately additional 60 cases are expected to occur from March 2 to March 9, and approximately additional 100 children cases are expected from March 9 to March 23. After March 23, the number of expected cases for children is 28.4 for 7 days and 33.6 for 14 days. CONCLUSION(S): The simulation results show that the government could reduce at least 200 cases, with two announcements by the Ministry of education. After March 23, although the possibility of massive transmission in the children's age group is lower, group transmission is possible to occur.

Kisely, S., et al. (2020). "Occurrence, prevention, and management of the psychological effects of emerging virus outbreaks on healthcare workers: rapid review and meta-analysis." BMJ **369**: m1642.

OBJECTIVE: To examine the psychological effects on clinicians of working to manage novel viral outbreaks, and successful measures to manage stress and psychological distress.

DESIGN: Rapid review and meta-analysis.

DATA SOURCES: Cochrane Central Register of Controlled Trials, PubMed/Medline, PsycInfo, Scopus, Web of Science, Embase, and Google Scholar, searched up to late March 2020.

ELIGIBILITY CRITERIA FOR STUDY SELECTION: Any study that described the psychological reactions of healthcare staff working with patients in an outbreak of any emerging virus in any clinical setting, irrespective of any comparison with other clinicians or the general population.

RESULTS: 59 papers met the inclusion criteria: 37 were of severe acute respiratory syndrome (SARS), eight of coronavirus disease 2019 (covid-19), seven of Middle East respiratory syndrome (MERS), three each of Ebola virus disease and influenza A virus subtype H1N1, and one of influenza A virus subtype H7N9. Of the 38 studies that compared psychological outcomes of healthcare workers in direct contact with affected patients, 25 contained data that could be combined in a pairwise meta-analysis comparing healthcare workers at high and low risk of exposure. Compared with lower risk controls, staff in contact with affected patients had greater levels of both acute or post-traumatic stress (odds ratio 1.71, 95% confidence interval 1.28 to 2.29) and psychological distress (1.74, 1.50 to 2.03), with similar results for continuous outcomes. These findings were the same as in the other studies not included in the meta-analysis. Risk factors for psychological distress included being younger, being more junior, being the parents of dependent children, or having an infected family member. Longer quarantine, lack of practical support, and stigma also contributed. Clear communication, access to adequate personal protection, adequate rest, and both practical and psychological support were associated with reduced morbidity.

CONCLUSIONS: Effective interventions are available to help mitigate the psychological distress experienced by staff caring for patients in an emerging disease outbreak. These interventions were similar despite the wide range of settings and types of outbreaks covered in this review, and thus could be applicable to the current covid-19 outbreak.

Kitano, N., et al. (2020). "Seasonal variation in epidemiology of Kawasaki disease-related coronary artery abnormalities in Japan, 1999-2017." Journal of epidemiology. **22**.

BACKGROUND: Epidemiological studies show a U-shaped tendency in Kawasaki disease (KD)-related coronary artery abnormalities (CAAs) across age categories. Since studies suggest seasonal variations in KD onset, this study aimed to clarify the epidemiologic features of CAAs, considering the seasons of KD-occurrence. METHOD(S): We analyzed 2106 (males=1215, females=891) consecutive KD cases from October 1999 to September 2017 using our electronic database of annual surveys, targeting all hospitals with pediatric departments across Wakayama, Japan. The primary outcome was the presence/absence of CAAs measured by echocardiography

1 month after KD onset. Odds ratios (ORs) and 95% confidence intervals (CIs) of combined patient age and sex for CAAs were calculated using logistic regression models adjusted for four seasons. RESULT(S): The median age was 25 (range, 1-212) months. The proportion of males decreased with increasing age. The youngest age group (<6 months) showed an inverse summer/autumn to winter/spring ratio (>1.0) in KD-occurrence. CAAs were observed in 2.8% of cases (males=3.4%, females=2.1%), which significantly lessened in summer than in other seasons. Moreover, 50% (n=4/8) of cases with giant aneurysms experienced KD in autumn. Adjusted ORs for CAAs among males aged >=60 months (3.0, 95%, CI 1.2-7.5) and females aged <6 months (3.6, 95%, CI 1.1-11.8) were significantly higher than those among males aged 12-35 months. CONCLUSION(S): Cumulative 18-year data of consecutive KD cases from one area suggest the influence of interactions between patient age and sex on the development of KD-related CAAs. The season of KD-occurrence may reflect the diversity of agents.

Klein, J. D., et al. (2020). "Promoting and supporting children's health and healthcare during COVID-19 - International Paediatric Association Position Statement." Archives of Disease in Childhood **07**: 07.

Kleinwechter, H. and K. Laubner (2020). "Coronavirus disease 2019 (COVID-19) and pregnancy: Overview and report of the first German case with COVID-19 and gestational diabetes. [German]." Diabetologe **16**(3): 242-246.
Since the beginning of the coronavirus pandemic with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in January 2020, more than 100 cases of pregnant Chinese women have been published, including individuals with gestational diabetes (GDM). The descriptive overview reports on the clinical presentation of COVID-19 as well as on obstetric and neonatal outcome data. The main symptoms of the overall milder course of infection are fever, cough and dyspnea. So far, there is no evidence of intrauterine transmission of the virus and no evidence of breast milk transfer. Postnatal infections of infants of infected mothers are documented, but the course is usually mild. The available data are informative for preparing health professionals for the expected infections in pregnant women with the comorbidity diabetes mellitus. Copyright © 2020, Springer Medizin Verlag GmbH, ein Teil von Springer Nature.

Koo, J. R., et al. (2020). "Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study." The Lancet Infectious Diseases **23**: 23.
BACKGROUND: Since the coronavirus disease 2019 outbreak began in the Chinese city of Wuhan on Dec 31, 2019, 68 imported cases and 175 locally acquired infections have been reported in Singapore. We aimed to investigate options for early intervention in Singapore should local containment (eg, preventing disease spread through contact tracing efforts) be unsuccessful.
METHODS: We adapted an influenza epidemic simulation model to estimate the likelihood of human-to-human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a simulated Singaporean population. Using this model, we estimated the cumulative number of SARS-CoV-2 infections at 80 days, after detection of 100 cases of community transmission, under three infectivity scenarios (basic reproduction number [R₀] of 1.5, 2.0, or 2.5) and assuming 7.5% of infections are asymptomatic. We first ran the model assuming no intervention was in place (baseline scenario), and then assessed the effect of four intervention scenarios compared with a baseline scenario on the size and progression of the outbreak for each R₀ value. These scenarios included isolation measures for infected individuals and quarantining of family members (hereafter referred to as quarantine); quarantine plus school closure; quarantine plus workplace distancing; and quarantine, school closure, and workplace distancing (hereafter referred to as the combined intervention). We also did sensitivity analyses by altering the asymptomatic fraction of infections (22.7%, 30.0%, 40.0%, and 50.0%) to compare outbreak sizes under the same control measures.
FINDINGS: For the baseline scenario, when R₀ was 1.5, the median cumulative number of infections at day 80 was 279 000 (IQR 245 000-320 000), corresponding to 7.4% (IQR 6.5-8.5) of the resident population of Singapore. The median number of infections increased with higher

infectivity: 727 000 cases (670 000-776 000) when R₀ was 2.0, corresponding to 19.3% (17.8-20.6) of the Singaporean population, and 1 207 000 cases (1 164 000-1 249 000) when R₀ was 2.5, corresponding to 32% (30.9-33.1) of the Singaporean population. Compared with the baseline scenario, the combined intervention was the most effective, reducing the estimated median number of infections by 99.3% (IQR 92.6-99.9) when R₀ was 1.5, by 93.0% (81.5-99.7) when R₀ was 2.0, and by 78.2% (59.0 -94.4) when R₀ was 2.5. Assuming increasing asymptomatic fractions up to 50.0%, up to 277 000 infections were estimated to occur at day 80 with the combined intervention relative to 1800 for the baseline at R₀ of 1.5.

INTERPRETATION: Implementing the combined intervention of quarantining infected individuals and their family members, workplace distancing, and school closure once community transmission has been detected could substantially reduce the number of SARS-CoV-2 infections. We therefore recommend immediate deployment of this strategy if local secondary transmission is confirmed within Singapore. However, quarantine and workplace distancing should be prioritised over school closure because at this early stage, symptomatic children have higher withdrawal rates from school than do symptomatic adults from work. At higher asymptomatic proportions, intervention effectiveness might be substantially reduced requiring the need for effective case management and treatments, and preventive measures such as vaccines.

FUNDING: Singapore Ministry of Health, Singapore Population Health Improvement Centre.

Korean Society of Infectious, D., et al. (2020). "Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020." Journal of Korean Medical Science **35**(10): e112.

Since the first case of coronavirus disease19 (COVID-19) was reported in Wuhan, China, as of March 2, 2020, the total number of confirmed cases of COVID-19 was 89,069 cases in 67 countries and regions. As of 0 am, March 2, 2020, the Republic of Korea had the second-largest number of confirmed cases (n = 4,212) after China (n = 80,026). This report summarizes the epidemiologic features and the snapshots of the outbreak in the Republic of Korea from January 19 and March 2, 2020.

Kotecha, R. S. (2020). "Challenges posed by COVID-19 to children with cancer." The Lancet Oncology **21**(5): e235.

Kumar, P. and J. P. Goyal (2020). "Management of Asthma in Children during COVID-19 Pandemic." Indian pediatrics. **04**.

Kumrah, R., et al. (2020). "Immunogenetics of Kawasaki disease." Clinical Reviews in Allergy and Immunology.

Kawasaki disease (KD) is a medium vessel vasculitis that affects young children. Despite extensive research over the last 50 years, the etiology of KD remains an enigma. Seasonal change in wind patterns was shown to have correlation with the epidemics of KD in Japan. Occurrence of disease in epidemiological clusters, seasonal variation, and a very low risk of recurrence suggest that KD is triggered by an infectious agent. The identification of oligoclonal IgA response in the affected tissues suggests an antigen-driven inflammation. The recent identification of a viral antigen in the cytoplasm of bronchial ciliated epithelium also favors infection as the main trigger for KD. Pointers that suggest a genetic basis of KD include a high disease prevalence in North-East Asian populations, a high risk among siblings, and familial occurrence of cases. Dysregulated innate and adaptive immune responses are evident in the acute stages of KD. In addition to the coronary wall inflammation, endothelial dysfunction and impaired vascular remodeling contribute to the development of coronary artery abnormalities (CAAs) and thrombosis. Genetic aberrations in certain intracellular signaling pathways involving immune effector functions are found to be associated with increased susceptibility to KD and development of coronary artery abnormalities (CAAs). Several susceptible genes have been

identified through genome-wide association studies (GWAS) and linkage studies (GWLS). The genes that are studied in KD can be classified under 4 major groups-enhanced T cell activation (ITPKC, ORAI1, STIM1), dysregulated B cell signaling (CD40, BLK, FCGR2A), decreased apoptosis (CASP3), and altered transforming growth factor beta signaling (TGFB2, TGFBR2, MMP, SMAD). The review aims to highlight the role of several genetic risk factors that are linked with the increased susceptibility to KD. Copyright © 2020, Springer Science+Business Media, LLC, part of Springer Nature.

Lagana, S. M., et al. (2020). "COVID-19 Associated Hepatitis Complicating Recent Living Donor Liver Transplantation." Archives of pathology & laboratory medicine. **17**.
We present a case of COVID-19 hepatitis in a living donor liver allograft recipient whose donor subsequently tested positive for COVID-19. The patient is a female infant with biliary atresia (failed Kasai procedure). She recovered well, with improving liver function tests for 4 days. On post-operative day (POD) 4 the patient developed respiratory distress and fever. COVID-19 testing (polymerase chain reaction) was positive. Liver function tests increased approximately 5-fold. Liver biopsy showed moderate acute hepatitis with prominent clusters of apoptotic hepatocytes and associated cellular debris. Lobular lymphohistiocytic inflammation was noted. Typical portal features of mild to moderate acute cellular rejection were also noted.

Lai, C. C., et al. (2020). "Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths." Journal of Microbiology, Immunology & Infection **04**: 04.
Since the emergence of coronavirus disease 2019 (COVID-19) (formerly known as the 2019 novel coronavirus [2019-nCoV]) in Wuhan, China in December 2019, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 75,000 cases have been reported in 32 countries/regions, resulting in more than 2000 deaths worldwide. Despite the fact that most COVID-19 cases and mortalities were reported in China, the WHO has declared this outbreak as the sixth public health emergency of international concern. The COVID-19 can present as an asymptomatic carrier state, acute respiratory disease, and pneumonia. Adults represent the population with the highest infection rate; however, neonates, children, and elderly patients can also be infected by SARS-CoV-2. In addition, nosocomial infection of hospitalized patients and healthcare workers, and viral transmission from asymptomatic carriers are possible. The most common finding on chest imaging among patients with pneumonia was ground-glass opacity with bilateral involvement. Severe cases are more likely to be older patients with underlying comorbidities compared to mild cases. Indeed, age and disease severity may be correlated with the outcomes of COVID-19. To date, effective treatment is lacking; however, clinical trials investigating the efficacy of several agents, including remdesivir and chloroquine, are underway in China. Currently, effective infection control intervention is the only way to prevent the spread of SARS-CoV-2.

Lassandro, G., et al. (2020). "Covid-19 and children with immune thrombocytopenia: Emerging issues." Mediterranean Journal of Hematology and Infectious Diseases **12 (1) (no pagination)**(e2020028).

Le, H. T., et al. (2020). "The first infant case of COVID-19 acquired from a secondary transmission in Vietnam." The Lancet Child and Adolescent Health **4**(5): 405-406.

Lee, E., et al. (2020). "Annual and seasonal patterns in etiologies of pediatric community-acquired pneumonia due to respiratory viruses and Mycoplasma pneumoniae requiring hospitalization in South Korea." BMC Infectious Diseases **20 (1) (no pagination)**(132).
Background: Community-acquired pneumonia (CAP) is one of the leading worldwide causes of childhood morbidity and mortality. Its disease burden varies by age and etiology and is time dependent. We aimed to investigate the annual and seasonal patterns in etiologies of pediatric

CAP requiring hospitalization. Method(s): We conducted a retrospective study in 30,994 children (aged 0-18 years) with CAP between 2010 and 2015 at 23 nationwide hospitals in South Korea. Mycoplasma pneumoniae (MP) pneumonia was clinically classified as macrolide-sensitive MP, macrolide-less effective MP (MLEP), and macrolide-refractory MP (MRMP) based on fever duration after initiation of macrolide treatment, regardless of the results of in vitro macrolide sensitivity tests. Result(s): MP and respiratory syncytial virus (RSV) were the two most commonly identified pathogens of CAP. With the two epidemics of MP pneumonia (2011 and 2015), the rates of clinical MLEP and MRMP pneumonia showed increasing trends of 36.4% of the total MP pneumonia. In children < 2 years of age, RSV (34.0%) was the most common cause of CAP, followed by MP (9.4%); however, MP was the most common cause of CAP in children aged 2-18 years of age (45.3%). Systemic corticosteroid was most commonly administered for MP pneumonia. The rate of hospitalization in intensive care units was the highest for RSV pneumonia, and ventilator care was most commonly needed in cases of adenovirus pneumonia. Conclusion(s): The present study provides fundamental data to establish public health policies to decrease the disease burden due to CAP and improve pediatric health. Copyright © 2020 The Author(s).

L'Huillier, A. G. and S. A. Asner (2020). "Pediatric impact of COVID-19. [French]." Revue medicale suisse **16**(N 6912): 839-841.

Li, B., et al. (2020). "Radiographic and Clinical Features of Children with 2019 Novel Coronavirus (COVID-19) Pneumonia." Indian pediatrics. **07**.
OBJECTIVE: The purpose of this study was to investigate chest computed tomography (CT) findings in children with coronavirus disease-19 (COVID-19) pneumonia in our hospital. METHOD(S): This study included 22 pediatric patients with confirmed COVID-19 from January to March 2020. The chest CT images and clinical data were reviewed. RESULT(S): The most prevalent presenting symptoms were fever (64%) and cough (59%), and a mildly elevated mean (SD) C-reactive protein (CRP) level of 11.22(11.06) and erythrocyte sedimentation rate of 18.8 (15.17) were detected. The major CT abnormalities observed were mixed ground-glass opacity and consolidation lesions (36%), consolidations (32%), and ground-glass opacities (14%). Peripheral distribution (45%) of lung lesions was predominant. Most of the lesions were multilobar (68%), with an average of three lung segments involved. CONCLUSION(S): Children with COVID-19 had relatively milder symptoms and less severe lung inflammation than adults. Chest CT plays an important role in the management of children with COVID-19 pneumonia.

Li, D., et al. (2020). "False-Negative Results of Real-Time Reverse-Transcriptase Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus 2: Role of Deep-Learning-Based CT Diagnosis and Insights from Two Cases." Korean Journal of Radiology **21**(4): 505-508.
The epidemic of 2019 novel coronavirus, later named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still gradually spreading worldwide. The nucleic acid test or genetic sequencing serves as the gold standard method for confirmation of infection, yet several recent studies have reported false-negative results of real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). Here, we report two representative false-negative cases and discuss the supplementary role of clinical data with rRT-PCR, including laboratory examination results and computed tomography features. Coinfection with SARS-COV-2 and other viruses has been discussed as well.

Li, H. Y., et al. (2020). "A qualitative study of zoonotic risk factors among rural communities in southern China." International Health **12**(2): 77-85.
BACKGROUND: Strategies are urgently needed to mitigate the risk of zoonotic disease emergence in southern China, where pathogens with zoonotic potential are known to circulate in wild animal populations. However, the risk factors leading to emergence are poorly understood, which presents a challenge in developing appropriate mitigation strategies for local communities.

METHODS: Residents in rural communities of Yunnan, Guangxi and Guangdong provinces were recruited and enrolled in this study. Data were collected through ethnographic interviews and field observations, and thematically coded and analysed to identify both risk and protective factors for zoonotic disease emergence at the individual, community and policy levels.
RESULTS: Eighty-eight ethnographic interviews and 55 field observations were conducted at nine selected sites. Frequent human-animal interactions and low levels of environmental biosecurity in local communities were identified as risks for zoonotic disease emergence. Policies and programmes existing in the communities provide opportunities for zoonotic risk mitigation.
CONCLUSIONS: This study explored the relationship among zoonotic risk and human behaviour, environment and policies in rural communities in southern China. It identifies key behavioural risk factors that can be targeted for development of tailored risk-mitigation strategies to reduce the threat of novel zoonoses.

Li, J., et al. (2020). "An infant with a mild SARS-CoV-2 infection detected only by anal swabs: a case report." Brazilian Journal of Infectious Diseases **06**: 06.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China and has spread rapidly worldwide. We present a mild SARS-CoV-2 infection in a baby with non-productive cough and normal chest computed tomography, in whom only anal swabs tested positive by real-time PCR testing for SARS-CoV-2. She was given atomization inhalation therapy with recombinant human interferon alfa-1b for 10 days. Her anal swabs remained positive for eight days, whereas her throat swabs were persistently negative by real-time PCR testing. Mild and asymptomatic cases, especially in children, might present with PCR negative pharyngeal/nasal swabs and PCR positive anal swabs. Those patients are potential sources of infection via fecal-oral transmission for COVID-19.

Li, W., et al. (2020). "Chest computed tomography in children with COVID-19 respiratory infection." Pediatric Radiology **50**(6): 796-799.
BACKGROUND: Infection with COVID-19 is currently rare in children.
OBJECTIVE: To describe chest CT findings in children with COVID-19.
MATERIALS AND METHODS: We studied children at a large tertiary-care hospital in China, during the period from 28 January 2019 to 8 February 2020, who had positive reverse transcriptase polymerase chain reaction (RT-PCR) for COVID-19. We recorded findings at any chest CT performed in the included children, along with core clinical observations.
RESULTS: We included five children from 10 months to 6 years of age (mean 3.4 years). All had had at least one CT scan after admission. Three of these five had CT abnormality on the first CT scan (at 2 days, 4 days and 9 days, respectively, after onset of symptoms) in the form of patchy ground-glass opacities; all normalised during treatment.
CONCLUSION: Compared to reports in adults, we found similar but more modest lung abnormalities at CT in our small paediatric cohort.

Li, Y., et al. (2020). "Insight into COVID-2019 for pediatricians." Pediatric Pulmonology **55**(5): E1-E4.
Since December 2019, patients with unexplained pneumonia have been found in Wuhan City, Hubei Province, China. The pathogen in these cases is a new type of coronavirus. The World Health Organization confirmed this diagnosis and named the pathogen SARSCoV-2. The disease caused by SARSCoV-2 is called Corona Virus Disease (COVID-2019). The virus is highly infectious and pathogenic, causing human-to-human transmission. At present, SARSCoV-2 is still rampant in the world. Zhengzhou City in Henan Province serves as an example, 102 people have been confirmed to be infected with SARSCoV-2 (at 24:00 on February 5th, 2020), including three children, the youngest is 4 years old. From the perspective of clinical pediatricians as the first line fighting the epidemic, this paper will discuss the clinical characteristics, prevention and control measures, outcomes, diagnosis, and treatment of pediatric cases.

Licciardi, F., et al. (2020). "COVID-19 and what pediatric rheumatologists should know: A review from a

highly affected country." Pediatric Rheumatology **18 (1) (no pagination)**(35).
On March 11th, 2020 the World Health Organization declared COVID-19 a global pandemic. The infection, transmitted by 2019 novel coronavirus (2019-nCov), was first discovered in December 2019, in Wuhan, Hubei Province, and then rapidly spread worldwide. Italy was early and severely involved, with a critical spread of the infection and a very high number of victims. Person-to-person spread mainly occurs via respiratory droplets and contact. The median incubation period is 5 days. The spectrum of respiratory symptoms may range from mild to severe, strictly depending on the age of the patient and the underlying comorbidities. In children COVID-19 related disease is less frequent and less aggressive. In Italy 1% of positive cases are under 18 years of age, and no deaths have been recorded before 29 years of age. For patients affected by rheumatic disease, despite the concerns related to the imbalance of their immune response and the effect of immunosuppressive treatments, there are still few data to understand the real consequences of this infection. Major scientific societies have issued recommendations to help rheumatologists in caring their patients. Interestingly, some of the drugs mostly used by rheumatologists appear to be promising in critical COVID-19 infected patients, where the hyperinflammation and cytokine storm seem to drive to the multiorgan failure. Pediatric rheumatologists are expected to play a supporting role in this new front of COVID-19 pandemic, both as general pediatricians treating infected children, and as rheumatologists taking care of their rheumatic patients, as well as offering their experience in the possible alternative use of immunomodulatory drugs. Copyright © 2020 The Author(s).

Lin, D., et al. (2020). "Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients." Science China. Life sciences **63**(4): 606-609.

Lin, J., et al. (2020). "The isolation period should be longer: Lesson from a child infected with SARS-CoV-2 in Chongqing, China." Pediatric Pulmonology **55**(6): E6-E9.
In December 2019, COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbroke in Wuhan, the capital city of Hubei province, China. The disease rapidly spread to other areas in China due to a huge population movement during the New Year Festival. Here, a 7-year-old child with SARS-CoV-2 infection in Chongqing, outside of Wuhan, Hubei province, was reported. This case suggested that children infected with SARS-CoV-2 are more likely to present milder manifestations than adults. The continuous positive real-time reverse transcription-polymerase chain reaction assay for SARS-CoV-2 in the child's throat swab sample indicated the isolation period for suspected child cases should be longer than 14 days.

Liu, D., et al. (2020). "Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis." Ajr **American journal of roentgenology.**: 1-6.
OBJECTIVE. The purpose of this study was to describe the clinical manifestations and CT features of coronavirus disease (COVID-19) pneumonia in 15 pregnant women and to provide some initial evidence that can be used for guiding treatment of pregnant women with COVID-19 pneumonia. MATERIALS AND METHODS. We reviewed the clinical data and CT examinations of 15 consecutive pregnant women with COVID-19 pneumonia in our hospital from January 20, 2020, to February 10, 2020. A semiquantitative CT scoring system was used to estimate pulmonary involvement and the time course of changes on chest CT. Symptoms and laboratory results were analyzed, treatment experiences were summarized, and clinical outcomes were tracked. RESULTS. Eleven patients had successful delivery (10 cesarean deliveries and one vaginal delivery) during the study period, and four patients were still pregnant (three in the second trimester and one in the third trimester) at the end of the study period. No cases of neonatal asphyxia, neonatal death, stillbirth, or abortion were reported. The most common early finding on chest CT was ground-glass opacity (GGO). With disease progression, crazy paving pattern and consolidations were seen on CT. The abnormalities showed absorptive changes at the end of the study period for all patients. The most common onset symptoms of COVID-19 pneumonia in

pregnant women were fever (13/15 patients) and cough (9/15 patients). The most common abnormal laboratory finding was lymphocytopenia (12/15 patients). CT images obtained before and after delivery showed no signs of pneumonia aggravation after delivery. The four patients who were still pregnant at the end of the study period were not treated with antiviral drugs but had achieved good recovery. CONCLUSION. Pregnancy and childbirth did not aggravate the course of symptoms or CT features of COVID-19 pneumonia. All the cases of COVID-19 pneumonia in the pregnant women in our study were the mild type. All the women in this study-some of whom did not receive antiviral drugs-achieved good recovery from COVID-19 pneumonia.

Liu, G., et al. (2020). "Risk factors of intravenous immunoglobulin resistance in children with Kawasaki disease: A meta-analysis of case-control studies." Frontiers in Pediatrics **8 (no pagination)**(187).
Previous studies have shown that children with Kawasaki disease (KD) who fail to respond to intravenous immunoglobulin (IVIG) therapy are at higher risk of developing coronary artery lesions (CALs). We aimed to conduct a meta-analysis to uncover the risk factors associated with IVIG resistance in children with KD. PubMed, Embase, and Cochrane Library databases were searched up to 31st October 2019, and 23 case-control studies were finally eligible, enrolling 2,053 patients of IVIG resistance and 16,635 patients of IVIG sensitivity. Potential factors were comprehensively analyzed by using stata15 software with a standard meta-analysis procedure and consequently found that in addition to patients with polymorphous rash or swelling of extremities symptoms had a tendency to be non-responders, IVIG resistance was more likely to occur in patients with severe anemia, hypoalbuminemia, decreased baseline platelet count, and elevated levels of erythrocyte sedimentation rate (ESR), total bilirubin, alanine aminotransferase (ALT) and neutrophils percentage. Particularly, male sex, hyponatraemia, increased aspartate aminotransferase (AST), and C-reactive protein (CRP) were confirmed as the risk factors favor IVIG resistance in Mongoloids from Asia countries, but not in Caucasians from non-Asia regions. In summary, we report several risk factors relevant to IVIG resistance in children with KD, which may provide guidance for the prediction of IVIG resistance. But a proposing of an optimal prediction system with high specificity and sensitivity needs further studies because of confounding factors. Copyright © 2020 Liu, Wang and Du.

Liu, H., et al. (2020). "Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children." Journal of Infection **80**(5): e7-e13.
BACKGROUND: The ongoing outbreak of COVID-19 pneumonia is globally concerning. We aimed to investigate the clinical and CT features in the pregnant women and children with this disease, which have not been well reported.
METHODS: Clinical and CT data of 59 patients with COVID-19 from January 27 to February 14, 2020 were retrospectively reviewed, including 14 laboratory-confirmed non-pregnant adults, 16 laboratory-confirmed and 25 clinically-diagnosed pregnant women, and 4 laboratory-confirmed children. The clinical and CT features were analyzed and compared.
FINDINGS: Compared with the non-pregnant adults group (n=14), initial normal body temperature (9 [56%] and 16 [64%]), leukocytosis (8 [50%] and 9 [36%]) and elevated neutrophil ratio (14 [88%] and 20 [80%]), and lymphopenia (9 [56%] and 16 [64%]) were more common in the laboratory-confirmed (n=16) and clinically-diagnosed (n=25) pregnant groups. Totally 614 lesions were detected with predominantly peripheral and bilateral distributions in 54 (98%) and 37 (67%) patients, respectively. Pure ground-glass opacity (GGO) was the predominant presence in 94/131 (72%) lesions for the non-pregnant adults. Mixed consolidation and complete consolidation were more common in the laboratory-confirmed (70/161 [43%]) and clinically-diagnosed (153/322 [48%]) pregnant groups than 37/131 (28%) in the non-pregnant adults (P=0.007, P<0.001). GGO with reticulation was less common in 9/161 (6%) and 16/322 (5%) lesions for the two pregnant groups than 24/131 (18%) for the non-pregnant adults (P=0.001, P<0.001). The pulmonary involvement in children with COVID-19 was mild with a

focal GGO or consolidation. Twenty-three patients underwent follow-up CT, revealing progression in 9/13 (69%) at 3 days whereas improvement in 8/10 (80%) at 6-9 days after initial CT scans. INTERPRETATION: Atypical clinical findings of pregnant women with COVID-19 could increase the difficulty in initial identification. Consolidation was more common in the pregnant groups. The clinically-diagnosed cases were vulnerable to more pulmonary involvement. CT was the modality of choice for early detection, severity assessment, and timely therapeutic effects evaluation for the cases with epidemic and clinical features of COVID-19 with or without laboratory confirmation. The exposure history and clinical symptoms were more helpful for screening in children versus chest CT.

Liu, H., et al. (2020). "Why are pregnant women susceptible to COVID-19? An immunological viewpoint." Journal of Reproductive Immunology **139 (no pagination)**(103122).
The 2019 novel coronavirus disease (COVID-19) was first detected in December 2019 and became epidemic in Wuhan, Hubei Province, China. COVID-19 has been rapidly spreading out in China and all over the world. The virus causing COVID-19, SARS-CoV-2 has been known to be genetically similar to severe acute respiratory syndrome coronavirus (SARS-CoV) but distinct from it. Clinical manifestation of COVID-19 can be characterized by mild upper respiratory tract infection, lower respiratory tract infection involving non-life threatening pneumonia, and life-threatening pneumonia with acute respiratory distress syndrome. It affects all age groups, including newborns, to the elders. Particularly, pregnant women may be more susceptible to COVID-19 since pregnant women, in general, are vulnerable to respiratory infection. In pregnant women with COVID-19, there is no evidence for vertical transmission of the virus, but an increased prevalence of preterm deliveries has been noticed. The COVID-19 may alter immune responses at the maternal-fetal interface, and affect the well-being of mothers and infants. In this review, we focused on the reason why pregnant women are more susceptible to COVID-19 and the potential maternal and fetal complications from an immunological viewpoint. Copyright © 2020 Elsevier B.V.

Liu, J. and W. Wang (2020). "Imaging examination, diagnosis, and control and prevention of nosocomial infection for coronavirus disease 2019: Expert consensus of Hunan radiologist." Zhong Nan da Xue Xue Bao. Yi Xue Ban = Journal of Central South University. Medical Sciences **45**(3): 221-228.
The outbreak of coronavirus disease 2019 (COVID-19) is a huge threat to global public health because it develops rapidly. There is no specific treatment so far. Chest imaging examination is an important auxiliary examination method in diagnosis of COVID-19. To further standardize the imaging examination and diagnosis of COVID-19, Hunan Society of Radiology together with Imaging Technology Professional Committee of Hunan Medical Association reach an expert consensus document on imaging examination, diagnosis, and control and prevention of nosocomial infection for COVID-19. This document summarizes the epidemiological characteristics, clinical features, imaging examination procedure, imaging findings, CT staging, the value of imaging examination, and the methods for control and prevention of nosocomial infection for COVID-19 during imaging examination. Furthermore, it extends the clinical characteristics and imaging manifestations of COVID-19 in children.

Liu, M., et al. (2020). "High-Resolution Computed Tomography Manifestations of 5 Pediatric Patients With 2019 Novel Coronavirus." Journal of computer assisted tomography. **25**.
We present clinical and chest computed tomography (CT) features of 5 cases of pediatric patients with 2019 novel coronavirus. Two patients had fever and dry cough, whereas the rest of 3 patients were asymptomatic. Three patients had unilateral ground glass opacities with or without consolidation in the subpleural region on high-resolution chest CT, 1 patient had bilateral ground glass opacities, and 1 patient was negative for CT. We note that up to 66.7% asymptomatic patients had pulmonary lesions, so the asymptomatic children with Wuhan contact are recommended to do a 2019 novel coronavirus real-time fluorescence polymerase chain reaction screening. Unlike adult patients, only a small amount of patients had multilobes affected, so we

speculate that the pediatric patients generally have milder CT findings than adults.

Liu, R., et al. (2020). "Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020." Clinica Chimica Acta **505**: 172-175.
BACKGROUND: There's an outbreak of a novel coronavirus (SARS-CoV-2) infection since December 2019, first in China, and currently with more than 80 thousand confirmed infection globally in 29 countries till March 2, 2020. Identification, isolation and caring for patients early are essential to limit human-to-human transmission including reducing secondary infections among close contacts and health care workers, preventing transmission amplification events. The RT-PCR detection of viral nucleic acid test (NAT) was one of the most quickly established laboratory diagnosis method in a novel viral pandemic, just as in this COVID-19 outbreak.
METHODS: 4880 cases that had respiratory infection symptoms or close contact with COVID-19 patients in hospital in Wuhan, China, were tested for SARS-CoV-2 infection by use of quantitative RT-PCR (qRT-PCR) on samples from the respiratory tract. Positive rates were calculated in groups divided by genders or ages.
RESULTS: The positive rate was about 38% for the total 4880 specimens. Male and older population had a significant higher positive rates. However, 57% was positive among the specimens from the Fever Clinics. Binary logistic regression analysis showed that age, not gender, was the risk factor for SARS-CoV-2 infection in fever clinics.
CONCLUSIONS: Therefore, we concluded that viral NAT played an important role in identifying SARS-CoV-2 infection.

Liu, W., et al. (2020). "Clinical characteristics of 19 neonates born to mothers with COVID-19." Frontiers of medicine. **13**.
The aim of this study was to investigate the clinical characteristics of neonates born to SARS-CoV-2 infected mothers and increase the current knowledge on the perinatal consequences of COVID-19. Nineteen neonates were admitted to Tongji Hospital from January 31 to February 29, 2020. Their mothers were clinically diagnosed or laboratory-confirmed with COVID-19. We prospectively collected and analyzed data of mothers and infants. There are 19 neonates included in the research. Among them, 10 mothers were confirmed COVID-19 by positive SARS-CoV-2 RT-PCR in throat swab, and 9 mothers were clinically diagnosed with COVID-19. Delivery occurred in an isolation room and neonates were immediately separated from the mothers and isolated for at least 14 days. No fetal distress was found. Gestational age of the neonates was 38.6 +/- 1.5 weeks, and average birth weight was 3293 +/- 425 g. SARS-CoV-2 RT-PCR in throat swab, urine, and feces of all neonates were negative. SARS-CoV-2 RT-PCR in breast milk and amniotic fluid was negative too. None of the neonates developed clinical, radiologic, hematologic, or biochemical evidence of COVID-19. No vertical transmission of SARS-CoV-2 and no perinatal complications in the third trimester were found in our study. The delivery should occur in isolation and neonates should be separated from the infected mothers and care givers.

Liu, W., et al. (2020). "Detection of Covid-19 in Children in Early January 2020 in Wuhan, China." New England Journal of Medicine **382**(14): 1370-1371.

Liu, Y., et al. (2020). "What are the underlying transmission patterns of COVID-19 outbreak? An age-specific social contact characterization." EClinicalMedicine **(no pagination)**(100354).
Background: COVID-19 has spread to 6 continents. Now is opportune to gain a deeper understanding of what may have happened. The findings can help inform mitigation strategies in the disease-affected countries. Method(s): In this work, we examine an essential factor that characterizes the disease transmission patterns: the interactions among people. We develop a computational model to reveal the interactions in terms of the social contact patterns among the population of different age-groups. We divide a city's population into seven age-groups: 0-6 years old (children); 7-14 (primary and junior high school students); 15-17 (high school

students); 18-22 (university students); 23-44 (young/middle-aged people); 45-64 years old (middle-aged/elderly people); and 65 or above (elderly people). We consider four representative settings of social contacts that may cause the disease spread: (1) individual households; (2) schools, including primary/high schools as well as colleges and universities; (3) various physical workplaces; and (4) public places and communities where people can gather, such as stadiums, markets, squares, and organized tours. A contact matrix is computed to describe the contact intensity between different age-groups in each of the four settings. By integrating the four contact matrices with the next-generation matrix, we quantitatively characterize the underlying transmission patterns of COVID-19 among different populations. Finding(s): We focus our study on 6 representative cities in China: Wuhan, the epicenter of COVID-19 in China, together with Beijing, Tianjin, Hangzhou, Suzhou, and Shenzhen, which are five major cities from three key economic zones. The results show that the social contact-based analysis can readily explain the underlying disease transmission patterns as well as the associated risks (including both confirmed and unconfirmed cases). In Wuhan, the age-groups involving relatively intensive contacts in households and public/communities are dispersedly distributed. This can explain why the transmission of COVID-19 in the early stage mainly took place in public places and families in Wuhan. We estimate that Feb. 11, 2020 was the date with the highest transmission risk in Wuhan, which is consistent with the actual peak period of the reported case number (Feb. 4-14). Moreover, the surge in the number of new cases reported on Feb. 12 and 13 in Wuhan can readily be captured using our model, showing its ability in forecasting the potential/unconfirmed cases. We further estimate the disease transmission risks associated with different work resumption plans in these cities after the outbreak. The estimation results are consistent with the actual situations in the cities with relatively lenient policies, such as Beijing, and those with strict policies, such as Shenzhen. Interpretation(s): With an in-depth characterization of age-specific social contact-based transmission, the retrospective and prospective situations of the disease outbreak, including the past and future transmission risks, the effectiveness of different interventions, and the disease transmission risks of restoring normal social activities, are computationally analyzed and reasonably explained. The conclusions drawn from the study not only provide a comprehensive explanation of the underlying COVID-19 transmission patterns in China, but more importantly, offer the social contact-based risk analysis methods that can readily be applied to guide intervention planning and operational responses in other countries, so that the impact of COVID-19 pandemic can be strategically mitigated. Funding(s): General Research Fund of the Hong Kong Research Grants Council; Key Project Grants of the National Natural Science Foundation of China. Copyright © 2020 The Author(s)

Liu, Y., et al. (2020). "Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury." Science China. Life sciences **63**(3): 364-374.
The outbreak of the 2019-nCoV infection began in December 2019 in Wuhan, Hubei province, and rapidly spread to many provinces in China as well as other countries. Here we report the epidemiological, clinical, laboratory, and radiological characteristics, as well as potential biomarkers for predicting disease severity in 2019-nCoV-infected patients in Shenzhen, China. All 12 cases of the 2019-nCoV-infected patients developed pneumonia and half of them developed acute respiratory distress syndrome (ARDS). The most common laboratory abnormalities were hypoalbuminemia, lymphopenia, decreased percentage of lymphocytes (LYM) and neutrophils (NEU), elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH), and decreased CD8 count. The viral load of 2019-nCoV detected from patient respiratory tracts was positively linked to lung disease severity. ALB, LYM, LYM (%), LDH, NEU (%), and CRP were highly correlated to the acute lung injury. Age, viral load, lung injury score, and blood biochemistry indexes, albumin (ALB), CRP, LDH, LYM (%), LYM, and NEU (%), may be predictors of disease severity. Moreover, the Angiotensin II level in the plasma sample from 2019-nCoV infected patients was markedly elevated and linearly associated to viral load and lung injury. Our results suggest a number of potential diagnosis biomarkers and angiotensin receptor blocker (ARB) drugs for potential repurposing treatment of 2019-nCoV infection.

Lo, M. S. (2020). "A framework for understanding Kawasaki disease pathogenesis." Clinical Immunology **214 (no pagination)**(108385).
Kawasaki disease (KD) is a common vasculitis of childhood, typically affecting children under the age of five. Despite many aspects of its presentation that bear resemblence to acute infection, no causative infectious agent has been identified despite years of intense scrutiny. Unlike most infections, however, there are significant differences in racial predilection that suggest a strong genetic influence. The inflammatory response in KD specifically targets the coronary arteries, also unusual for an infectious condition. In this review, we discuss recent hypotheses on KD pathogenesis as well as new insights into the innate immune response and mechanisms behind vascular damage. The pathogenesis is complex, however, and remains inadequately understood. Copyright © 2020

Locatelli, A. G., et al. (2020). "Histologic features of long lasting chilblain-like lesions in a pediatric COVID-19 patient." Journal of the European Academy of Dermatology and Venereology : JEADV. **09**.
Since the beginning of the pandemic of Coronavirus disease (COVID-19) an increasing number of skin manifestations have been reported.1,2 Most reports concern adult patients and describe various patterns of skin eruptions, in most of cases with low specificity and no univocal temporal association with the onset of systemic symptoms of COVID-19.1-3. Copyright This article is protected by copyright. All rights reserved.

Long, X. R., et al. (2020). "[Epidemiology and clinical features of highly pathogenic human coronavirus infection in children]." Zhonghua Erke Zazhi **58**(5): E014.

Lou, X. X., et al. (2020). "Three children who recovered from novel coronavirus 2019 pneumonia." Journal of Paediatrics and Child Health **56**(4): 650-651.

Lowe, B. and B. Bopp (2020). "COVID-19 vaginal delivery - a case report." Australian and New Zealand Journal of Obstetrics and Gynaecology.
The novel coronavirus termed SARS-CoV-2 is a major public health challenge. Many maternity units around the country are currently considering management protocols for these patients. We report a case from a tertiary Australian hospital describing an uncomplicated vaginal birth in a SARS-CoV-2 positive mother. To our knowledge this is also the first case described of a mother with COVID-19 not separated from her infant. Management provided supports the current Royal College of Obstetricians and Gynaecologists and World Health Organization guidelines suggesting that it is possible to consider rooming in post delivery for COVID-19 positive parents. Encouragement of breast feeding appears possible and safe when viral precautions are observed. Copyright This article is protected by copyright. All rights reserved.

Lu, Q. and Y. Shi (2020). "Coronavirus disease (COVID-19) and neonate: What neonatologist need to know." Journal of Medical Virology **92**(6): 564-567.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause china epidemics with high morbidity and mortality, the infection has been transmitted to other countries. About three neonates and more than 230 children cases are reported. The disease condition of the main children was mild. There is currently no evidence that SARS-CoV-2 can be transmitted transplacentally from mother to the newborn. The treatment strategy for children with Coronavirus disease (COVID-19) is based on adult experience. Thus far, no deaths have been reported in the pediatric age group. This review describes the current understanding of COVID-19 infection in newborns and children. Copyright © 2020 Wiley Periodicals, Inc.

Lu, X., et al. (2020). "SARS-CoV-2 infection in children - Understanding the immune responses and controlling the pandemic." Pediatric allergy and immunology : official publication of the European

Society of Pediatric Allergy and Immunology. **24**.
In December 2019, a cluster of patients with severe pneumonia caused by a novel coronavirus (SARS-CoV-2) emerged in the city of Wuhan, China. The disease is now termed coronavirus disease 2019 (COVID-19). In the early reports, the patients were mainly middle-aged and elderly men, and children appeared to be less susceptible to this infection. With modern and efficient transportation, the disease quickly spread to almost all corners of the world and the mortality far exceeds those caused by severe acute respiratory syndrome coronavirus (SARS) or Middle East respiratory syndrome coronavirus (MERS). As the number of children with COVID-19 gradually increases, the disease has been documented in premature babies, infants, children and adolescents. Severe and fatal cases in children are relatively rare. The burden of disease in children has been relatively low, but the high proportions of asymptomatic or mildly symptomatic infections in children deserve careful attention. Clear understanding of the immune responses to the virus in children and the transmission potential of asymptomatic children are of paramount importance for the development of specific treatments and vaccine in order to effectively control the ongoing pandemic. Copyright This article is protected by copyright. All rights reserved.

Lu, X., et al. (2020). "COVID-19: lessons to date from China." Archives of Disease in Childhood **12**: 12.
The pandemic due to a novel coronavirus has been sweeping across different regions of the globe since January 2020. Early reports of this infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) consisted of mostly adult patients. As the outbreak spreads rapidly beyond the epicentre of Wuhan, it becomes clear that infants and children of all ages are susceptible to this infection. In China, there have been more than 1200 paediatric cases. Most paediatric patients acquire the infection through household contact with infected adults. The disease in children is usually self-limiting and most infected children will recover uneventfully within 7-10 days. Other than symptoms of the respiratory tract, many children may present with gastrointestinal symptoms. Older children are more likely to have asymptomatic infection. Although deaths related to SARS-CoV-2 are rarely reported in the paediatric age group, young children and those with underlying medical conditions are more likely to develop severe illness. Only a small fraction of neonates born to infected mother would acquire the virus by vertical transmission. Because a large proportion of children and adolescents may have asymptomatic or mildly symptomatic infection, children are likely to play an important role in community transmission of this infection. Screening of children who have a definitive contact history will facilitate early diagnosis and isolation of all infected children. This review summarises the lessons learned in China with regard to the current understanding of SARS-CoV-2 infection in the paediatric population.

Lu, X., et al. (2020). "SARS-CoV-2 Infection in Children." New England Journal of Medicine **382**(17): 1663-1665.

Lu, Y., et al. (2020). "Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan." The Pediatric infectious disease journal. **05**.
BACKGROUND: Information regarding viral shedding in children with coronavirus disease 2019 (COVID-19) was limited. This study aims to investigate the clinical and laboratory characteristics associated with viral shedding in children with mild COVID-19. METHOD(S): The clinical and laboratory information of 110 children with COVID-19 at Wuhan Children's Hospital, Wuhan, China, from January 30 to March 10, 2020, were analyzed retrospectively. RESULT(S): The median age was 6 years old. The median period of viral shedding of COVID-19 was 15 days (interquartile range [IQR], 11-20 days) as measured from illness onset to discharge. This period was shorter in asymptomatic patients (26.4%) compared with symptomatic patients (73.6%) (11 days vs. 17 days). Multivariable regression analysis showed increased odds of symptomatic infection was associated with age <6 years (odds ratio [OR] 8.94, 95% confidence interval [CI]: 2.55-31.35; P = 0.001), hypersensitive C-reactive protein >3.0 mg/L (OR 4.89; 95% CI:

1.10-21.75; P = 0.037) and presenting pneumonia in chest radiologic findings (OR 8.45; 95% CI: 2.69-26.61; P < 0.001). Kaplan-Meier analysis displayed symptomatic infection (P < 0.001), fever (P = 0.006), pneumonia (P = 0.003) and lymphocyte counts <2.0 x 10/L (P = 0.008) in children with COVID-19 were associated with prolonged duration of viral shedding in children with COVID-19. CONCLUSION(S): Prolonged duration of viral shedding in children with COVID-19 was associated with symptomatic infection, fever, pneumonia and lymphocyte count =2.0 x 10/L. Monitoring of symptoms could help to know the viral shedding in children with COVID-19.

Lu, Y., et al. (2020). "Clinical characteristics and radiological features of children infected with the 2019 novel coronavirus." Clinical Radiology.
AIM: To identify and summarise the common findings from 2019 novel coronavirus (2019-nCoV) infections in children. MATERIALS AND METHODS: The clinical characteristics and radiological findings (chest radiography and chest computed tomography [CT]) of nine children infected with the 2019-nCoV were reviewed in this retrospective case series. RESULT(S): Among the children, six had fever (including two children with cough), one had only cough, one had a stuffy nose when initially diagnosed, and one was an asymptomatic carrier. Chest radiographs seemed mostly normal in six cases whereas increased and/or disordered bilateral bronchovascular shadows and dense hilar shadows were seen in three cases. Chest CT exhibited no obvious abnormal signs in four cases. Typical CT findings included patchy, peripheral ground-grass opacities, subpleural lamellar dense shadows, and parenchymal bands. Pleural effusions, mediastinal lymphadenopathy, cavitation, and pleural thickening were absent. CONCLUSION(S): The clinical manifestations and radiological findings of the 2019-nCoV-infected children were mild and lacked a typical pattern. Copyright © 2020 The Royal College of Radiologists

Ludvigsson, J. F. (2020). "Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults." Acta Paediatrica, International Journal of Paediatrics.
Aim: The coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people. Data on symptoms and prognosis in children are rare. Method(s): A systematic literature review was carried out to identify papers on COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the MEDLINE and Embase databases between January 1 and March 18, 2020. Result(s): The search identified 45 relevant scientific papers and letters. The review showed that children have so far accounted for 1%-5% of diagnosed COVID-19 cases, they often have milder disease than adults and deaths have been extremely rare. Diagnostic findings have been similar to adults, with fever and respiratory symptoms being prevalent, but fewer children seem to have developed severe pneumonia. Elevated inflammatory markers were less common in children, and lymphocytopenia seemed rare. Newborn infants have developed symptomatic COVID-19, but evidence of vertical intrauterine transmission was scarce. Suggested treatment included providing oxygen, inhalations, nutritional support and maintaining fluids and electrolyte balances. Conclusion(s): The coronavirus disease 2019 has occurred in children, but they seemed to have a milder disease course and better prognosis than adults. Deaths were extremely rare. Copyright © 2020 The Authors. Acta Paediatrica published by John Wiley & Sons Ltd on behalf of Foundation Acta Paediatrica.

Ma, H., et al. (2020). "A single-center, retrospective study of COVID-19 features in children: a descriptive investigation." BMC Medicine **18**(1): 123.
BACKGROUND: Compared to adults, there are relatively few studies on COVID-19 infection in children, and even less focusing on the unique features of COVID-19 in children in terms of laboratory findings, locations of computerized tomography (CT) lesions, and the role of CT in evaluating clinical recovery. The objective of this study is to report the results from patients at Wuhan Children's Hospital, located within the initial center of the outbreak.
METHODS: Clinical, imaging, and laboratory data of 76 children were collected retrospectively and analyzed with the Fisher exact test and Cox regression statistical methods.

RESULTS: Among 50 children with a positive COVID-19 real-time reverse-transcriptase polymerase chain reaction (PCR), five had negative PCR results initially but showed positive results in subsequent tests. Eight (16%) patients had lymphopenia, seven (14%) with thrombocytopenia, four (8%) with lymphocytosis, two (4%) with thrombocytosis, ten (20%) with elevated C-reactive protein, four (8%) with hemoglobin above, and six (12%) with below standard reference values. Seven (14%) of the 50 had no radiologic evidence of disease on chest CT. For the 43 patients who had abnormal CT findings, in addition to previously reported patterns of ground-glass opacity (67%), local patchy shadowing (37%), local bilateral patchy shadowing (21%), and lesion location of lower lobes (65%), other CT features include that an overwhelming number of pediatric patients had lesions in the subpleural area (95%) and 22 of the 28 lower lobe lesions were in the posterior segment (78%). Lesions in most of the 15 patients (67%) who received chest CT at discharge were not completely absorbed, and 26% of these pediatric patients had CT lesions that were either unchanged or worse.
CONCLUSIONS: There were a few differences between COVID-19 children and COVID-19 adults in terms of laboratory findings and CT characteristics. CT is a powerful tool to detect and characterize COVID-19 pneumonia but has little utility in evaluating clinical recovery for children. These results oppose current COVID-19 hospital discharge criteria in China, as one requirement is that pulmonary imaging must show significant lesion absorption prior to discharge. These differences between pediatric and adult cases of COVID-19 may necessitate pediatric-specific discharge criteria.

Ma, H., et al. (2020). "High resolution CT features of COVID-19 in children. [Chinese]." Chinese Journal of Radiology (China) **54**(4): 310-313.
Objective: To investigate the high resolution CT (HRCT) features of COVID-19 in children. Method(s): A retrospective analysis was performed on the chest HRCT findings of 22 children who were diagnosed as COVID-19 by clinical and nucleic acid testing in Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 25 to February 5, 2020. There were 12 boys and 10 girls, aged from 2 months to 14 years old, with a median age of 4 years, and 14 patients were under 5 years old. The characteristics of lung lesions on HRCT such as distribution, shape, density and so on and whether there were hilar and mediastinal lymph node enlargement and pleural changes were evaluated by 2 radiologists. Result(s): In all of the 22 patients, the chest CT manifestations were normal in 3 patients (3/22), meanwhile the lung involvement of the lesion was found in 19 patients (19/22). Among them, 7 patients had unilateral lung involvement, and 12 patients had bilateral involvement. The HRCT manifestations were as follows. The HRCT showed the ground glass opacity (GGO) in 6 patients, including 4 cases with light opacity and 2 with typical crazy paving sign. Four patients had lung consolidation, with local fibrous stripes and patchy hyperdensity. Six patients had mixed GGO, including 1 case with right white lung. The bronchopneumonia-like changes were seen in 3 cases with scattered spot-like or mixed patchy. The lesions in the lower lobe were more serious than those in the upper lobe, and the lesions in the lateroposterior zone of the lung were more common than those in the apical and central area of the lung. No enlarged lymph nodes and pleural effusion were seen in all patients, but 1 case had thickened interlobar pleura. Conclusion(s): The HRCT manifestations of COVID-19 in children are varied, and the comprehensive assessment need to be made in combination with epidemiological data, clinical manifestations and laboratory tests. However, the chest HRCT plays an important role in early diagnosis, prevention and management of COVID-19.

Ma, X., et al. (2020). "Do children need a longer time to shed SARS-CoV-2 in stool than adults?" Journal of Microbiology, Immunology and Infection.
SARS-CoV-2 can be shed in the stool of patients in the recovery phase. Children show a longer shedding time than adults. We analyzed the possible causes of this finding and recommend that a negative stool sample be included in a patient's discharge criteria.

Ma, Y. L., et al. (2020). "[Clinical features of children with SARS-CoV-2 infection: an analysis of 115 cases]." Zhongguo Dangdai Erke Zazhi **22**(4): 290-293.
OBJECTIVE: To study the clinical features of children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
METHODS: A retrospective analysis was performed for the clinical data of 115 children who were diagnosed with SARS-CoV-2 infection in the Wuhan Children's Hospital, including general information, history of close contact with individuals of SARS-CoV-2 infection, early clinical symptoms, laboratory examination results, and lung CT results.
RESULTS: Among the 115 children, there were 73 boys (63.5%) and 42 girls (36.5%), with a male/female ratio of 1:0.58. Of the 115 children, 105 (91.3%) had a definite history of close contact with individuals of SARS-CoV-2-infection. An increase in alanine aminotransferase was observed in 11 children (9.6%) and an increase in CK-MB was found in 34 children (29.6%). As for clinical symptoms, 29 children (25.2%) had fever, 47 (40.9%) had respiratory symptoms (including cough, rhinorrhea, and nasal congestion), and 61 (53.0%) were asymptomatic. Lung CT findings showed ground glass opacity, fiber opacities, patchy changes, and pulmonary consolidation in 49 children (42.6%), among whom 2 children had "white lung"; 39 children (33.9%) only had lung texture enhancement and 27 children (23.5%) had no pulmonary imaging changes. Among the 115 children, 3 were critically ill, among whom 1 had been cured and the other 2 were under continuous treatment.
CONCLUSIONS: Most of the children with SARS-CoV-2 infection have a close contact history. Critical cases are rare and there is a high proportion of asymptomatic infection.

Mailhot, G. and J. H. White (2020). "Vitamin D and immunity in infants and children." Nutrients **12 (5) (no pagination)**(1233).
The last couple of decades have seen an explosion in our interest and understanding of the role of vitamin D in the regulation of immunity. At the molecular level, the hormonal form of vitamin D signals through the nuclear vitamin D receptor (VDR), a ligand-regulated transcription factor. The VDR and vitamin D metabolic enzymes are expressed throughout the innate and adaptive arms of the immune system. The advent of genome-wide approaches to gene expression profiling have led to the identification of numerous VDR-regulated genes implicated in the regulation of innate and adaptive immunity. The molecular data infer that vitamin D signaling should boost innate immunity against pathogens of bacterial or viral origin. Vitamin D signaling also suppresses inflammatory immune responses that underlie autoimmunity and regulate allergic responses. These findings have been bolstered by clinical studies linking vitamin D deficiency to increased rates of infections, autoimmunity, and allergies. Our goals here are to provide an overview of the molecular basis for immune system regulation and to survey the clinical data from pediatric populations, using randomized placebo-controlled trials and meta-analyses where possible, linking vitamin D deficiency to increased rates of infections, autoimmune conditions, and allergies, and addressing the impact of supplementation on these conditions. Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland.

Mallineni, S. K., et al. (2020). "Coronavirus disease (COVID-19): Characteristics in children and considerations for dentists providing their care." International journal of paediatric dentistry **30**(3): 245-250.
The emergence of the novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19) has led to a global pandemic and one of the most significant challenges to the healthcare profession. Dental practices are focal points for cross-infection, and care must be taken to minimise the risk of infection to, from, or between dental care professionals and patients. The COVID-19 epidemiological and clinical characteristics are still being collated but children's symptoms seem to be milder than those that adults experience. It is unknown whether certain groups, for example children with comorbidities, might be at a higher risk of more severe illness. Emerging data on disease spread in children, affected

by COVID-19, have not been presented in detail. The purpose of this article was to report current data on the paediatric population affected with COVID-19 and highlight considerations for dentists providing care for children during this pandemic. All members of the dental team have a professional responsibility to keep themselves informed of current guidance and be vigilant in updating themselves as recommendations are changing so quickly. Copyright © 2020 BSPD, IAPD and John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Mansour, A., et al. (2020). "First Case of an Infant with COVID-19 in the Middle East." Cureus **12**(4): e7520.

The novel coronavirus (COVID-19) has been declared a worldwide pandemic. It was initially thought to spare children and adolescents as significantly smaller number of cases have been reported in the pediatric population in comparison to adults. Here, we report the case of a 16-month-old female infant from Lebanon who presented with fever and severe diarrhea and tested positive for COVID-19. Her symptoms started six days prior to presentation with no cough, rhinorrhea, or other respiratory manifestations reported. Chest radiography showed lobar consolidation and bronchial infiltrates. Blood culture was positive for Streptococcus pneumoniae. Stool and urine cultures were negative. She was treated with ceftriaxone and metronidazole. Her RT-PCR test was negative after five days of treatment, suggesting that children can clear the virus faster than adults. The patient likely contracted the virus from her parents, who because of the fear of social stigma hide recent history of respiratory illness. These findings serve as a practical reference for the clinical diagnosis and medical treatment of children with COVID-19.

Mao, L. J., et al. (2020). "A child with household transmitted COVID-19." BMC Infectious Diseases **20**(1): 329.

BACKGROUND: Although people of all ages are susceptible to the novel coronavirus infection, which is presently named "Coronavirus Disease 2019" (COVID-19), there has been relatively few cases reported among children. Therefore, it is necessary to understand the clinical characteristics of COVID-19 in children and the differences from adults. CASE PRESENTATION: We report one pediatric case of COVID-19. A 14-month-old boy was admitted to the hospital with a symptom of fever, and was diagnosed with a mild form of COVID-19. The child's mother and grandmother also tested positive for SARS-CoV-2 RNA. However, the lymphocyte counts were normal. The chest computed tomography (CT) revealed scattered ground glass opacities in the right lower lobe close to the pleura and resorption after the treatment. The patient continued to test positive for SARS-CoV-2 RNA in the nasopharyngeal swabs and stool at 17days after the disappearance of symptoms. CONCLUSION(S): The present pediatric case of COVID-19 was acquired through household transmission, and the symptoms were mild. Lymphocyte counts did not significantly decrease. The RNA of SARS-CoV-2 in stool and nasopharyngeal swabs remained positive for an extended period of time after the disappearance of symptoms. This suggests that attention should be given to the potential contagiousness of pediatric COVID-19 cases after clinical recovery.

Marraro, G. A. and C. Spada (2020). "Consideration of the respiratory support strategy of severe acute respiratory failure caused by SARS-CoV-2 infection in children." Zhongguo Dangdai Erke Zazhi **22**(3): 183-194.

The recent ongoing outbreak of severe pneumonia associated with a novel coronavirus (SARS-CoV-2), currently of unknown origin, creates a world emergency that has put global public health institutions on high alert. At present there is limited clinical information of the SARS-CoV-2 and there is no specific treatment recommended, although technical guidances and suggestions have been developed and will continue to be updated as additional information becomes available. Preventive treatment has an important role to control and avoid the spread of severe respiratory disease, but often is difficult to obtain and sometimes cannot be effective to reduce the risk of deterioration of the underlining lung pathology. In order to define an effective and safe treatment for SARS-CoV-2-associated disease, we provide considerations on the actual

treatments, on how to avoid complications and the undesirable side effects related to them and to select and apply earlier the most appropriate treatment. Approaching to treat severe respiratory disease in infants and children, the risks related to the development of atelectasis starting invasive or non-invasive ventilation support and the risk of oxygen toxicity must be taken into serious consideration. For an appropriate and effective approach to treat severe pediatric respiratory diseases, two main different strategies can be proposed according to the stage and severity of the patient conditions: patient in the initial phase and with non-severe lung pathology and patient with severe initial respiratory impairment and/or with delay in arrival to observation. The final outcome is strictly connected with the ability to apply an appropriate treatment early and to reduce all the complications that can arise during the intensive care admission.

Mastnak, W. (2020). "Psychopathological problems related to the COVID-19 pandemic and possible prevention with music therapy." Acta Paediatrica **12**: 12.
COVID-19 is having a profound effect on societies worldwide and the impact that it is having on children cannot be underestimated. Although Brodin (1) stated that the disease tends to be mild in children, psychopathological considerations allow us to assume that the pandemic will have a high risk of long-term paediatric psychiatric sequelae and interdisciplinary preventative measures are needed.

Matricardi, P. M., et al. (2020). "The first, holistic immunological model of COVID-19: implications for prevention, diagnosis, and public health measures." Pediatric Allergy & Immunology **02**: 02.
The natural history of COVID-19 caused by SARS-CoV-2 is extremely variable, ranging from asymptomatic or mild infection, mainly in children, to multi-organ failure, eventually fatal, mainly in the eldest. We propose here the first model, explaining how the outcome of first, crucial 10-15 days after infection, hangs on the balance between the cumulative dose of viral exposure and the efficacy of the local innate immune response (natural IgA and IgM antibodies, Mannose Binding Lectin). If SARS-CoV-2 runs the blockade of this innate immunity and spreads from the upper airways to the alveoli in the early phases of the infections, it can replicate with no local resistance, causing pneumonia and releasing high amounts of antigens. The delayed and strong adaptive immune response (high affinity IgM and IgG antibodies) that follows, causes severe inflammation and triggers mediator cascades (complement, coagulation, and cytokine storm) leading to complications often requiring intensive therapy and being, in some patients, fatal. Low-moderate physical activity can still be recommended. However, extreme physical activity and hyperventilation during the incubation days and early stages of COVID-19, facilitates early direct penetration of high numbers of virus particles in the lower airways and the alveoli, without impacting on the airway's mucosae covered by neutralizing antibodies. This allows the virus bypassing the efficient immune barrier of the upper airways mucosa in already infected, young and otherwise healthy athletes. In conclusion, whether the virus or the adaptative immune response reach the lungs first, is a crucial factor deciding the fate of the patient. This "quantitative and time-sequence dependent" model has several implications for prevention, diagnosis, and therapy of COVID-19 at all ages.

Matthai, J., et al. (2020). "Coronavirus Disease (COVID-19) and the Gastrointestinal System in Children." Indian Pediatrics **12**: 12.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), though primarily a respiratory pathogen, also involves the gastrointestinal tract. Similar to the respiratory mucosa, angiotensin converting enzyme-2 (ACE-2) receptor and transmembrane serine protease 2 TMPRSS2) co-express in the gastrointestinal tract, which facilitates viral entry into the tissue. Less than 10% of children with infection develop diarrhea and vomiting. Prolonged RT PCR positivity in the stool has raised the possibility of feco-oral transmission. Elevated transaminases are common, especially in those with severe coronavirus disease-2019 (COVID -19) disease. Children with inflammatory bowel disease and post liver transplant patients do not have an increased risk of disease, and should remain on medications they are already on. Children with chronic liver

disease should continue their medications as usual. All elective procedures like endoscopy should be postponed.

McGenity, T. J., et al. (2020). "Visualizing the invisible: class excursions to ignite children's enthusiasm for microbes." Microbial Biotechnology **14**: 14.
We have recently argued that, because microbes have pervasive - often vital - influences on our lives, and that therefore their roles must be taken into account in many of the decisions we face, society must become microbiology-literate, through the introduction of relevant microbiology topics in school curricula (Timmis et al. 2019. Environ Microbiol 21: 1513-1528). The current coronavirus pandemic is a stark example of why microbiology literacy is such a crucial enabler of informed policy decisions, particularly those involving preparedness of public-health systems for disease outbreaks and pandemics. However, a significant barrier to attaining widespread appreciation of microbial contributions to our well-being and that of the planet is the fact that microbes are seldom visible: most people are only peripherally aware of them, except when they fall ill with an infection. And it is disease, rather than all of the positive activities mediated by microbes, that colours public perception of 'germs' and endows them with their poor image. It is imperative to render microbes visible, to give them life and form for children (and adults), and to counter prevalent misconceptions, through exposure to imagination-capturing images of microbes and examples of their beneficial outputs, accompanied by a balanced narrative. This will engender automatic mental associations between everyday information inputs, as well as visual, olfactory and tactile experiences, on the one hand, and the responsible microbes/microbial communities, on the other hand. Such associations, in turn, will promote awareness of microbes and of the many positive and vital consequences of their actions, and facilitate and encourage incorporation of such consequences into relevant decision-making processes. While teaching microbiology topics in primary and secondary school is key to this objective, a strategic programme to expose children directly and personally to natural and managed microbial processes, and the results of their actions, through carefully planned class excursions to local venues, can be instrumental in bringing microbes to life for children and, collaterally, their families. In order to encourage the embedding of microbiology-centric class excursions in current curricula, we suggest and illustrate here some possibilities relating to the topics of food (a favourite pre-occupation of most children), agriculture (together with horticulture and aquaculture), health and medicine, the environment and biotechnology. And, although not all of the microbially relevant infrastructure will be within reach of schools, there is usually access to a market, local food store, wastewater treatment plant, farm, surface water body, etc., all of which can provide opportunities to explore microbiology in action. If children sometimes consider the present to be mundane, even boring, they are usually excited with both the past and the future so, where possible, visits to local museums (the past) and research institutions advancing knowledge frontiers (the future) are strongly recommended, as is a tapping into the natural enthusiasm of local researchers to leverage the educational value of excursions and virtual excursions. Children are also fascinated by the unknown, so, paradoxically, the invisibility of microbes makes them especially fascinating objects for visualization and exploration. In outlining some of the options for microbiology excursions, providing suggestions for discussion topics and considering their educational value, we strive to extend the vistas of current class excursions and to: (i) inspire teachers and school managers to incorporate more microbiology excursions into curricula; (ii) encourage microbiologists to support school excursions and generally get involved in bringing microbes to life for children; (iii) urge leaders of organizations (biopharma, food industries, universities, etc.) to give school outreach activities a more prominent place in their mission portfolios, and (iv) convey to policymakers the benefits of providing schools with

Mehan, A., et al. (2020). "COVID-19 in pregnancy: risk of adverse neonatal outcomes." Journal of Medical Virology **30**: 30.
We read with great interest the study by Siyu Chen and colleagues. The authors evaluated the clinical features and outcomes of five pregnant patients with COVID-19 at term, whose delivery

was uneventful and led to favorable perinatal outcomes for both mother and neonate. We would like to draw attention to a growing body of evidence that now points towards an under-addressed association between preterm maternal SARS-CoV-2 infection, preterm delivery and adverse neonatal outcomes, which is not reflected in Chen et al.'s small cohort. We also stress that vertical transmission, which was not tested for by Chen et al., should not be excluded as a potential mechanism for viral spread. Centers should therefore be meticulous in their approach to a SARS-CoV-2+ pregnancy to optimize clinical outcomes for both mother and child. This article is protected by copyright. All rights reserved.

Mehta-Lee, S. S. (2020). "Touch in the Era of COVID-19." BJOG : an international journal of obstetrics and gynaecology. **07**.
I moved out of our shared bedroom of nearly 10 years on 3/22/2020. It was not a difficult decision as we have two young children and wondered what would happen if both of us became ill at the same time. As a Maternal-Fetal medicine physician in New York City, I was acutely aware of the coming COVID-19 crisis, and its potential ramifications on the health of my family, friends, patients and community. I am trained to function well in emergencies, and in this case, it was a quick and seemingly logical next-step to sleep separately. Copyright This article is protected by copyright. All rights reserved.

Memish, Z. A., et al. (2020). "Middle East respiratory syndrome." Lancet **395**(10229): 1063-1077.
The Middle East respiratory syndrome coronavirus (MERS-CoV) is a lethal zoonotic pathogen that was first identified in humans in Saudi Arabia and Jordan in 2012. Intermittent sporadic cases, community clusters, and nosocomial outbreaks of MERS-CoV continue to occur. Between April 2012 and December 2019, 2499 laboratory-confirmed cases of MERS-CoV infection, including 858 deaths (34.3% mortality) were reported from 27 countries to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths). Large outbreaks of human-to-human transmission have occurred, the largest in Riyadh and Jeddah in 2014 and in South Korea in 2015. MERS-CoV remains a high-threat pathogen identified by WHO as a priority pathogen because it causes severe disease that has a high mortality rate, epidemic potential, and no medical countermeasures. This Seminar provides an update on the current knowledge and perspectives on MERS epidemiology, virology, mode of transmission, pathogenesis, diagnosis, clinical features, management, infection control, development of new therapeutics and vaccines, and highlights unanswered questions and priorities for research, improved management, and prevention.

Meng, Y., et al. (2020). "Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: A retrospective study of 168 severe patients." PLoS Pathogens **16**(4): e1008520.
To confirm the relationship between sex and the progression of Coronavirus Disease-19 (COVID-19), and its potential mechanism, among severe patients. For this retrospective study, we included 168 consecutive severe patients with pathogen-confirmed COVID-19 who were hospitalized between January 16th and February 4th, 2020, at Tongji Hospital in Wuhan, China. Clinical characteristics, laboratory parameters, and outcomes were compared and analyzed between males and females. In the present study, we analyzed 168 severe patients with COVID-19, including 86 males and 82 females, and 48 patients (28.6%) were diagnosed as critically ill. Of 86 male patients, 12.8% (11/86) died and 75.6% (65/86) were discharged; of 82 female patients, 7.3% (6/82) died and 86.6% (71/82) were discharged. Eleven laboratory parameters showed significant differences between male and female patients, and six of them were higher during the whole clinical course in patients who died than in patients who were discharged. In adjusted logistic regression analysis, males with comorbidities presented a higher risk of being critically ill than males without comorbidities (OR = 3.824, 95% CI = 1.279-11.435). However, this association attenuated to null in female patients (OR = 2.992, 95% CI = 0.937-9.558). A similar sex-specific trend was observed in the relation between age and critically

ill conditions. We highlighted sex-specific differences in clinical characteristics and prognosis. Male patients appeared to be more susceptible to age and comorbidities. Sex is an important biological variable that should be considered in the prevention and treatment of COVID-19.

Minotti, C., et al. (2020). "How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review." Journal of Infection.
Objectives: SARS-CoV-2 infection has now a global resonance. Data on how COVID-19 is affecting immunocompromised patients are however few. With our study we aimed to systematically review the current knowledge on SARS-CoV-2 cases in children and adults with immunosuppression, to evaluate outcomes in this special population. Method(s): A systematic review of literature was carried out to identify relevant articles, searching the EMBASE, Medline, and Google Scholar databases. Studies reporting data on pre-defined outcomes and related to immunosuppressed adults and children with SARS-CoV-2 were included. Result(s): Sixteen relevant articles were identified with 110 immunosuppressed patients, mostly presenting cancer, along with transplantation and immunodeficiency. Cancer was more often associated with a more severe course, but not necessarily with a bad prognosis. Our data show that both children and adults with immunosuppression seem to have a favorable disease course, as compared to the general population. Conclusion(s): Immunosuppressed patients with COVID-19 seem to be few in relation to the overall figures, and to present a favorable outcome as compared to other comorbidities. This might be explained by a hypothetical protective role of a weaker immune response, determining a milder disease presentation and thus underdiagnosis. Nevertheless, surveillance on this special population should be encouraged. Copyright © 2020 Elsevier Ltd

Moghadam, E. A., et al. (2020). "Increased QT interval dispersion is associated with coronary artery involvement in children with kawasaki disease." Oman Medical Journal **35**(1).
Objectives: Coronary artery (CA) involvement is the most well known complication of Kawasaki disease (KD). Previous studies have suggested that QT dispersion has a predictive value in diagnosing cardiac ischemia, ventricular arrhythmia, and sudden cardiac death. However, limited data exits regarding the application of QT dispersion in KD. Therefore, we sought to determine whether there is a relationship between QT dispersion and CA involvement in patients with KD. Methods: We performed a cross-sectional study of all consecutive patients with KD who were followed-up at the Pediatric Rheumatology Department (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) from September 2013 to November 2015. Patients who met the criteria for KD, based on the American Heart Association guideline, were enrolled in the study. We collected data regarding patients' demographics, clinical manifestations, laboratory, and echocardiographic findings. Results: A total of 70 KD patients were identified, including 43 males (61.4%) and 27 females (38.6%). The median age of patients was 21.0 (11.0–48.0) months. We found statistically significant differences between age, gender, and platelet count among patients with and without CA involvement ($p < 0.050$). Median corrected QT dispersion in patients with CA involvement calculated from 12 leads in the acute phase was significantly higher compared to the non-CA involvement group (108.0 (89.5–138.5) ms vs. 63.0 (54.0–74.5) ms, respectively ($p < 0.001$)). Conclusions: Prolonged QT dispersion (corrected or non-corrected) during the acute and convalescence phases in patients with KD is associated with coronary involvement. © 2020, Oman Medical Specialty Board. All rights reserved.

Mogharab, V., et al. (2020). "The first case of COVID-19 infection in a 75-day-old infant in Jahrom City, south of Iran." Journal of the Formosan Medical Association **119**(5): 995-997.

Molloy, E. J. (2020). "The Doctor's Dilemma: lessons from GB Shaw in a modern pandemic COVID-19." Pediatric Research.
In the current COVID 19 pandemic, the only treatments are supportive as no definitive pharmacological intervention is available. The heterogeneity of the immune response in different patient groups is clear with less severe illness in children. Understanding these disparities is

particularly important as severely affected patients with COVID19 cannot always be predicted before they experience a cytokine storm and multiorgan dysfunction. Over 100 years ago, the concept of individualised immunotherapy was introduced by Sir Almroth Wright and immortalised in GB Shaw's play The Doctor's Dilemma. Shaw's play The Doctor's Dilemma explores the issues of private medical practice, equality of health care delivery, rationing of scarce resources (intensive care) and high-risk therapies. The play also describes the dilemma of rationing of resources and selecting the correct patient for new experimental therapies. Immunological theories of the time are now reflected in current understanding of inflammatory responses in sepsis and immunomodulation during the COVID19 pandemic. Copyright © 2020, International Pediatric Research Foundation, Inc.

Molloy, E. J. and N. Murphy (2020). "Vitamin D, Covid-19 and Children." Irish medical journal **113**(4): 64.

Morand, A., et al. (2020). "COVID-19 virus and children: What do we know?" Archives de Pediatrie **27**(3): 117-118.

Morand, A., et al. (2020). "Child with liver transplant recovers from COVID-19 infection. A case report." Archives de Pediatrie.
We present the case of a 55-month-old girl who recovered from coronavirus disease 2019 (COVID-19) infection 5 months after undergoing liver transplantation; she had a co-infection with Epstein-Barr virus (EBV). To the best of our knowledge, this is the first case report of a COVID-19 infection in a pediatric patient with liver transplantation. Additionally, this is also the first report of confirmed co-infection between COVID-19 and EBV. On the basis of this case, we suggest that liver transplantation is not associated with COVID-19 symptom severity and development. Moreover, COVID-19 and EBV co-infections do not seem to aggravate the clinical outcome. Copyright © 2020 French Society of Pediatrics

Morray, B. H., et al. (2020). "Resource Allocation and Decision Making for Pediatric and Congenital Cardiac Catheterization During the Novel Coronavirus SARS-CoV-2 (COVID-19) Pandemic: A U.S. Multi-Institutional Perspective." The Journal of invasive cardiology **32**(5): E103-E109.
BACKGROUND: The novel coronavirus (COVID-19) pandemic has placed severe stress on healthcare systems around the world. There is limited information on current practices in pediatric cardiac catheterization laboratories in the United States (US). OBJECTIVE(S): To describe current practice patterns and make recommendations regarding potential resource allocation for congenital cardiac catheterization during the COVID-19 pandemic. METHOD(S): A web-based survey was distributed regarding case candidacy and catheterization laboratory preparedness. Centers were categorized based on the current degree of disease burden in that community (as of April 1, 2020). Data and consensus opinion were utilized to develop recommendations. RESULT(S): Respondents belonged to 56 unique US centers, with 27 (48.2%) located in counties with a high number of COVID-19 cases. All centers have canceled elective procedures. There was relative uniformity (>88% agreement) among centers as to which procedures were considered elective. To date, only three centers have performed a catheterization on a confirmed COVID-19 positive patient. Centers located in areas with a higher number of COVID-9 cases have been more involved in a simulation of donning and doffing personal protective equipment (PPE) than low-prevalence centers (46.7% vs 10.3%, respectively; P<.001). Currently, only a small fraction of operators has been reassigned to provide clinical services outside their scope of practice. CONCLUSION(S): At this stage in the COVID-19 pandemic, pediatric/congenital catheterization laboratories have dramatically reduced case volumes. This document serves to define current patterns and provides guidance and recommendations on the preservation and repurposing of resources to help pediatric cardiac programs develop strategies for patient care during this unprecedented crisis.

Muldoon, K. M., et al. (2020). "SARS-CoV-2: Is it the newest spark in the TORCH?" Journal of Clinical

Virology **127**: 104372.
Amid the rapidly evolving global coronavirus disease 2019 (COVID-19) pandemic that has already had profound effects on public health and medical infrastructure globally, many questions remain about its impact on child health. The unique needs of neonates and children, and their role in the spread of the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) should be included in preparedness and response plans. Fetuses and newborn infants may be uniquely vulnerable to the damaging consequences of congenitally- or perinatally-acquired SARS-CoV-2 infection, but data are limited about outcomes of COVID-19 disease during pregnancy. Therefore, information on illnesses associated with other highly pathogenic coronaviruses (i.e., severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome [MERS]), as well as comparisons to common congenital infections, such as cytomegalovirus (CMV), are warranted. Research regarding the potential routes of acquisition of SARS-CoV-2 infection in the prenatal and perinatal setting is of a high public health priority. Vaccines targeting women of reproductive age, and in particular pregnant patients, should be evaluated in clinical trials and should include the endpoints of neonatal infection and disease.

Mullins, E., et al. (2020). "Coronavirus in pregnancy and delivery: rapid review." Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology **55**(5): 586-592.
OBJECTIVES: There are limited case series reporting the impact on women affected by coronavirus during pregnancy. In women affected by severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the case fatality rate appears higher in those affected in pregnancy compared with non-pregnant women. We conducted a rapid review to guide health policy and management of women affected by COVID-19 during pregnancy, which was used to develop the Royal College of Obstetricians and Gynaecologists' (RCOG) guidelines on COVID-19 infection in pregnancy. METHOD(S): Searches were conducted in PubMed and MedRxiv to identify primary case reports, case series, observational studies and randomized controlled trials describing women affected by coronavirus in pregnancy. Data were extracted from relevant papers. This review has been used to develop guidelines with representatives of the Royal College of Paediatrics and Child Health (RCPCH) and RCOG who provided expert consensus on areas in which data were lacking. RESULT(S): From 9965 search results in PubMed and 600 in MedRxiv, 21 relevant studies, all of which were case reports or case series, were identified. From reports of 32 women to date affected by COVID-19 in pregnancy, delivering 30 babies (one set of twins, three ongoing pregnancies), seven (22%) were asymptomatic and two (6%) were admitted to the intensive care unit (ICU), one of whom remained on extracorporeal membrane oxygenation. No maternal deaths have been reported to date. Delivery was by Cesarean section in 27 cases and by vaginal delivery in two, and 15 (47%) delivered preterm. There was one stillbirth and one neonatal death. In 25 babies, no cases of vertical transmission were reported; 15 were reported as being tested with reverse transcription polymerase chain reaction after delivery. Case fatality rates for SARS and MERS were 15% and 27%, respectively. SARS was associated with miscarriage or intrauterine death in five cases, and fetal growth restriction was noted in two ongoing pregnancies affected by SARS in the third trimester. CONCLUSION(S): Serious morbidity occurred in 2/32 women with COVID-19, both of whom required ICU care. Compared with SARS and MERS, COVID-19 appears less lethal, acknowledging the limited number of cases reported to date and that one woman remains in a critical condition. Preterm delivery affected 47% of women hospitalized with COVID-19, which may put considerable pressure on neonatal services if the UK's reasonable worst-case scenario of 80% of the population being affected is realized. Based on this review, RCOG, in consultation with RCPCH, developed guidance for delivery and neonatal care in pregnancies affected by COVID-19, which recommends that delivery mode be determined primarily by obstetric indication and recommends against routine separation of affected mothers and their babies. We hope that this review will be helpful for maternity and neonatal services planning their response to COVID-19.

on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

Munro, A. P. S. and S. N. Faust (2020). "Children are not COVID-19 super spreaders: time to go back to school." Archives of Disease in Childhood **05**: 05.

Ng, K. F., et al. (2020). "COVID-19 in Neonates and Infants: Progression and Recovery." The Pediatric infectious disease journal. **06**.
Between March 10, 2020 and April 17, 2020, of 8/70 (11.4%) SARS-CoV-2 positive infants that presented, 5/8 (63%) developed fever, 4/8 (50%) had lower respiratory tract involvement, 2/8 (25%) had neutropenia and thrombocytosis, and 4/8 infants (50%) were treated for suspected sepsis with broad-spectrum antibiotics. Only 1/8 (13%) required pediatric intensive care. All patients were eventually discharged home well.

Nilsson, A., et al. (2020). "Fatal encephalitis associated with coronavirus OC43 in an immunocompromised child." Infectious Diseases **52**(6): 419-422.
A child with pre-B acute lymphoblastic leukaemia (ALL) developed fatal encephalitis associated with human coronavirus OC43 (HCoV-OC43). During chemotherapy the child had a persistent HCoV-OC43 respiratory infection and later developed progressive encephalitis. Cerebrospinal fluid was negative for pathogens including HCoV-OC43, but a brain biopsy was HCoV-OC43-positive by metagenomic next-generation sequencing.

Nkengasong, J. (2020). "Let Africa into the market for COVID-19 diagnostics." Nature **580**(7805): 565.

Novice, T., et al. (2020). "A Germline Mutation in the C2 Domain of PLCgamma2 Associated with Gain-of-Function Expands the Phenotype for PLCG2-Related Diseases." Journal of Clinical Immunology **40**(2): 267-276.
We report three new cases of a germline heterozygous gain-of-function missense (p.(Met1141Lys)) mutation in the C2 domain of phospholipase C gamma 2 (PLCG2) associated with symptoms consistent with previously described auto-inflammation and phospholipase Cgamma2 (PLCgamma2)-associated antibody deficiency and immune dysregulation (APLAID) syndrome and pediatric common variable immunodeficiency (CVID). Functional evaluation showed platelet hyper-reactivity, increased B cell receptor-triggered calcium influx and ERK phosphorylation. Expression of the altered p.(Met1141Lys) variant in a PLCgamma2-knockout DT40 cell line showed clearly enhanced BCR-triggered influx of external calcium when compared to control-transfected cells. Our results further expand the molecular basis of pediatric CVID and phenotypic spectrum of PLCgamma2-related defects. Copyright © 2019, Springer Science+Business Media, LLC, part of Springer Nature.

Ogimi, C., et al. (2020). "What's New With the Old Coronaviruses?" Journal of the Pediatric Infectious Diseases Society **9**(2): 210-217.
Coronaviruses contribute to the burden of respiratory diseases in children, frequently manifesting in upper respiratory symptoms considered to be part of the "common cold." Recent epidemics of novel coronaviruses recognized in the 21st century have highlighted issues of zoonotic origins of transmissible respiratory viruses and potential transmission, disease, and mortality related to these viruses. In this review, we discuss what is known about the virology, epidemiology, and disease associated with pediatric infection with the common community-acquired human coronaviruses, including species 229E, OC43, NL63, and HKU1, and the coronaviruses responsible for past world-wide epidemics due to severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus. Copyright © The Author(s) 2020. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Pan, A., et al. (2020). "Association of Public Health Interventions With the Epidemiology of the COVID-19

Outbreak in Wuhan, China." JAMA **10**: 10.
Importance: Coronavirus disease 2019 (COVID-19) has become a pandemic, and it is unknown whether a combination of public health interventions can improve control of the outbreak.
Objective: To evaluate the association of public health interventions with the epidemiological features of the COVID-19 outbreak in Wuhan by 5 periods according to key events and interventions.
Design, Setting, and Participants: In this cohort study, individual-level data on 32583 laboratory-confirmed COVID-19 cases reported between December 8, 2019, and March 8, 2020, were extracted from the municipal Notifiable Disease Report System, including patients' age, sex, residential location, occupation, and severity classification.
Exposures: Nonpharmaceutical public health interventions including cordons sanitaire, traffic restriction, social distancing, home confinement, centralized quarantine, and universal symptom survey.
Main Outcomes and Measures: Rates of laboratory-confirmed COVID-19 infections (defined as the number of cases per day per million people), across age, sex, and geographic locations were calculated across 5 periods: December 8 to January 9 (no intervention), January 10 to 22 (massive human movement due to the Chinese New Year holiday), January 23 to February 1 (cordons sanitaire, traffic restriction and home quarantine), February 2 to 16 (centralized quarantine and treatment), and February 17 to March 8 (universal symptom survey). The effective reproduction number of SARS-CoV-2 (an indicator of secondary transmission) was also calculated over the periods.
Results: Among 32 583 laboratory-confirmed COVID-19 cases, the median patient age was 56.7 years (range, 0-103; interquartile range, 43.4-66.8) and 16 817 (51.6%) were women. The daily confirmed case rate peaked in the third period and declined afterward across geographic regions and sex and age groups, except for children and adolescents, whose rate of confirmed cases continued to increase. The daily confirmed case rate over the whole period in local health care workers (130.5 per million people [95% CI, 123.9-137.2]) was higher than that in the general population (41.5 per million people [95% CI, 41.0-41.9]). The proportion of severe and critical cases decreased from 53.1% to 10.3% over the 5 periods. The severity risk increased with age: compared with those aged 20 to 39 years (proportion of severe and critical cases, 12.1%), elderly people (>=80 years) had a higher risk of having severe or critical disease (proportion, 41.3%; risk ratio, 3.61 [95% CI, 3.31-3.95]) while younger people (<20 years) had a lower risk (proportion, 4.1%; risk ratio, 0.47 [95% CI, 0.31-0.70]). The effective reproduction number fluctuated above 3.0 before January 26, decreased to below 1.0 after February 6, and decreased further to less than 0.3 after March 1.
Conclusions and Relevance: A series of multifaceted public health interventions was temporally associated with improved control of the COVID-19 outbreak in Wuhan, China. These findings may inform public health policy in other countries and regions.

Pan, S. L., et al. (2020). "Information Resource Orchestration during the COVID-19 Pandemic: A Study of Community Lockdowns in China." International Journal of Information Management: 102143.
The outbreak of the COVID-19 pandemic has created significant challenges for people worldwide. To combat the virus, one of the most dramatic measures was the lockdown of 4 billion people in what is believed to be the largest quasi-quarantine in human history. As a response to the call to study information behavior during a global health crisis, we adopted a resource orchestration perspective to investigate six Chinese families who survived the lockdown. We explored how elderly, young and middle-aged individuals and children resourced information and how they adapted their information behavior to emerging online technologies. Two information resource orchestration practices (information resourcing activities and information behavior adaptation activities) and three mechanisms (online emergence and convergence in community resilience, the overcoming of information flow impediments, and the application of absorptive capacity) were identified in the study.

Pan, X., et al. (2020). "Asymptomatic cases in a family cluster with SARS-CoV-2 infection." The Lancet Infectious Diseases **20**(4): 410-411.

Paret, M., et al. (2020). "SARS-CoV-2 infection (COVID-19) in febrile infants without respiratory distress." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **17**.
We report two cases of SARS-CoV-2 infection (COVID-19) in infants presenting with fever in the absence of respiratory distress who required hospitalization for evaluation of possible invasive bacterial infections. The diagnoses resulted from routine isolation and real-time RT-PCR-based testing for SARS-CoV-2 for febrile infants in an outbreak setting. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Parikh, S. R., et al. (2020). "Collaborative Multidisciplinary Incident Command at Seattle Children's Hospital for Rapid Preparatory Pediatric Surgery Countermeasures to the COVID-19 Pandemic." Journal of the American College of Surgeons **11**: 11.
Washington was the first US state to have a patient test positive for COVID-19. Before this, our children's hospital proactively implemented an incident command structure that allowed for collaborative creation of safety measures, policies, and procedures for patients, families, staff, and providers. Although the treatment and protective standards are continuously evolving, this commentary shares our thoughts on how an institution, and specifically, surgical services, may develop collaborative process improvement to accommodate for rapid and ongoing change. Specific changes outlined include early establishment of incident command; personal protective equipment conservation; workforce safety; surgical and ambulatory patient triage; and optimization of trainee education. Please note that the contents of this manuscript are shared in the interest of providing collaborative information and are under continuous development as our regional situation changes. We recognize the limitations of this commentary and do not suggest that our approaches represent validated best practices.

Park, J. Y., et al. (2020). "First Pediatric Case of Coronavirus Disease 2019 in Korea." Journal of Korean Medical Science **35**(11): e124.
The large outbreak of coronavirus disease 2019 (COVID-19) that started in Wuhan, China has now spread to many countries worldwide. Current epidemiologic knowledge suggests that relatively few cases are seen among children, which limits opportunities to address pediatric specific issues on infection control and the children's contribution to viral spread in the community. Here, we report the first pediatric case of COVID-19 in Korea. The 10-year-old girl was a close contact of her uncle and her mother who were confirmed to have COVID-19. In this report, we present mild clinical course of her pneumonia that did not require antiviral treatment and serial viral test results from multiple specimens. Lastly, we raise concerns on the optimal strategy of self-quarantine and patient care in a negative isolation room for children.

Pasma, H., et al. (2020). "Epidemiology of Kawasaki disease before and after universal Bacille Calmette-Guerin vaccination program was discontinued." Acta Paediatrica, International Journal of Paediatrics **109**(4): 842-846.
Aim: Bacille Calmette-Guerin (BCG) vaccine (BCG) has been suggested to induce the primary immunity needed for the subsequent Kawasaki disease (KD). We studied the epidemiology of KD before and after the universal BCG vaccination ended in Finland in September 2006. Method(s): Kawasaki disease cases were retrieved from national health registries from 1996 to 2016 for annual incidence rates. We then compared 612 433 children born in the BCG vaccination era, from 1 January 1996 to 30 August 2006, to 604 163 born after BCG era, from 1 September 2006 to 31 December 2016. Result(s): The annual incidence rates did not change after the BCG vaccination stopped. We found 370 first visits for KD by children born in the BCG era and 341 after universal BCG vaccination ended. The mean age at diagnosis increased from 2.6 years to 3.0 years (95% CI-0.64 to -0.012, P =.04) and the proportion of children with Kawasaki disease under 5 years decreased from 87% to 81% (95% CI 1%-12%, P =.02). Conclusion(s):

Discontinuing the universal BCG vaccination programme did not change the incidence rates of KD. The increased age at diagnosis could suggest that the pathogenesis of KD may be associated with the immunological pathways primed by BCG immunisation. Copyright © 2019 Foundation Acta Paediatrica. Published by John Wiley & Sons Ltd

Pattisapu, P., et al. (2020). "Defining Essential Services for Deaf and Hard of Hearing Children during the COVID-19 Pandemic." Otolaryngology - Head & Neck Surgery: 194599820925058.
COVID-19 is a rapidly growing global pandemic caused by a novel coronavirus. With no vaccine or definitive treatment, public health authorities have recommended a strategy of "social distancing," reducing individual interaction, canceling elective procedures, and limiting nonessential services. Health care providers must determine what procedures are considered "elective," balancing risk of treatment delays with that of coronavirus exposure to patient, family, and providers. Given critical periods for language development and the long-term impact of auditory deprivation, some audiologic and otologic services should be considered essential. In this article, we describe the experience of a quaternary referral pediatric hospital in Seattle, the epicenter of COVID-19 in the United States, and share strategies for risk minimization employed by Seattle Children's Hospital. We hope that this work can be a reference for other centers continuing care for children who are deaf and hard of hearing during the COVID-19 and future resource-limiting crises.

Pavone, P., et al. (2020). "Outbreak of COVID-19 infection in children: fear and serenity." European Review for Medical & Pharmacological Sciences **24**(8): 4572-4575.
OBJECTIVE: The recent outbreak of SARS-CoV-2 greatly involves the resources of the global healthcare system, as it affects newborns, adults, and elders. This infection runs in three major stages: a mild cold-like illness, a moderate respiratory syndrome and a severe acute interstitial pneumonia. SARS-CoV-2 infection seems to have a more benign evolution in children. As a matter of fact, low susceptibility and minor aggressivity have been highlighted in most cases. There are currently no effective antiviral drugs treatment for the affected children. No sufficient results have been reached by the use of interferon (IFN), lopinavir/ritonavir, orbidol, and oseltamivir in the treatment of the coronaviruses infection. The aim of this short review is to highlight the differences existing between COVID-19 cases in adults and children.

Pecoraro, L., et al. (2020). "The psycho-physical impact that COVID-19 has on children must not be underestimated." Acta Paediatrica **13**: 13.
Italy has been one of the European countries that has been most affected by the COVID-19 pandemic. By 16 April 2020, 159,107 Italian residents had tested positive for COVID-19 and these included 1,123 children, up to nine years of age (0.7%) and 1,804 adolescents, aged between 10 and 19 years old (1.1%) (1). These data were in line with the case studies reported for the Chinese population, where the respective percentage (proportion) was 0.9% and 1.2% respectively (2). A five-year-old Italian child, who had been affected by many previous and unspecified pathologies, died after testing positive for COVID-19 infection (1). The lower vulnerability of the paediatric population to COVID-19 seems evident.

Pediatric Branch of Hubei Medical, A., et al. (2020). "[Recommendation for the diagnosis and treatment of novel coronavirus infection in children in Hubei (Trial version 1)]." Zhongguo Dangdai Erke Zazhi **22**(2): 96-99.
Since December 2019, a cluster of patients have been diagnosed to be infected with 2019 novel coronavirus (2019-nCoV) in Wuhan, China. The epidemic has been spreading to other areas of the country and abroad. A few cases have progressed rapidly to acute respiratory distress syndrome and/or multiple organ function failure. The epidemiological survey has indicated that the general population is susceptible to 2019-nCoV. A total of 14 children (6 months to 14 years of age, including 5 cases in Wuhan) have been confirmed to be infected with 2019-nCoV in China so far. In order to further standardize and enhance the clinical management of 2019-nCoV

infection in children, reduce the incidence, and decrease the number of severe cases, we have formulated this diagnosis and treatment recommendation according to the recent information at home and abroad.

Peng, J., et al. (2020). "[Management plan for prevention and control of novel coronavirus pneumonia among children in Xiangya Hospital of Central South University]." Zhongguo Dangdai Erke Zazhi **22**(2): 100-105.
Since December 2019, an epidemic of novel coronavirus pneumonia (NCP) has occurred in China. How to effectively prevent and control NCP among children with limited resources is an urgent issue to be explored. Under the unified arrangement of the Xiangya Hospital of Central South University, the Department of Pediatrics has formulated an action plan with Xiangya unique model to prevent and control NCP among children according to the current epidemic situation and diagnostic and therapeutic program in China.

Peng, Z., et al. (2020). "Unlikely SARS-CoV-2 vertical transmission from mother to child: A case report." Journal of Infection and Public Health **13**(5): 818-820.
As the 2019 novel coronavirus disease (COVID-19) rapidly spread across China and to more than 70 countries, an increasing number of pregnant women were affected. The vertical transmission potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of great concern to the obstetrics, neonatologists, and public health agencies. Though some studies indicated the risk of vertical transmission is low, few cases have been reported with comprehensive serial tests from multiple specimens. In this case, a female preterm infant was born to a mother with confirmed COVID-19. She presented with mild respiratory distress and received general management and a short period of nasal continuous positive airway pressure support. During her stay at the hospital, a series of SARS-CoV-2 nucleic test from her throat and anal swab, serum, bronchoalveolar lavage fluid, and urine were negative. The nucleic acid test from the mother's amniotic fluid, vaginal secretions, cord blood, placenta, serum, anal swab, and breast milk were also negative. The most comprehensively tested case reported to date confirmed that the vertical transmission of COVID is unlikely, but still, more evidence is needed. Copyright © 2020 The Authors

Pereira, L. J., et al. (2020). "Biological and social aspects of Coronavirus Disease 2019 (COVID-19) related to oral health." Pesquisa Odontologica Brasileira = Brazilian Oral Research **34**: e041.
The expansion of coronavirus disease 2019 (COVID-19) throughout the world has alarmed all health professionals. Especially in dentistry, there is a growing concern due to it's high virulence and routes of transmission through saliva aerosols. The virus keeps viable on air for at least 3 hours and on plastic and stainless-steel surfaces up to 72 hours. In this sense, dental offices, both in the public and private sectors, are high-risk settings of cross infection among patients, dentists and health professionals in the clinical environment (including hospital's intensive dental care facilities). This manuscript aims to compile current available evidence on prevention strategies for dental professionals. Besides, we briefly describe promising treatment strategies recognized until this moment. The purpose is to clarify dental practitioners about the virus history and microbiology, besides guiding on how to proceed during emergency consultations based on international documents. Dentists should consider that a substantial number of individuals (including children) who do not show any signs and symptoms of COVID-19 may be infected and can disseminate the virus. Currently, there is no effective treatment and fast diagnosis is still a challenge. All elective dental treatments and non-essential procedures should be postponed, keeping only urgent and emergency visits to the dental office. The use of teledentistry (phone calls, text messages) is a very promising tool to keep contact with the patient without being at risk of infection.

Perera, R. A., et al. (2020). "Serological assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), March 2020." Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles

= European Communicable Disease Bulletin **25**(16): 04.
BackgroundThe ongoing coronavirus disease (COVID-19) pandemic has major impacts on health systems, the economy and society. Assessing infection attack rates in the population is critical for estimating disease severity and herd immunity which is needed to calibrate public health interventions. We have previously shown that it is possible to achieve this in real time to impact public health decision making.AimOur objective was to develop and evaluate serological assays applicable in large-scale sero-epidemiological studies. Methods We developed an ELISA to detect IgG and IgM antibodies to the receptor-binding domain (RBD) of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We evaluated its sensitivity and specificity in combination with confirmatory microneutralisation (MN) and 90% plaque reduction neutralisation tests (PRNT₉₀) in 51 sera from 24 patients with virologically confirmed COVID-19 and in age-stratified sera from 200 healthy controls. Results IgG and IgM RBD ELISA, MN and PRNT₉₀ were reliably positive after 29 days from illness onset with no detectable cross-reactivity in age-stratified controls. We found that PRNT₉₀ tests were more sensitive in detecting antibody than MN tests carried out with the conventional 100 tissue culture infectious dose challenge. Heparinised plasma appeared to reduce the infectivity of the virus challenge dose and may confound interpretation of neutralisation test. Conclusion Using IgG ELISA based on the RBD of the spike protein to screen sera for SARS-CoV-2 antibody, followed by confirmation using PRNT₉₀, is a valid approach for large-scale sero-epidemiology studies.

Perkins, G. D., et al. (2020). "International Liaison Committee on Resuscitation: COVID-19 consensus on science, treatment recommendations and task force insights." Resuscitation **151**: 145-147.
Consensus on Science and Treatment recommendations aim to balance the benefits of early resuscitation with the potential for harm to care providers during the COVID-19 pandemic. Chest compressions and cardiopulmonary resuscitation have the potential to generate aerosols. During the current COVID-19 pandemic lay rescuers should consider compressions and public-access defibrillation. Lay rescuers who are willing, trained and able to do so, should consider providing rescue breaths to infants and children in addition to chest compressions. Healthcare professionals should use personal protective equipment for aerosol generating procedures during resuscitation and may consider defibrillation before donning personal protective equipment for aerosol generating procedures.

Peyronnet, V., et al. (2020). "[SARS-CoV-2 infection during pregnancy. Information and proposal of management care. CNGOF]." Gynecologie, Obstetrique, Fertilite & Senologie **48**(5): 436-443.
A new coronavirus (SARS-CoV-2) highlighted at the end of 2019 in China is spreading across all continents. Most often at the origin of a mild infectious syndrome, associating mild symptoms (fever, cough, myalgia, headache and possible digestive disorders) to different degrees, SARS-Covid-2 can cause serious pulmonary pathologies and sometimes death. Data on the consequences during pregnancy are limited. The first Chinese data published seem to show that the symptoms in pregnant women are the same as those of the general population. There are no cases of intrauterine maternal-fetal transmission, but cases of newborns infected early suggest that there could be vertical perpartum or neonatal transmission. Induced prematurity and cases of respiratory distress in newborns of infected mothers have been described. Pregnancy is known as a period at higher risk for the consequences of respiratory infections, as for influenza, so it seems important to screen for Covid-19 in the presence of symptoms and to monitor closely pregnant women. In this context of the SARS-Covid-2 epidemic, the societies of gynecology-obstetrics, infectious diseases and neonatalogy have proposed a French protocol for the management of possible and proven cases of SARS-Covid-2 in pregnant women. These proposals may evolve on a daily basis with the advancement of the epidemic and knowledge in pregnant women. Subsequently, an in-depth analysis of cases in pregnant women will be necessary in order to improve knowledge on the subject.

Philips, K., et al. (2020). "Rapid Implementation of an Adult COVID-19 Unit in a Children's Hospital." Journal of Pediatrics **28**: 28.
OBJECTIVE: To describe the rapid implementation of an adult coronavirus disease 2019 (COVID-19) unit using pediatric physician and nurse providers in a children's hospital and to examine the characteristics and outcomes of the first 100 adult patients admitted.
STUDY DESIGN: We describe our approach to surge-in-place at a children's hospital to meet the local demands of the COVID-19 pandemic. Instead of re-deploying pediatric providers to work with internist-led teams throughout a medical center, pediatric physicians and nurses organized and staffed a 40-bed adult COVID-19 treatment unit within a children's hospital. We adapted internal medicine protocols, developed screening criteria to select appropriate patients for admission, and reorganized staffing and equipment to accommodate adult COVID-19 patients. We used patient counts and descriptive statistics to report sociodemographic, system, and clinical outcomes.
RESULTS: The median patient age was 46 years; 69% were male. On admission, 78 (78%) required oxygen supplementation. During hospitalization, 13 (13%) eventually were intubated. Of the first 100 patients, 14 are still admitted to a medical unit, 6 are in the intensive care unit, 74 have been discharged, 4 died after transfer to the ICU, and 2 died on the unit. The median length of stay for discharged or deceased patients was 4 days (IQR 2,7).
CONCLUSIONS: Our pediatric team screened, admitted, and cared for hospitalized adults by leveraging the familiarity of our system, adaptability of our staff, and high-quality infrastructure. This experience may be informative for other healthcare systems that will be re-deploying pediatric providers and nurses to address a regional COVID-19 surge elsewhere.

Phillips, B. (2020). "Towards evidence-based medicine for paediatricians." Archives of Disease in Childhood **105**(5): 506.

Phuong, L. K., et al. (2020). "What paediatricians need to know about the updated 2017 American Heart Association Kawasaki disease guideline." Archives of Disease in Childhood **105**(1): 10-12.

Pietrobelli, A., et al. (2020). "Effects of COVID-19 Lockdown on Lifestyle Behaviors in Children with Obesity Living in Verona, Italy: A Longitudinal Study." Obesity **30**.
OBJECTIVE: To test the hypothesis that youths with obesity, when removed from structured school activities and confined to their homes during the COVID-19 pandemic, will display unfavorable trends in lifestyle behaviors. METHOD(S): The sample included 41 children and adolescents with obesity participating in a longitudinal observational study located in Verona, Italy. Lifestyle information including diet, activity, and sleep behaviors were collected at baseline and three weeks into the national lockdown during which home confinement was mandatory. Changes in outcomes over the two study time points were evaluated for significance using paired t-tests. RESULT(S): There were no changes in reported vegetable intake; fruit intake increased (p=0.055) during the lockdown. By contrast, potato chip, red meat, and sugary drink intakes increased significantly during the lockdown (p-value range, 0.005 to <0.001). Time spent in sports activities decreased (X+/-SD) by 2.30+/-4.60 hours/week (p=0.003) and sleep time increased by 0.65+/-1.29 hours/day (p=0.003). Screen time increased by 4.85+/-2.40 hours/day (p<0.001). CONCLUSION(S): Recognizing these adverse collateral effects of the COVID-19 pandemic lockdown is critical in avoiding depreciation of weight control efforts among youths afflicted with excess adiposity. Depending on duration, these untoward lockdown effects may have a lasting impact on a child's or adolescent's adult adiposity level. Copyright This article is protected by copyright. All rights reserved.

Pilania, R. K., et al. (2020). "Letter to the editor." Journal of Paediatrics and Child Health **56**(2): 347-348.

Plaçais, L. and Q. Richier (2020). "COVID-19: Clinical, biological and radiological characteristics in adults, infants and pregnant women. An up-to-date review at the heart of the pandemic." Revue de Medecine Interne **41**(5): 308-318.

The spread of the new coronavirus SARS-CoV-2, discovered in China in January 2020, led to a pandemic as early as March 2020, forcing every health care system in the affected countries to adapt quickly. In order to better address this major health crisis, which has given rise to numerous scientific publications, we have synthesized the main original clinical studies to facilitate the day-to-day management of patients with COVID-19. We detail the early signs and progression of the disease as well as the different clinical forms, including extra-pulmonary, as known at the beginning of this pandemic. We focus on clinical, biological and CT markers predictive of severity or mortality. Finally, we discuss the impact of SARS-CoV-2 infection in populations suspected to be at high risk of severe forms. © 2020 Société Nationale Française de Médecine Interne (SNFMI)

Poli, P., et al. (2020). "Asymptomatic case of Covid-19 in an infant with cystic fibrosis." Journal of Cystic Fibrosis.

Pollaers, K., et al. (2020). "Pediatric Microlaryngoscopy and Bronchoscopy in the COVID-19 Era." JAMA otolaryngology head & neck surgery. **28**.
Importance: As an aerosol-generating procedure, traditional pediatric microlaryngoscopy and bronchoscopy techniques must be adapted in order to reduce the risk of transmission of severe acute respiratory syndrome coronavirus 2. Objective(s): To describe a modified technique for pediatric microlaryngoscopy and bronchoscopy for use in the COVID-19 era and present a case series of patients for whom the technique has been used. Design, Setting, and Participant(s): Observational case series of pediatric patients undergoing emergency or urgent airway procedures performed at a tertiary pediatric otolaryngology department in Australia. Procedures were completed between March 23 and April 9, 2020, with a median (range) follow-up of 24.5 (11-28) days. Exposures: Modified technique for microlaryngoscopy and bronchoscopy, minimizing aerosolization of respiratory tract secretions. Main Outcomes and Measures: The main outcome was the feasibility of technique, which was measured by ability to perform microlaryngoscopy and bronchoscopy with comparable success to the usual technique (ie, adequate examination of the patient for diagnostic procedures and ability to perform interventional procedures). Result(s): The technique was used successfully in 8 patients (median [range] age, 160 days [27 days to 2 years 6 months]); 5 patients were male, and 3 were female. Intervention was performed on 6 patients; 2 balloon dilations for subglottic stenosis, 2 injections of hyaluronic acid for type 1 clefts, and 2 cold-steel supraglottoplasties. No adverse events occurred. Conclusions and Relevance: In this case series, feasibility of a modified technique for pediatric microlaryngoscopy and bronchoscopy was demonstrated. By reconsidering the surgical approach in light of specific COVID-19 infection risks, this technique may be associated with reduced spread of aerosolized respiratory secretions perioperatively and intraoperatively, but the technique and patient outcomes require further study.

Prem, K., et al. (2020). "The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study." The Lancet Public Health **5**(5): e261-e270.
Background: In December, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, emerged in Wuhan, China. Since then, the city of Wuhan has taken unprecedented measures in response to the outbreak, including extended school and workplace closures. We aimed to estimate the effects of physical distancing measures on the progression of the COVID-19 epidemic, hoping to provide some insights for the rest of the world. Method(s): To examine how changes in population mixing have affected outbreak progression in Wuhan, we used synthetic location-specific contact patterns in Wuhan and adapted these in the presence of school closures, extended workplace closures, and a reduction in mixing in the general community. Using these matrices and the latest estimates of the epidemiological parameters of the Wuhan outbreak, we simulated the ongoing trajectory of an outbreak in Wuhan using an age-structured susceptible-exposed-infected-removed (SEIR) model for several

physical distancing measures. We fitted the latest estimates of epidemic parameters from a transmission model to data on local and internationally exported cases from Wuhan in an age-structured epidemic framework and investigated the age distribution of cases. We also simulated lifting of the control measures by allowing people to return to work in a phased-in way and looked at the effects of returning to work at different stages of the underlying outbreak (at the beginning of March or April). Finding(s): Our projections show that physical distancing measures were most effective if the staggered return to work was at the beginning of April; this reduced the median number of infections by more than 92% (IQR 66-97) and 24% (13-90) in mid-2020 and end-2020, respectively. There are benefits to sustaining these measures until April in terms of delaying and reducing the height of the peak, median epidemic size at end-2020, and affording health-care systems more time to expand and respond. However, the modelled effects of physical distancing measures vary by the duration of infectiousness and the role school children have in the epidemic. Interpretation(s): Restrictions on activities in Wuhan, if maintained until April, would probably help to delay the epidemic peak. Our projections suggest that premature and sudden lifting of interventions could lead to an earlier secondary peak, which could be flattened by relaxing the interventions gradually. However, there are limitations to our analysis, including large uncertainties around estimates of R<inf>0</inf> and the duration of infectiousness. Funding(s): Bill & Melinda Gates Foundation, National Institute for Health Research, Wellcome Trust, and Health Data Research UK. Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license

Promislow, D. E. L. (2020). "A geroscience perspective on COVID-19 mortality." Journals of Gerontology Series A Biological Sciences & Medical Sciences **17**: 17.
A novel coronavirus, SARS-CoV-2, emerged in December 2019, leading within a few months to a global pandemic. COVID-19, the disease caused by this highly contagious virus, can have serious health consequences, though risks of complications are highly age-dependent. Rates of hospitalization and death are less than 0.1% in children, but increase to 10% or more in older people. Moreover, at all ages, men are more likely than women to suffer serious consequences from COVID-19. These patterns are familiar to the geroscience community. The effects of age and sex on mortality rates from COVID-19 mirror the effects of aging on almost all major causes of mortality. These similarities are explored here, and underscore the need to consider the role of basic biological mechanisms of aging on potential treatment and outcomes of COVID-19.

Puertas, R. R. (2020). "ACE2 Activators for the Treatment of Covid 19 Patients." Journal of Medical Virology **07**: 07.
The paper of Cheng H. et al., describes an interesting hypothesis regarding the organ protective effects of ACE2 activation against the malignant effects of SARS-CoV-2 infection in humans, and describes interesting previous results reporting ACE2 higher levels in children, young people and women that is coincident with a lower morbidity and health problems associated to COVID19. In the present comment the treatment of COVID19 patients with ACE2 activators, such as diminazene aceturate (DIZE), which are currently used as antiparasitic drugs, is proposed. This article is protected by copyright. All rights reserved.

Qian, G., et al. (2020). "A COVID-19 Transmission within a family cluster by presymptomatic infectors in China." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **23**.
We report a COVID-19 family cluster caused by a presymptomatic case. There were 9 family members, including 8 laboratory-confirmed with COVID-19, and a 6-year-old child had no evidence of infection. Amongst the 8 patients, one adult and one 13-month-old infant were asymptomatic, one adult was diagnosed as having severe pneumonia. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America.

Qiu, H., et al. (2020). "Clinical and epidemiological features of 36 children with coronavirus disease 2019

(COVID-19) in Zhejiang, China: an observational cohort study." The Lancet Infectious Diseases. Background: Since December, 2019, an outbreak of coronavirus disease 2019 (COVID-19) has spread globally. Little is known about the epidemiological and clinical features of paediatric patients with COVID-19. Method(s): We retrospectively retrieved data for paediatric patients (aged 0-16 years) with confirmed COVID-19 from electronic medical records in three hospitals in Zhejiang, China. We recorded patients' epidemiological and clinical features. Finding(s): From Jan 17 to March 1, 2020, 36 children (mean age 8.3 [SD 3.5] years) were identified to be infected with severe acute respiratory syndrome coronavirus 2. The route of transmission was by close contact with family members (32 [89%]) or a history of exposure to the epidemic area (12 [33%]); eight (22%) patients had both exposures. 19 (53%) patients had moderate clinical type with pneumonia; 17 (47%) had mild clinical type and either were asymptomatic (ten [28%]) or had acute upper respiratory symptoms (seven [19%]). Common symptoms on admission were fever (13 [36%]) and dry cough (seven [19%]). Of those with fever, four (11%) had a body temperature of 38.5degreeC or higher, and nine (25%) had a body temperature of 37.5-38.5degreeC. Typical abnormal laboratory findings were elevated creatine kinase MB (11 [31%]), decreased lymphocytes (11 [31%]), leucopenia (seven [19%]), and elevated procalcitonin (six [17%]). Besides radiographic presentations, variables that were associated significantly with severity of COVID-19 were decreased lymphocytes, elevated body temperature, and high levels of procalcitonin, D-dimer, and creatine kinase MB. All children received interferon alfa by aerosolisation twice a day, 14 (39%) received lopinavir-ritonavir syrup twice a day, and six (17%) needed oxygen inhalation. Mean time in hospital was 14 (SD 3) days. By Feb 28, 2020, all patients were cured. Interpretation(s): Although all paediatric patients in our cohort had mild or moderate type of COVID-19, the large proportion of asymptomatic children indicates the difficulty in identifying paediatric patients who do not have clear epidemiological information, leading to a dangerous situation in community-acquired infections. Funding(s): Ningbo Clinical Research Center for Children's Health and Diseases, Ningbo Reproductive Medicine Centre, and Key Scientific and Technological Innovation Projects of Wenzhou. Copyright © 2020 Elsevier Ltd

Qiu, L., et al. (2020). "A Typical Case of Critically Ill Infant of Coronavirus Disease 2019 With Persistent Reduction of T Lymphocytes." The Pediatric infectious disease journal. **01**.
BACKGROUND: The outbreak of coronavirus disease 2019 (COVID-19) is becoming a global threat. However, our understanding of the clinical characteristics and treatment of critically ill pediatric patients and their ability of transmitting the coronavirus that causes COVID-19 still remains inadequate because only a handful pediatric cases of COVID-19 have been reported. METHOD(S): Epidemiology, clinical characteristics, treatment, laboratory data and follow-up information and the treatment of critically ill infant were recorded. RESULT(S): The infant had life-threatening clinical features including high fever, septic shock, recurrent apnea, petechiae and acute kidney injury and persistent declined CD3+, CD4+ and CD8+ T cells. The duration of nasopharyngeal virus shedding lasted for 49 days even with the administration of lopinavir/ritonavir for 8 days. The CD3+, CD4+ and CD8+ T cells was partially recovered 68 days post onset of the disease. Accumulating of effector memory CD4+ T cells (CD4+TEM) was observed among T-cell compartment. The nucleic acid tests and serum antibody for the severe acute respiratory syndrome coronavirus 2 of the infant's mother who kept intimate contact with the infant were negative despite no strict personal protection. CONCLUSION(S): The persistent reduction of CD4+ and CD8+ T cells was the typical feature of critically ill infant with COVID-19. CD4+ and CD8+ T cells might play a key role in aggravating COVID-19 and predicts a more critical course in children. The prolonged nasopharyngeal virus shedding was related with the severity of respiratory injury. The transmission of SARS-CoV-2 from infant (even very critical cases) to adult might be unlikely.

Quaedackers, J., et al. (2020). "Clinical and surgical consequences of the COVID-19 pandemic for patients with pediatric urological problems: Statement of the EAU guidelines panel for paediatric urology, March 30 2020." Journal of pediatric urology **09**: 09.

The COVID-19-pandemic forces hospitals to reorganize into a dual patient flow system. Healthcare professionals are forced to make decisions in patient prioritization throughout specialties. Most pediatric urology pathologies do not require immediate or urgent care, however, delay may compromise future renal function or fertility. Contact with patients and parents, either physical in safe conditions or by (video)telephone must continue. The Paediatric-Urology-Guidelines-panel of the EAU proposes recommendations on prioritization of care. Pediatric-Urology program directors must ensure education, safety and attention for mental health of staff. Upon resumption of care, adequate prioritization must ensure minimal impact on outcome.

Rahimi, F. and A. Talebi Bezmin Abadi (2020). "Practical Strategies Against the Novel Coronavirus and COVID-19-the Imminent Global Threat." Archives of Medical Research **27**: 27.
The last month of 2019 harbingered the emergence of a viral outbreak that is now a major public threat globally. COVID-19 was first diagnosed and confirmed in a couple of cases with unknown pneumonia; the patients lived in, or travelled to, Wuhan, the capital of China's Hubei province. People now face a complex challenge that deserves urgent intervention by all involved in medical healthcare globally. Conventional antiviral therapies or vaccines are the most referred means of tackling the virus, but we think establishing these ideal management strategies is presently far-fetched. In-house isolation or quarantine of suspected cases to keep hospital admissions manageable and prevent in-hospital spread of the virus, and promoting general awareness about transmission routes are the practical strategies used to tackle the spread of COVID-19. Cases with weakened or compromised immune systems-for example, elderly individuals, young children, and those with pre-existing conditions such as diabetes, cancer, hypertension, and chronic respiratory diseases-are particularly more susceptible to COVID-19. Hopefully, cumulative data using whole-genome sequencing of the SARS-CoV-2 genome in parallel with mathematical modeling will help the molecular biologists to understand unknown features of the pathogenesis and epidemiology of COVID-19.

Rahmanzade, R., et al. (2020). "Respiratory Distress in Postanesthesia Care Unit: First Presentation of Coronavirus Disease 2019 in a 17-Year-Old Girl: A Case Report." A&A Practice **14**(7): e01227.
A 17-year-old healthy girl underwent an uneventful esthetic septorhinoplasty. She was easily extubated and transferred to the postanesthesia care unit (PACU) with oxygen saturation (SpO2) of 96%. About 30 minutes after arrival in the PACU, she developed dyspnea with SpO2 of 84% and promptly received oxygen with bilevel positive airway pressure in conjunction with low-dose corticosteroid. The subsequent chest computed tomography (CT) revealed bilateral patchy infiltrates similar to the radiologic findings of Coronavirus Disease 2019 (COVID-19). Finally, a reverse transcriptase polymerase chain reaction (RT-PCR) of a pharyngeal specimen confirmed the diagnosis of COVID-19.

Ralph, R., et al. (2020). "2019-nCoV (Wuhan virus), a novel Coronavirus: Human-to-human transmission, travel-related cases, and vaccine readiness." Journal of Infection in Developing Countries **14**(1): 3-17.
On 31 December 2019 the Wuhan Health Commission reported a cluster of atypical pneumonia cases that was linked to a wet market in the city of Wuhan, China. The first patients began experiencing symptoms of illness in mid-December 2019. Clinical isolates were found to contain a novel coronavirus with similarity to bat coronaviruses. As of 28 January 2020, there are in excess of 4,500 laboratory-confirmed cases, with > 100 known deaths. As with the SARS-CoV, infections in children appear to be rare. Travel-related cases have been confirmed in multiple countries and regions outside mainland China including Germany, France, Thailand, Japan, South Korea, Vietnam, Canada, and the United States, as well as Hong Kong and Taiwan. Domestically in China, the virus has also been noted in several cities and provinces with cases in all but one provinence. While zoonotic transmission appears to be the original source of infections, the most alarming development is that human-to-human transmission is now prevelant. Of particular

concern is that many healthcare workers have been infected in the current epidemic. There are several critical clinical questions that need to be resolved, including how efficient is human-to-human transmission? What is the animal reservoir? Is there an intermediate animal reservoir? Do the vaccines generated to the SARS-CoV or MERS-CoV or their proteins offer protection against 2019-nCoV? We offer a research perspective on the next steps for the generation of vaccines. We also present data on the use of in silico docking in gaining insight into 2019-nCoV Spike-receptor binding to aid in therapeutic development. Diagnostic PCR protocols can be found at https://www.who.int/health-topics/coronavirus/laboratory-diagnostics-for-novel-coronavirus.

Rasmussen, S. A. and D. J. Jamieson (2020). "Coronavirus Disease 2019 (COVID-19) and Pregnancy: Responding to a Rapidly Evolving Situation." Obstetrics & Gynecology **135**(5): 999-1002.
As the world confronts coronavirus disease 2019 (COVID-19), an illness caused by yet another emerging pathogen (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), obstetric care providers are asking what this means for pregnant women. The global spread has been swift, and many key questions remain. The case-fatality rate for persons cared for in the United States and whether asymptomatic persons transmit the virus are examples of questions that need to be answered to inform public health control measures. There are also unanswered questions specific to pregnant women, such as whether pregnant women are more severely affected and whether intrauterine transmission occurs. Although guidelines for pregnant women from the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention have been rapidly developed based on the best available evidence, additional information is critically needed to inform key decisions, such as whether pregnant health care workers should receive special consideration, whether to temporarily separate infected mothers and their newborns, and whether it is safe for infected women to breastfeed. Some current recommendations are well supported, based largely on what we know from seasonal influenza: patients should avoid contact with ill persons, avoid touching their face, cover coughs and sneezes, wash hands frequently, disinfect contaminated surfaces, and stay home when sick. Prenatal clinics should ensure all pregnant women and their visitors are screened for fever and respiratory symptoms, and symptomatic women should be isolated from well women and required to wear a mask. As the situation with COVID-19 rapidly unfolds, it is critical that obstetricians keep up to date.

Rasmussen, S. A., et al. (2020). "Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know." American Journal of Obstetrics & Gynecology **222**(5): 415-426.
Coronavirus disease 2019 is an emerging disease with a rapid increase in cases and deaths since its first identification in Wuhan, China, in December 2019. Limited data are available about coronavirus disease 2019 during pregnancy; however, information on illnesses associated with other highly pathogenic coronaviruses (ie, severe acute respiratory syndrome and the Middle East respiratory syndrome) might provide insights into coronavirus disease 2019's effects during pregnancy. Coronaviruses cause illness ranging in severity from the common cold to severe respiratory illness and death. Currently the primary epidemiologic risk factors for coronavirus disease 2019 include travel from mainland China (especially Hubei Province) or close contact with infected individuals within 14 days of symptom onset. Data suggest an incubation period of ~5 days (range, 2-14 days). Average age of hospitalized patients has been 49-56 years, with a third to half with an underlying illness. Children have been rarely reported. Men were more frequent among hospitalized cases (54-73%). Frequent manifestations include fever, cough, myalgia, headache, and diarrhea. Abnormal testing includes abnormalities on chest radiographic imaging, lymphopenia, leukopenia, and thrombocytopenia. Initial reports suggest that acute respiratory distress syndrome develops in 17-29% of hospitalized patients. Overall case fatality rate appears to be ~1%; however, early data may overestimate this rate. In 2 reports describing 18 pregnancies with coronavirus disease 2019, all were infected in the third trimester, and clinical

findings were similar to those in nonpregnant adults. Fetal distress and preterm delivery were seen in some cases. All but 2 pregnancies were cesarean deliveries and no evidence of in utero transmission was seen. Data on severe acute respiratory syndrome and Middle East respiratory syndrome in pregnancy are sparse. For severe acute respiratory syndrome, the largest series of 12 pregnancies had a case-fatality rate of 25%. Complications included acute respiratory distress syndrome in 4, disseminated intravascular coagulopathy in 3, renal failure in 3, secondary bacterial pneumonia in 2, and sepsis in 2 patients. Mechanical ventilation was 3 times more likely among pregnant compared with nonpregnant women. Among 7 first-trimester infections, 4 ended in spontaneous abortion. Four of 5 women with severe acute respiratory syndrome after 24 weeks' gestation delivered preterm. For Middle East respiratory syndrome, there were 13 case reports in pregnant women, of which 2 were asymptomatic, identified as part of a contact investigation; 3 patients (23%) died. Two pregnancies ended in fetal demise and 2 were born preterm. No evidence of in utero transmission was seen in severe acute respiratory syndrome or Middle East respiratory syndrome. Currently no coronavirus-specific treatments have been approved by the US Food and Drug Administration. Because coronavirus disease 2019 might increase the risk for pregnancy complications, management should optimally be in a health care facility with close maternal and fetal monitoring. Principles of management of coronavirus disease 2019 in pregnancy include early isolation, aggressive infection control procedures, oxygen therapy, avoidance of fluid overload, consideration of empiric antibiotics (secondary to bacterial infection risk), laboratory testing for the virus and coinfection, fetal and uterine contraction monitoring, early mechanical ventilation for progressive respiratory failure, individualized delivery planning, and a team-based approach with multispecialty consultations. Information on coronavirus disease 2019 is increasing rapidly. Clinicians should continue to follow the Centers for Disease Control and Prevention website to stay up to date with the latest information (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html).

Ravikumar, N., et al. (2020). "Novel Coronavirus 2019 (2019-nCoV) Infection: Part I - Preparedness and Management in the Pediatric Intensive Care Unit in Resource-limited Settings." Indian Pediatrics **57**(4): 324-334.
First reported in China, the 2019 novel coronavirus has been spreading across the globe. Till 26 March, 2020, 416,686 cases have been diagnosed and 18,589 have died the world over. The coronavirus disease mainly starts with a respiratory illness and about 5-16% require intensive care management for acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Children account for about 1-2% of the total cases, and 6% of these fall under severe or critical category requiring pediatric intensive care unit (PICU) care. Diagnosis involves a combination of clinical and epidemiological features with laboratory confirmation. Preparedness strategies for managing this pandemic are the need of the hour, and involve setting up cohort ICUs with isolation rooms. Re-allocation of resources in managing this crisis involves careful planning, halting elective surgeries and training of healthcare workers. Strict adherence to infection control like personal protective equipment and disinfection is the key to contain the disease transmission. Although many therapies have been tried in various regions, there is a lack of strong evidence to recommend anti-virals or immunomodulatory drugs. Copyright © 2020, Indian Academy of Pediatrics.

Rawat, M., et al. (2020). "COVID-19 in Newborns and Infants-Low Risk of Severe Disease: Silver Lining or Dark Cloud?" American journal of perinatology. **07**.
One hundred years after the 1918 influenza pandemic, we now face another pandemic with the severe acute respiratory syndrome-novel coronavirus-2 (SARS-CoV-2). There is considerable variability in the incidence of infection and severe disease following exposure to SARS-CoV-2. Data from China and the United States suggest a low prevalence of neonates, infants, and children, with those affected not suffering from severe disease. In this article, we speculate different theories why this novel agent is sparing neonates, infants, and young children. The low severity of SARS-CoV-2 infection in this population is associated with a high incidence of

asymptomatic or mildly symptomatic infection making them efficient carriers. KEY POINTS: . There is a low prevalence of novel coronavirus disease in neonates, infants, and children.. . The fetal hemoglobin may play a protective role against coronavirus in neonates.. . Immature angiotensin converting enzyme (ACE2) interferes with coronavirus entry into the cells.. Copyright Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

Reynolds, S. D., et al. (2020). "Systemic Immunosuppressive Therapy for Inflammatory Skin Diseases in Children: Expert-Consensus-Based Guidance for Clinical Decision Making During the COVID-19 Pandemic." Pediatric Dermatology **22**: 22.
BACKGROUND/OBJECTIVES: The COVID-19 pandemic has raised questions about the approach to management of systemic immunosuppressive therapies for dermatologic indications in children. Given the absence of data to address concerns related to SARS-CoV-2 infection while on these agents in an evidence-based manner, a Pediatric Dermatology COVID-19 Response Task Force (PDCRTF) was assembled to offer time-sensitive guidance for clinicians.
METHODS: A survey was distributed to an expert panel of 37 pediatric dermatologists on the PDCRTF to assess expert opinion and current practice related to three primary domains of systemic therapy: initiation, continuation, and laboratory monitoring.
RESULTS: Nearly all respondents (97%) reported that the COVID-19 pandemic had impacted their decision to initiate immunosuppressive medications. The majority of pediatric dermatologists (87%) reported that they were pausing or reducing the frequency of laboratory monitoring for certain immunosuppressive medications. In asymptomatic patients, continuing therapy was the most popular choice across all medications queried. The majority agreed that patients on immunosuppressive medications who have a household exposure to COVID-19 or test positive for acute infection should temporarily discontinue systemic and biologic medications, with the exception of systemic steroids, which may require tapering.
CONCLUSIONS: The ultimate decision regarding initiation, continuation and laboratory monitoring of immunosuppressive therapy during the pandemic requires careful deliberation, consideration of the little evidence available, and discussion with families. Consideration of an individual's adherence to COVID-19 preventive measures, risk of exposure, and the potential severity if infected must be weighed against the dermatological disease, medication, and risks to the patient of tapering or discontinuing therapies.

Rohani, P., et al. (2020). "Persistent elevation of aspartate aminotransferase in a child after incomplete Kawasaki disease: A case report and literature review." BMC Pediatrics **20 (1) (no pagination)**(73).
Background: Interpretation of abnormalities in liver function tests, especially in asymptomatic children, is a common problem faced by clinicians. Isolated elevation of aspartate aminotransferase may further puzzle physicians. Macro-aspartate aminotransferase (AST) results from complexes AST produces with other plasma components, such as immunoglobulin. To our knowledge, this is the first report on a case of macro-AST-associated incomplete Kawasaki disease (KD). It is to make physicians aware of this benign condition and help to prevent extensive, unnecessary investigations and invasive workups. Case presentation: A 16-month old boy with a 7-day history of fever was admitted to our pediatric ward for pyrexia workup. After complete investigations, KD was confirmed by a pediatric rheumatologist. During his admission and serial follow-up tests, an isolated AST elevation was noted. Comprehensive tests were performed and using the polyethylene glycol (PEG) precipitation method, macro-AST was confirmed. The patient has been followed up for 3 years, and so far, the benign nature of this condition has been confirmed. Conclusion(s): Clinicians should consider testing for macro-AST when elevated AST is the only abnormal lab finding. Although an uncommon finding, macro-AST may be seen in both children and adults. There are many reasons for this phenomenon, including resolved acute hepatitis or in some cases, inflammatory bowel disease, hepatic malignancy, monoclonal gammapathy, celiac disease, or KD; however, it may be observed in asymptomatic healthy children as well. Using the PEG precipitation method, a definitive diagnosis can be made.

In none of these conditions does macro-AST have any prognostic significance. An appreciation of macro-AST may prevent the need for more invasive investigations to which patients may be unnecessarily subjected. It is important to recognize this condition as benign and assure patients that no specific treatment is required. Copyright © 2020 The Author(s).

Rosenthal, D. M., et al. (2020). "Impacts of COVID-19 on vulnerable children in temporary accommodation in the UK." The Lancet Public Health **5**(5): e241-e242.

Rossetti, E., et al. (2020). "Early Leukapheresis Depletion in an Ex-Premature with Severe Acute Respiratory Distress Syndrome Due to Bordetella Pertussis and Coronavirus Infection." Blood Purification: 1-3.
We describe a 2 weeks corrected gestational age infant admitted in pediatric intensive care unit (PICU) for severe acute respiratory distress syndrome (ARDS) associated to Bordetella pertussis and Coronavirus infection. He developed leukocytosis as soon as ARDS required intubation and aggressive mechanical ventilation: hence he underwent 3 early therapeutic leukapheresis treatments in order to avoid the worsening of related cardiopulmonary complications, according to recent literature on pertussis infection in infants. The infant was discharged from PICU healthy.

Rothan, H. A. and S. N. Byrareddy (2020). "The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak." Journal of Autoimmunity **109**: 102433.
Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin of COVID-19. Person-to-person transmission of COVID-19 infection led to the isolation of patients that were subsequently administered a variety of treatments. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. In this review, we highlights the symptoms, epidemiology, transmission, pathogenesis, phylogenetic analysis and future directions to control the spread of this fatal disease.

Rowley, A. H., et al. (2020). "A Protein Epitope Targeted by the Antibody Response to Kawasaki Disease." The Journal of infectious diseases. **13**.
BACKGROUND: Kawasaki disease (KD) is the leading cause of childhood acquired heart disease in developed nations and can result in coronary artery aneurysms and death. Clinical and epidemiologic features implicate an infectious cause, but specific antigenic targets of the disease are unknown. Peripheral blood plasmablasts are normally highly clonally diverse but the antibodies they encode are ~70% antigen-specific 1-2 weeks after infection. METHOD(S): We isolated single peripheral blood plasmablasts from children with KD at 1-3 weeks after onset and prepared 60 monoclonal antibodies (mAbs). We used the mAbs to identify their target antigens and assessed serologic response among KD patients and controls to specific antigen. RESULT(S): Thirty-two mAbs from 9 of 11 patients recognize antigen within intracytoplasmic inclusion bodies in ciliated bronchial epithelial cells of fatal cases. Five of these mAbs, from 3 patients with coronary aneurysms, recognize a specific peptide, which blocks binding to the inclusion bodies. Sera from 5/8 KD patients at day >8 after illness onset, compared with 0/17 infant controls ($p<0.01$), recognized the KD peptide antigen. CONCLUSION(S): These results identify a protein epitope targeted by the antibody response to KD and provide a means to elucidate the pathogenesis of this important worldwide pediatric problem.

Roy, N. B. A., et al. (2020). "Protecting vulnerable patients with inherited anaemias from unnecessary death during the COVID-19 pandemic." British journal of haematology. **24**.
With the developing COVID-19 pandemic, patients with inherited anaemias require specific advice regarding isolation and changes to usual treatment schedules. The National Haemoglobinopathy Panel (NHP) has issued guidance on the care of patients with sickle cell disease, thalassaemia, Diamond Blackfan anaemia (DBA), congenital dyserythropoietic anaemia (CDA), sideroblastic anaemia, pyruvate kinase deficiency and other red cell enzyme and membrane disorders. Cascading of accurate information for clinicians and patients is paramount to preventing adverse outcomes, such as patients who are at increased risk of fulminant bacterial infection due to their condition or its treatment erroneously self-isolating if their fever is mistakenly attributed to a viral cause, delaying potentially life-saving antibiotic therapy. Outpatient visits should be minimised for most patients, however some, such as first transcranial dopplers for children with sickle cell anaemia should not be delayed as known risk of stroke will outweigh the unknown risk from COVID-19 infection. Blood transfusion programmes should be continued, but specific changes to usual clinical pathways can be instituted to reduce risk of patient exposure to COVID-19, as well as contingency planning for possible reductions in blood available for transfusions. Bone marrow transplants for these disorders should be postponed until further notice. With the current lack of evidence on the risk and complications of COVID-19 infection in these patients, national data collection is ongoing to record outcomes and eventually to identify predictors of disease severity, particularly important if further waves of infection travel through the population. Copyright © 2020 British Society for Haematology and John Wiley & Sons Ltd.

Russell, T. W., et al. (2020). "Estimating the infection and case fatality ratio for coronavirus disease (COVID-19) using age-adjusted data from the outbreak on the Diamond Princess cruise ship, February 2020." Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin **25**(12): 03.
Adjusting for delay from confirmation to death, we estimated case and infection fatality ratios (CFR, IFR) for coronavirus disease (COVID-19) on the Diamond Princess ship as 2.6% (95% confidence interval (CI): 0.89-6.7) and 1.3% (95% CI: 0.38-3.6), respectively. Comparing deaths on board with expected deaths based on naive CFR estimates from China, we estimated CFR and IFR in China to be 1.2% (95% CI: 0.3-2.7) and 0.6% (95% CI: 0.2-1.3), respectively.

Sankar, J., et al. (2020). "COVID-19 in Children: Clinical Approach and Management." Indian Journal of Pediatrics.
COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major public health crisis threatening humanity at this point in time. Transmission of the infection occurs by inhalation of infected droplets or direct contact with soiled surfaces and fomites. It should be suspected in all symptomatic children who have undertaken international travel in the last 14 d, all hospitalized children with severe acute respiratory illness, and asymptomatic direct and high-risk contacts of a confirmed case. Clinical symptoms are similar to any acute respiratory viral infection with less pronounced nasal symptoms. Disease seems to be milder in children, but situation appears to be changing. Infants and young children had relatively more severe illness than older children. The case fatality rate is low in children. Diagnosis can be confirmed by Reverse transcriptase - Polymerase chain reaction (RT-PCR) on respiratory specimen (commonly nasopharyngeal and oropharyngeal swab). Rapid progress is being made to develop rapid diagnostic tests, which will help ramp up the capacity to test and also reduce the time to getting test results. Management is mainly supportive care. In severe pneumonia and critically ill children, trial of hydroxychloroquine or lopinavir/ritonavir should be considered. As per current policy, children with mild disease also need to be hospitalized; if this is not feasible, these children may be managed on ambulatory basis with strict home isolation. Pneumonia, severe disease and critical illness require admission and aggressive management for acute lung injury and shock and/or multiorgan dysfunction, if present. An early intubation is preferred over non-invasive ventilation or heated, humidified, high flow nasal cannula oxygen, as these may

generate aerosols increasing the risk of infection in health care personnel. To prevent post discharge dissemination of infection, home isolation for 1-2 wk may be advised. As of now, no vaccine or specific chemotherapeutic agents are approved for children. Copyright © 2020, Dr. K C Chaudhuri Foundation.

Sartor, Z. and B. Hess (2020). "Increasing the Signal-to-Noise Ratio: COVID-19 Clinical Synopsis for Outpatient Providers." Journal of Primary Care & Community Health **11**: 2150132720922957.
The novel coronavirus (SARS-CoV-2), which is the cause of coronavirus disease (COVID-19 formally 2019-nCoV), has received widespread attention from the medical community. Despite the rapid publication of research on the virus and the disease it causes, there is a lack of concise and relevant material to help busy medical providers navigate recognition and management of the disease in the ambulatory setting. This review article aims to bridge this gap by briefly reviewing the key points of the evaluation and treatment of patients with COVID-19 in the ambulatory clinic environment.

Schwartz, D. A. and A. Dhaliwal (2020). "INFECTIONS IN PREGNANCY WITH COVID-19 AND OTHER RESPIRATORY RNA VIRUS DISEASES ARE RARELY, IF EVER, TRANSMITTED TO THE FETUS: EXPERIENCES WITH CORONAVIRUSES, HPIV, hMPV RSV, AND INFLUENZA." Archives of pathology & laboratory medicine. **27**.
SARS-CoV-2, the agent of COVID-19, is similar to two other coronaviruses, SARS-CoV and MERS-CoV, in causing life-threatening maternal respiratory infections and systemic complications. Because of global concern for potential intrauterine transmission of SARS-CoV-2 from pregnant women to their infants, this report analyzes the effects on pregnancy of infections caused by SARS-CoV-2 and other respiratory RNA viruses, and examines the frequency of maternal-fetal transmission with SARS-CoV-2, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, respiratory syncytial virus (RSV), parainfluenza (HPIV) and metapneumovirus (hMPV). There have been no confirmed cases of intrauterine transmission reported with COVID-19 or any other coronavirus infections. Influenza virus, despite causing approximately one billion annual infections globally, has only a few cases of confirmed or suspected intrauterine fetal infections reported. RSV is in an unusual cause of illness among pregnant women, and with the exception of one premature infant with congenital pneumonia, no other cases of maternal-fetal infection are described. Parainfluenza virus and human metapneumovirus can produce symptomatic maternal infections but do not cause intrauterine fetal infection. In summary, it appears that the absence thus far of maternal-fetal transmission of the SARS-CoV-2 virus during the COVID-19 pandemic is similar to other coronaviruses, and is also consistent with the extreme rarity of suggested or confirmed cases of intrauterine transmission of other respiratory RNA viruses. This observation has important consequences for pregnant women as it appears that if intrauterine transmission of SARSCoV-2 does eventually occur, it will be a rare event. Potential mechanisms of fetal protection from maternal viral infections are also discussed.

Schwartz, D. A. and A. L. Graham (2020). "Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections." Viruses **12**(2): 10.
In early December 2019 a cluster of cases of pneumonia of unknown cause was identified in Wuhan, a city of 11 million persons in the People's Republic of China. Further investigation revealed these cases to result from infection with a newly identified coronavirus, termed the 2019-nCoV. The infection moved rapidly through China, spread to Thailand and Japan, extended into adjacent countries through infected persons travelling by air, eventually reaching multiple countries and continents. Similar to such other coronaviruses as those causing the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), the new coronavirus was reported to spread via natural aerosols from human-to-human. In the early stages of this epidemic the case fatality rate is estimated to be approximately 2%, with the

majority of deaths occurring in special populations. Unfortunately, there is limited experience with coronavirus infections during pregnancy, and it now appears certain that pregnant women have become infected during the present 2019-nCoV epidemic. In order to assess the potential of the Wuhan 2019-nCoV to cause maternal, fetal and neonatal morbidity and other poor obstetrical outcomes, this communication reviews the published data addressing the epidemiological and clinical effects of SARS, MERS, and other coronavirus infections on pregnant women and their infants. Recommendations are also made for the consideration of pregnant women in the design, clinical trials, and implementation of future 2019-nCoV vaccines.

Schwartz, D. A. and A. L. Graham (2020). "Potential maternal and infant outcomes from coronavirus 2019-NCOV (SARS-CoV-2) infecting pregnant women: Lessons from SARS, MERS, and other human coronavirus infections." Viruses **12 (2) (no pagination)**(194).
In early December 2019 a cluster of cases of pneumonia of unknown cause was identified in Wuhan, a city of 11 million persons in the People's Republic of China. Further investigation revealed these cases to result from infection with a newly identified coronavirus, initially termed 2019-nCoV and subsequently SARS-CoV-2. The infection moved rapidly through China, spread to Thailand and Japan, extended into adjacent countries through infected persons travelling by air, eventually reaching multiple countries and continents. Similar to such other coronaviruses as those causing the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), the new coronavirus was reported to spread via natural aerosols from human-to-human. In the early stages of this epidemic the case fatality rate is estimated to be approximately 2%, with the majority of deaths occurring in special populations. Unfortunately, there is limited experience with coronavirus infections during pregnancy, and it now appears certain that pregnant women have become infected during the present 2019-nCoV epidemic. In order to assess the potential of the Wuhan 2019-nCoV to cause maternal, fetal and neonatal morbidity and other poor obstetrical outcomes, this communication reviews the published data addressing the epidemiological and clinical effects of SARS, MERS, and other coronavirus infections on pregnant women and their infants. Recommendations are also made for the consideration of pregnant women in the design, clinical trials, and implementation of future 2019-nCoV vaccines.

Schwierzeck, V., et al. (2020). "First reported nosocomial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **27**.
BACKGROUND: Coronavirus disease 2019 (COVID-19) is a life-threatening respiratory condition caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was initially detected in China in December 2019. Currently, in Germany over 140,000 cases of COVID-19 are confirmed. Here we report a nosocomial outbreak of SARS-CoV-2 infections in the pediatric dialysis unit of the University Hospital of Munster (UHM). METHOD(S): Single-step real-time RT-PCR from nasopharyngeal swaps was used to diagnose the index patient and identify infected contacts. Epidemiological links were analyzed by patient interviews and chart reviews. In addition, each contact was assessed for exposure to the index case and monitored for clinical symptoms. Threshold cycle (Ct) values of all positive test results were compared between symptomatic and asymptomatic cases. RESULT(S): Forty-eight cases were involved in this nosocomial outbreak. Nine contact cases developed laboratory confirmed COVID-19 infections. Two SARS-CoV-2 positive cases remained clinically asymptomatic. Eleven cases reported flu-like symptoms without positive results. Ct values were significantly lower in cases presenting typical COVID-19 symptoms, suggesting high viral shedding (p =0.007). CONCLUSION(S): Person-to-person transmission was at the heart of a hospital outbreak of SARS-CoV-2 between healthcare workers (HCWs) and patients in the pediatric dialysis unit at the UHM. Semi quantitative real-time RT-PCR results suggest that individuals with high viral load pose a risk to

spread SARS-CoV-2 in the hospital setting. Our epidemiological observation highlights the need to develop strategies to trace and monitor SARS-CoV-2 infected HCWs in order to prevent COVID-19 outbreaks in the hospital setting. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Sederdahl, B. K. and J. V. Williams (2020). "Epidemiology and clinical characteristics of influenza C virus." Viruses **12 (1) (no pagination)**(89).
Influenza C virus (ICV) is a common yet under-recognized cause of acute respiratory illness. ICV seropositivity has been found to be as high as 90% by 7-10 years of age, suggesting that most people are exposed to ICV at least once during childhood. Due to difficulty detecting ICV by cell culture, epidemiologic studies of ICV likely have underestimated the burden of ICV infection and disease. Recent development of highly sensitive RT-PCR has facilitated epidemiologic studies that provide further insights into the prevalence, seasonality, and course of ICV infection. In this review, we summarize the epidemiology and clinical characteristics of ICV. Copyright © 2020 by the authors.

See, K. C., et al. (2020). "COVID-19: Four Paediatric Cases in Malaysia." International Journal of Infectious Diseases **94**: 125-127.
Objective: This is a brief report of 4 paediatric cases of COVID-19 infection in Malaysia Background: COVID-19, a coronavirus, first detected in Wuhan, China has now spread rapidly to over 60 countries and territories around the world, infecting more than 85000 individuals. As the case count amongst children is low, there is need to report COVID-19 in children to better understand the virus and the disease. Cases: In Malaysia, until end of February 2020, there were four COVID-19 paediatric cases with ages ranging from 20 months to 11 years. All four cases were likely to have contracted the virus in China. The children had no symptoms or mild flu-like illness. The cases were managed symptomatically. None required antiviral therapy. Discussion(s): There were 2 major issues regarding the care of infected children. Firstly, the quarantine of an infected child with a parent who tested negative was an ethical dilemma. Secondly, oropharyngeal and nasal swabs in children were at risk of false negative results. These issues have implications for infection control. Consequently, there is a need for clearer guidelines for child quarantine and testing methods in the management of COVID-19 in children. Copyright © 2020 The Author(s)

Shah, P. S., et al. (2020). "Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates." Acta Obstetricia et Gynecologica Scandinavica **99**(5): 565-568.

She, J., et al. (2020). "COVID-19 epidemic: Disease characteristics in children." Journal of Medical Virology **31**: 31.
In mid-December 2019, a disease caused by infection with severe acute respiratory syndrome coronavirus-2, which began in Wuhan, China, has spread throughout the country and many countries around the world. The number of children with coronavirus disease-2019 (COVID-19) has also increased significantly. Although information regarding the epidemiology of COVID-19 in children has accumulated, relevant comprehensive reports are lacking. The present article reviews the epidemiological characteristics of COVID-19 in children.

Shekerdemian, L. S., et al. (2020). "Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units." JAMA Pediatrics **11**: 11.
Importance: The recent and ongoing coronavirus disease 2019 (COVID-19) pandemic has taken an unprecedented toll on adults critically ill with COVID-19 infection. While there is evidence that the burden of COVID-19 infection in hospitalized children is lesser than in their adult counterparts, to date, there are only limited reports describing COVID-19 in pediatric intensive

care units (PICUs).

Objective: To provide an early description and characterization of COVID-19 infection in North American PICUs, focusing on mode of presentation, presence of comorbidities, severity of disease, therapeutic interventions, clinical trajectory, and early outcomes.

Design, Setting, and Participants: This cross-sectional study included children positive for COVID-19 admitted to 46 North American PICUs between March 14 and April 3, 2020. with follow-up to April 10, 2020.

Main Outcomes and Measures: Prehospital characteristics, clinical trajectory, and hospital outcomes of children admitted to PICUs with confirmed COVID-19 infection.

Results: Of the 48 children with COVID-19 admitted to participating PICUs, 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years. Forty patients (83%) had significant preexisting comorbidities; 35 (73%) presented with respiratory symptoms and 18 (38%) required invasive ventilation. Eleven patients (23%) had failure of 2 or more organ systems. Extracorporeal membrane oxygenation was required for 1 patient (2%). Targeted therapies were used in 28 patients (61%), with hydroxychloroquine being the most commonly used agent either alone (11 patients) or in combination (10 patients). At the completion of the follow-up period, 2 patients (4%) had died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving extracorporeal membrane oxygenation. The median (range) PICU and hospital lengths of stay for those who had been discharged were 5 (3-9) days and 7 (4-13) days, respectively.

Conclusions and Relevance: This early report describes the burden of COVID-19 infection in North American PICUs and confirms that severe illness in children is significant but far less frequent than in adults. Prehospital comorbidities appear to be an important factor in children. These preliminary observations provide an important platform for larger and more extensive studies of children with COVID-19 infection.

Shen, K., et al. (2020). "Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement." World Journal of Pediatrics **07**: 07.

Since the outbreak of 2019 novel coronavirus infection (2019-nCoV) in Wuhan City, China, by January 30, 2020, a total of 9692 confirmed cases and 15,238 suspected cases have been reported around 31 provinces or cities in China. Among the confirmed cases, 1527 were severe cases, 171 had recovered and been discharged at home, and 213 died. And among these cases, a total of 28 children aged from 1 month to 17 years have been reported in China. For standardizing prevention and management of 2019-nCoV infections in children, we called up an experts' committee to formulate this experts' consensus statement. This statement is based on the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition) (National Health Committee) and other previous diagnosis and treatment strategies for pediatric virus infections. The present consensus statement summarizes current strategies on diagnosis, treatment, and prevention of 2019-nCoV infection in children.

Shen, K. L. and Y. H. Yang (2020). "Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue." World Journal of Pediatrics **05**: 05.

Shen, K. L., et al. (2020). "Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition)." World Journal of Pediatrics **24**: 24.

In the early February, 2020, we called up an experts' committee with more than 30 Chinese experts from 11 national medical academic organizations to formulate the first edition of consensus statement on diagnosis, treatment and prevention of coronavirus disease 2019 (COVID-19) in children, which has been published in this journal. With accumulated experiences in the diagnosis and treatment of COVID-19 in children, we have updated the consensus statement and released the second edition recently. The current version in English is a condensed version of the second edition of consensus statement on diagnosis, treatment and

prevention of COVID-19 in children. In the current version, diagnosis and treatement criteria have been optimized, and early identification of severe and critical cases is highlighted. The early warning indicators for severe pediatric cases have been summarized which is utmost important for clinical practice. This version of experts consensus will be valuable for better prevention, diagnosis and treatment of COVID-19 in children worldwide.

Shen, Q., et al. (2020). "Novel coronavirus infection in children outside of Wuhan, China." Pediatric Pulmonology **55**(6): 1424-1429.
BACKGROUND: Since December 8, 2019, an epidemic of coronavirus disease 2019 (COVID-19) has spread rapidly, but information about children with COVID-19 is limited.
METHODS: This retrospective and the single-center study were done at the Public Health Clinic Center of Changsha, Hunan, China. We identified all hospitalized children diagnosed with COVID-19 between January 8, 2019 and February 19, 2020, in Changsha. Epidemiological and clinical data of these children were collected and analyzed. Outcomes were followed until February 26th, 2020.
RESULTS: By February 19, 2020, nine pediatric patients were identified as having 2019-nCoV infection in Changsha. Six children had a family exposure and could provide the exact dates of close contact with someone who was confirmed to have 2019-nCoV infection, among whom the median incubation period was 7.5 days. The initial symptoms of the nine children were mild, including fever (3/9), diarrhea (2/9), cough (1/9), and sore throat (1/9), two had no symptoms. Two of the enrolled patients showed small ground-glass opacity of chest computed tomography scan. As of February 26, six patients had a negative RT-PCR for 2019-nCoV and were discharged. The median time from exposure to a negative RT-PCR was 14 days.
CONCLUSIONS: The clinical symptoms of the new coronavirus infection in children were not typical and showed a less aggressive clinical course than teenage and adult patients. Children who have a familial clustering or have a family member with a definite diagnosis should be reported to ensure a timely diagnosis.

Shen, Q., et al. (2020). "Consensus recommendations for the care of children receiving chronic dialysis in association with the COVID-19 epidemic." Pediatric Nephrology **24**: 24.
Coronavirus disease 2019 (COVID-19) has rapidly spread not only in China but throughout the world. Children with kidney failure (chronic kidney disease (CKD) stage 5) are at significant risk for COVID-19. In turn, a set of recommendations for the prevention and control of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 in pediatric hemodialysis (HD) centers and in home peritoneal dialysis (PD) settings have been proposed. The recommendations are based on the epidemiological features of the SARS-CoV-2 virus and COVID-19 disease, susceptibility factors, and preventive and control strategies. These recommendations will be updated as new information regarding SARS-CoV-2 and COVID-19 becomes available.

Shi, Y., et al. (2020). "Coronary sequelae of Kawasaki disease treated with rotational atherectomy and drug coated balloon: A case report." Medicine (United States) **99**(1).
Introduction:Kawasaki disease (KD) is an acute vasculitis syndrome that mainly affects children and is the first cause of acquired heart disease. Coronary artery lesion is the most serious complication of KD. Only two previous studies have reported similar cases, but we reported patient was younger and had a longer follow-up.Patient concerns:We reported a case of coronary sequelae of KD treated with rotational atherectomy and drug coated balloon (DCB). During the week after surgery, the patient complained of a slight chest pain intermittently, but no longer appeared after that.Diagnosis:We diagnosed by electrocardiogram and angiography. Angiography showed that the anterior descending branch (LAD) proximal stenosis was 95%, the right coronary artery (RCA) middle stenosis was 99%, and the calcification was severe.Interventions:We treat the patient with rotational atherectomy using a 1.25mm burr, pre-dilatation of the stenosis lesion with a 3.5mm×15mm non-compliant balloon was achieved.

Then 3.5mm×15mm drug eluting balloon was inflated at 10atm for 60seconds.Outcomes:After the 6-month follow-up (from October 2018 to March 2019), the symptom of angina disappeared. Coronary angiography 6 months later showed no apparent progression of vessel narrowing.Conclusion:The present case suggests that rotational atherectomy followed by DCB dilation could be an alternative revascularization therapy of choice in coronary KD sequelae complicated with atherosclerosis. © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

Shi, Y., et al. (2020). "A quickly, effectively screening process of novel corona virus disease 2019 (COVID-19) in children in Shanghai, China." Annals of Translational Medicine **8 (5) (no pagination)**(241).
Background: A recent cluster of pneumonia cases in China was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report the screening and diagnosis of corona virus disease 2019 (COVID-19) in our hospital. Method(s): Developed a procedure for the identification of children cases with COVID-19 in outpatient and emergency department of our hospital, then we observed how this process works. Result(s): (I) There were 56 cases considered suspected cases, and 10 cases were confirmed as COVID-19. (II) Of the 10 confirmed COVID-19 cases admitted in our hospital, 5 were males and 5 were females, aged from 7 months to 11 years, the average age is 6.0+/-4.2 years, 6 cases were mild pneumonia, the others were upper respiratory tract infection. (III) We followed up 68 patients in isolation at home until symptoms disappeared. Non were missed in the patient's first visit. The sensitivity of this method is 100% and the specificity is 71.3%. Conclusion(s): Our screening process works well, and it is also necessary to establish a screening network in the hospital. Copyright © Annals of Translational Medicine. All rights reserved.

Shneider, A., et al. (2020). "Can melatonin reduce the severity of COVID-19 pandemic?" International Reviews of Immunology: 1-10.
The current COVID-19 pandemic is one of the most devastating events in recent history. The virus causes relatively minor damage to young, healthy populations, imposing life-threatening danger to the elderly and people with diseases of chronic inflammation. Therefore, if we could reduce the risk for vulnerable populations, it would make the COVID-19 pandemic more similar to other typical outbreaks. Children don't suffer from COVID-19 as much as their grandparents and have a much higher melatonin level. Bats are nocturnal animals possessing high levels of melatonin, which may contribute to their high anti-viral resistance. Viruses induce an explosion of inflammatory cytokines and reactive oxygen species, and melatonin is the best natural antioxidant that is lost with age. The programmed cell death coronaviruses cause, which can result in significant lung damage, is also inhibited by melatonin. Coronavirus causes inflammation in the lungs which requires inflammasome activity. Melatonin blocks these inflammasomes. General immunity is impaired by anxiety and sleep deprivation. Melatonin improves sleep habits, reduces anxiety and stimulates immunity. Fibrosis may be the most dangerous complication after COVID-19. Melatonin is known to prevent fibrosis. Mechanical ventilation may be necessary but yet imposes risks due to oxidative stress, which can be reduced by melatonin. Thus, by using the safe over-the-counter drug melatonin, we may be immediately able to prevent the development of severe disease symptoms in coronavirus patients, reduce the severity of their symptoms, and/or reduce the immuno-pathology of coronavirus infection on patients' health after the active phase of the infection is over.

Sieni, E., et al. (2020). "Favourable outcome of Coronavirus-19 in a 1-year-old girl with acute myeloid leukaemia and severe treatment-induced immunosuppression." British Journal of Haematology **05**: 05.
Since the beginning of coronavirus disease 2019 (COVID-19) pandemic outbreak, it has emerged that the clinical course and outcome of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is definitely more favourable in children than in adults.¹ Few cases of infection in children with cancer are described; also in these patients, except for one reported

case,² the disease was largely asymptomatic.³ Nevertheless, the management of COVID-19 in young patients with comorbidities, particularly cancer, remains a challenge for the clinician; further data are required to optimize the clinical approach to these cases.

Singh, T., et al. (2020). "Lessons from COVID-19 in children: Key hypotheses to guide preventative and therapeutic strategies." Clinical Infectious Diseases **08**: 08.
The current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), reveals a peculiar trend of milder disease and lower case fatality in children compared to adults. Consistent epidemiologic evidence of reduced severity of infection in children across different populations and countries suggests there are underlying biologic differences between children and adults that mediate differential disease pathogenesis. This presents a unique opportunity to learn about disease modifying host factors from pediatric populations. Our review summarizes the current knowledge of pediatric clinical disease, role in transmission, risks for severe disease, protective immunity, as well as novel therapies and vaccine trials for children. We then define key hypotheses and areas for future research that can use the pediatric model of disease, transmission, and immunity to develop preventive and therapeutic strategies for people of all age groups.

Sinha, I. P., et al. (2020). "COVID-19 infection in children." The Lancet Respiratory Medicine **8**(5): 446-447.

Smit, C., et al. (2020). "Chloroquine for SARS-CoV-2: Implications of Its Unique Pharmacokinetic and Safety Properties." Clinical Pharmacokinetics.
Since in vitro studies and a preliminary clinical report suggested the efficacy of chloroquine for COVID-19-associated pneumonia, there is increasing interest in this old antimalarial drug. In this article, we discuss the pharmacokinetics and safety of chloroquine that should be considered in light of use in SARS-CoV-2 infections. Chloroquine is well absorbed and distributes extensively resulting in a large volume of distribution with an apparent and terminal half-life of 1.6 days and 2 weeks, respectively. Chloroquine is metabolized by cytochrome P450 and renal clearance is responsible for one third of total clearance. The lack of reliable information on target concentrations or doses for COVID-19 implies that for both adults and children, doses that proved effective and safe in malaria should be considered, such as 'loading doses' in adults (30 mg/kg over 48 h) and children (70 mg/kg over 5 days), which reported good tolerability. Here, plasma concentrations were < 2.5 mumol/L, which is associated with (minor) toxicity. While the influence of renal dysfunction, critical illness, or obesity seems small, in critically ill patients, reduced absorption may be anticipated. Clinical experience has shown that chloroquine has a narrow safety margin, as three times the adult therapeutic dosage for malaria can be lethal when given as a single dose. Although infrequent, poisoning in children is extremely dangerous where one to two tablets can potentially be fatal. In conclusion, the pharmacokinetic and safety properties of chloroquine suggest that chloroquine can be used safely for an acute virus infection, under corrected QT monitoring, but also that the safety margin is small, particularly in children. Copyright © 2020, The Author(s).

Society of Pediatrics, C. M. A. and C. J. o. P. Editorial Board (2020). "[Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition)]." Zhonghua Erke Zazhi **58**(3): 169-174.

Song, F., et al. (2020). "Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia." Radiology **295**(1): 210-217.
BackgroundThe chest CT findings of patients with 2019 Novel Coronavirus (2019-nCoV) pneumonia have not previously been described in detail.PurposeTo investigate the clinical, laboratory, and imaging findings of emerging 2019-nCoV pneumonia in humans.Materials and

MethodsFifty-one patients (25 men and 26 women; age range 16-76 years) with laboratory-confirmed 2019-nCoV infection by using real-time reverse transcription polymerase chain reaction underwent thin-section CT. The imaging findings, clinical data, and laboratory data were evaluated. Results Fifty of 51 patients (98%) had a history of contact with individuals from the endemic center in Wuhan, China. Fever (49 of 51, 96%) and cough (24 of 51, 47%) were the most common symptoms. Most patients had a normal white blood cell count (37 of 51, 73%), neutrophil count (44 of 51, 86%), and either normal (17 of 51, 35%) or reduced (33 of 51, 65%) lymphocyte count. CT images showed pure ground-glass opacity (GGO) in 39 of 51 (77%) patients and GGO with reticular and/or interlobular septal thickening in 38 of 51 (75%) patients. GGO with consolidation was present in 30 of 51 (59%) patients, and pure consolidation was present in 28 of 51 (55%) patients. Forty-four of 51 (86%) patients had bilateral lung involvement, while 41 of 51 (80%) involved the posterior part of the lungs and 44 of 51 (86%) were peripheral. There were more consolidated lung lesions in patients 5 days or more from disease onset to CT scan versus 4 days or fewer (431 of 712 lesions vs 129 of 612 lesions; P < .001). Patients older than 50 years had more consolidated lung lesions than did those aged 50 years or younger (212 of 470 vs 198 of 854; P < .001). Follow-up CT in 13 patients showed improvement in seven (54%) patients and progression in four (31%) patients. Conclusion Patients with fever and/or cough and with conspicuous ground-glass opacity lesions in the peripheral and posterior lungs on CT images, combined with normal or decreased white blood cells and a history of epidemic exposure, are highly suspected of having 2019 Novel Coronavirus (2019-nCoV) pneumonia.© RSNA, 2020.

Song, R., et al. (2020). "Clinical and epidemiological features of COVID-19 family clusters in Beijing, China." Journal of Infection.
Background: Since its discovery, SARS-CoV-2 has been spread throughout China before becoming a global pandemic. In Beijing, family clusters are the main mode of human-human transmission accounting for 57.6% of the total confirmed cases. Method(s): We present the epidemiological and clinical features of the clusters of three large and one small families. Result(s): Our results revealed that SARS-CoV-2 is transmitted quickly through contact with index case, and a total of 22/24 infections were observed. Among those infected, 20/22 had mild symptoms and only two had moderate to severe clinical manifestations. Children in the families generally showed milder symptoms. The incubation period varied from 2 to 13 days, and the shedding of virus from the upper respiratory tract lasted from 5 to over 30 days. A prolonged period of virus shedding (>30 days) in upper respiratory tract was observed in 6/24 cases. Conclusion(s): SARS-CoV-2 is transmitted quickly in the form of family clusters. While the infection rate is high within the cluster, the disease manifestations, latent period, and virus shedding period varied greatly. We therefore recommend rigorously testing contacts even during the no-symptom phase and consider whether viral shedding has ceased before stopping isolation measures for an individual. Copyright © 2020 Elsevier Ltd

Song, W., et al. (2020). "Clinical features of pediatric patients with coronavirus disease (COVID-19)." Journal of Clinical Virology **127 (no pagination)**(104377).
Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has spread around the world, and reports of children with COVID-19 are increasing. Objective(s): To assess clinical profiles of pediatric COVID-19. Study design: A retrospective analysis was undertaken using clinical data of sixteen children (11 months-14 years) diagnosed with COVID-19 between January 1, 2020 and March 17, 2020 at Xiangyang Central Hospital, Hubei province, China. Result(s): All children had positive epidemiologic histories, 12 (12/16, 75 %) involving family units. The illnesses were either mild (5/16, 31.3 %) or ordinary (11/16, 68.8 %), presenting as follows: asymptomatic (8/16, 50 %), fever and/or cough (8/16, 50 %). Four asymptomatic patients (4/16, 25 %) in ordinary cases had chest computed tomography (CT) abnormalities. Leukocyte counts were normal in 14 cases(88 %), but 2 patients (12.5 %) had leukopenia, and 1 (6.3 %) was lymphopenic. There were 11 patients with chest CT abnormalities, some nodular, others

small patchy and others ground-glass opacities. In asymptomatic children, the median time to SRAS-CoV-2 nucleic acid test(NAT) positivity once exposed to a family member with confirmed infection was 15.5 days (range, 10-26 days). The median time to first NAT-negative conversion was 5.5 days (range, 1-23 days). Conclusion(s): COVID-19 in children of Xiangyang city is often family acquired and not serious, with favorable outcomes. Asymptomatic children can be diagnosed as pneumonia because of chest CT abnormalities. It is essential to actively screen this segment of the population. Copyright © 2020 Elsevier B.V.

Soni, P. R., et al. (2020). "A Comprehensive Update on Kawasaki Disease Vasculitis and Myocarditis." Current Rheumatology Reports **22**(2): 6.
PURPOSE OF THE REVIEW: Kawasaki disease (KD) is a childhood systemic vasculitis of unknown etiology that causes coronary artery aneurysms (CAA), and if left undiagnosed can result in long-term cardiovascular complications and adult cardiac disease. Up to 20% of KD children fail to respond to IVIG, the mainstay of therapy, highlighting the need for novel therapeutic strategies. Here we review the latest findings in the field regarding specific etiology, genetic associations, and advancements in treatment strategies to prevent coronary aneurysms.
RECENT FINDINGS: Recent discoveries using the Lactobacillus casei cell wall extract (LCWE)-induced KD vasculitis mouse model have accelerated the study of KD pathophysiology and have advanced treatment strategies including clinical trials for IL-1R antagonist, Anakinra. KD remains an elusive pediatric vasculitis syndrome and is the leading cause of acquired heart disease among children in the USA and developed countries. Advancements in combination treatment for refractory KD with further understanding of novel genetic risk factors serve as a solid foundation for future research endeavors in the field.

Stojanović, V., et al. (2020). "Kawasaki disease complicated with cerebral vasculitis and severe encephalitis." Annals of Indian Academy of Neurology **23**(2): 228-232.
We report a case of a 7-year-old boy with Kawasaki disease (KD) complicated with cerebral vasculitis and encephalitis. The patient was admitted with signs of encephalopathy, seizures, and coma. The diagnosis of KD was made on the 2nd day of hospitalization based on the clinical features (fever >5 days, maculopapular rash, nonpurulent conjunctivitis, fissured lips, and cervical adenopathy). Brain magnetic resonance imaging findings suggested cerebral vasculitis. Treatment with intravenous immunoglobulin was followed by mild improvement. After a single dose of immunoglobulin, pulse methylprednisolone therapy was started resulting in gradual improvement of consciousness and eventual complete motor and cognitive function recovery with regression of brain magnetic resonance lesions. KD can present with marked neurological symptomatology. Therefore, it should be considered in the differential diagnosis of encephalitis and encephalopathy etiologies in children. © 2006 - 2020 Annals of Indian Academy of Neurology Published by Wolters Kluwer - Medknow.

Stower, H. (2020). "Clinical and epidemiological characteristics of children with COVID-19." Nature Medicine **26**(4): 465.

Streng, A., et al. (2020). "COVID-19 in hospitalized children and adolescents: A systematic review on published case series (as of 31.03.2020) and first data from Germany. [German]." Monatsschrift fur Kinderheilkunde.
Background: The clinical knowledge about the course, complications and treatment of COVID-19 in children and adolescents is so far limited. Aim(s): This systematic review summarizes the current scientific evidence regarding the clinical presentation of COVID-19 in hospitalized children based on available case series from China. In addition, first data from a nationwide pediatric hospital survey conducted by the German Society for Pediatric Infectious Diseases (DGPI) are presented. Method(s): This study evaluated 12 case series from China with 6-2143 children infected with SARS-CoV-2, which were identified by a literature search in PubMed up to 31 March 2020. The database of the German nationwide DGPI COVID-19 survey was accessed on 6 April

2020. Result(s): The median patient age in the case series was between 2 and 7 years and 18-45% were infants <1 year of age. The duration of hospital stay was 5-20 days. Most commonly reported symptoms were fever and cough; in 40-100% of cases involvement of the lower respiratory tract was reported, usually confirmed by computed tomography (CT). Severe and critical courses of disease were reported in up to 8% of the children including 2 fatalities. So far the German DGPI COVID-19 survey reported 33 hospitalized children up to 6 April 2020, mostly with upper airway infections. Of these children, 45% were infants and 32% had an underlying medical condition. So far 3 children (9%) needed admission to an intensive care unit. Conclusion(s): COVID-19 in hospitalized children usually presented as an uncomplicated febrile upper airway infection or mild pneumonia. Severe cases or fatalities rarely occurred in children. Information on neonates and children with underlying chronic conditions as well as on therapeutic and preventive measures are urgently needed. Copyright © 2020, Der/die Autor(en).

Stumpfe, F. M., et al. (2020). "SARS-CoV-2 Infection in Pregnancy - a Review of the Current Literature and Possible Impact on Maternal and Neonatal Outcome." Geburtshilfe und Frauenheilkunde **80**(4): 380-390.
In December 2019, cases of pneumonia of unknown cause first started to appear in Wuhan in China; subsequently, a new coronavirus was soon identified as the cause of the illness, now known as Coronavirus Disease 2019 (COVID-19). Since then, infections have been confirmed worldwide in numerous countries, with the number of cases steadily rising. The aim of the present review is to provide an overview of the new severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) and, in particular, to deduce from it potential risks and complications for pregnant patients. For this purpose, the available literature on cases of infection in pregnancy during the SARS epidemic of 2002/2003, the MERS (Middle East respiratory syndrome) epidemic ongoing since 2012, as well as recent publications on cases infected with SARS-CoV-2 in pregnancy are reviewed and reported. Based on the literature available at the moment, it can be assumed that the clinical course of COVID-19 disease may be complicated by pregnancy which could be associated with a higher mortality rate. It may also be assumed at the moment that transmission from mother to child in utero is unlikely. Breastfeeding is possible once infection has been excluded or the disease declared cured. Copyright © 2020 Georg Thieme Verlag. All rights reserved.

Su, L., et al. (2020). "The different clinical characteristics of corona virus disease cases between children and their families in China - the character of children with COVID-19." Emerging Microbes & Infections **9**(1): 707-713.
This study aims to analyze the different clinical characteristics between children and their families infected with severe acute respiratory syndrome coronavirus 2. Clinical data from nine children and their 14 families were collected, including general status, clinical, laboratory test, and imaging characteristics. All the children were detected positive result after their families onset. Three children had fever (22.2%) or cough (11.2%) symptoms and six (66.7%) children had no symptom. Among the 14 adult patients, the major symptoms included fever (57.1%), cough (35.7%), chest tightness/pain (21.4%), fatigue (21.4%) and sore throat (7.1%). Nearly 70% of the patients had normal (71.4%) or decreased (28.6%) white blood cell counts, and 50% (7/14) had lymphocytopenia. There were 10 adults (71.4%) showed abnormal imaging. The main manifestations were pulmonary consolidation (70%), nodular shadow (50%), and ground glass opacity (50%). Five discharged children were admitted again because their stool showed positive result in SARS-CoV-2 PCR. COVID-19 in children is mainly caused by family transmission, and their symptoms are mild and prognosis is better than adult. However, their PCR result in stool showed longer time than their families. Because of the mild or asymptomatic clinical process, it is difficult to recognize early for pediatrician and public health staff.

Subspecialty Group of, E., et al. (2020). "[Recommendations on the identification and transfer of children with critical diabetes during the COVID-19 outbreak]." Zhongguo Dangdai Erke Zazhi **22**(4):

285-289.
Coronavirus disease 2019 (COVID-19) is the most serious public health problem in China. Children with diabetes are also among the population susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Traffic problems caused by epidemic prevention and control increase the difficulty in the management of children with severe diabetes. In order to control the spread of epidemic, children with mild diabetes are advised to be managed at home and in the community. However, how to treat children with severe diabetes effectively and safely during the outbreak of COVID-19 brings great challenges to primary doctors. The Subspecialty Group of Endocrinology and Metabolism, Society of Pediatrics, Chinese Medical Association and the Subspecialty Group of Endocrinology and Metabolism, Society of Pediatrics, Chinese Medical Doctor Association have developed the recommendations on the identification and transfer of children with critical diabetes during the COVID-19 outbreak, which provide a reference for primary doctors to quickly assess the severity of patient's condition and treat the illness accordingly, thus reducing the risk of referral infection and improving clinical prognosis.

Subspecialty Group of, H. and S. o. P. o. H. Oncology (2020). "[Standardized management guideline for pediatric wards of hematology and oncology during the epidemic of coronavirus disease 2019]." Zhongguo Dangdai Erke Zazhi **22**(3): 177-182.
With the spread of coronavirus disease 2019 (COVID-19) and growing knowledge of its diagnosis and treatment, it has been clear that children are also susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The children with hematological tumors are a special population with immunosuppression and special therapeutic characteristics. Here the management guideline for pediatric wards of hematology and oncology during COVID-19 epidemic is established based on the features of children with hematological tumors.

Sudo, D., et al. (2020). "Recurrent Kawasaki disease and cardiac complications: Nationwide surveys in Japan." Archives of Disease in Childhood **(no pagination)**(317238).
Introduction: Based on data obtained before high-dose (2 g/kg) intravenous immunoglobulin (IVIG) therapy prevailed in Japan, children with a history of Kawasaki disease (KD) were highly susceptible to disease recurrence and more likely to develop cardiac sequelae. We aimed to examine the epidemiological features of cardiac complications among patients with recurrent KD following the widespread use of high-dose IVIG therapy. Design(s): Two cohorts of patients with recurrent KD retrieved from Japanese nationwide surveys (previous cohort: 1989-1994; recent cohort: 2003-2012) were compared. Result(s): Of 1842 patients with recurrent KD in the recent cohort, 3.5% and 5.2% developed cardiac sequelae at the initial and second episodes, respectively, which were markedly decreased compared with those (>10%, respectively) in the previous cohort. Multivariate analyses showed that the risk factors for cardiac sequelae at the second episode were similar between the cohorts. Patients with recurrent KD in both cohorts were more likely to have coronary aneurysms at the second episode than at the initial episode. However, when patients with coronary aneurysms at the initial episode were excluded from analyses, the difference in the proportions of coronary aneurysms between KD episodes disappeared in the recent cohort. Residual rates of previously formed coronary aneurysms were similar between the cohorts (approximately 50%). Conclusion(s): This study suggests that KD recurrence is no longer a risk factor for developing cardiac complications, unless cardiac sequelae appear at the initial episode. However, residual rates of previously formed coronary aneurysms remain high. Therefore, the importance of carefully managing coronary aneurysms associated with KD remains unchanged. Copyright © Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

Sullivan, M., et al. (2020). "The COVID-19 pandemic: A rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global." Pediatric Blood & Cancer: e28409.
The COVID-19 pandemic is one of the most serious global challenges to delivering affordable and

equitable treatment to children with cancer we have witnessed in the last few decades. This Special Report aims to summarize general principles for continuing multidisciplinary care during the SARS-CoV-2 (COVID-19) pandemic. With contributions from the leadership of the International Society for Pediatric Oncology (SIOP), Children's Oncology Group (COG), St Jude Global program, and Childhood Cancer International, we have sought to provide a framework for healthcare teams caring for children with cancer during the pandemic. We anticipate the burden will fall particularly heavily on children, their families, and cancer services in low- and middle-income countries. Therefore, we have brought together the relevant clinical leads from SIOP Europe, COG, and SIOP-PODC (Pediatric Oncology in Developing Countries) to focus on the six most curable cancers that are part of the WHO Global Initiative in Childhood Cancer. We provide some practical advice for adapting diagnostic and treatment protocols for children with cancer during the pandemic, the measures taken to contain it (e.g., extreme social distancing), and how to prepare for the anticipated recovery period.

Sun, D., et al. (2020). "Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study." World Journal of Pediatrics.
Background: An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first detected in Wuhan, Hubei, China. People of all ages are susceptible to SARS-CoV-2 infection. No information on severe pediatric patients with COVID-19 has been reported. We aimed to describe the clinical features of severe pediatric patients with COVID-19. Method(s): We included eight severe or critically ill patients with COVID-19 who were treated at the Intensive Care Unit (ICU), Wuhan Children's Hospital from January 24 to February 24. We collected information including demographic data, symptoms, imaging data, laboratory findings, treatments and clinical outcomes of the patients with severe COVID-19. Result(s): The onset age of the eight patients ranged from 2 months to 15 years; six were boys. The most common symptoms were polypnea (8/8), followed by fever (6/8) and cough (6/8). Chest imaging showed multiple patch-like shadows in seven patients and ground-glass opacity in six. Laboratory findings revealed normal or increased whole blood counts (7/8), increased C-reactive protein, procalcitonin and lactate dehydrogenase (6/8), and abnormal liver function (4/8). Other findings included decreased CD16 + CD56 (4/8) and Th/Ts*(1/8), increased CD3 (2/8), CD4 (4/8) and CD8 (1/8), IL-6 (2/8), IL-10 (5/8) and IFN-gamma (2/8). Treatment modalities were focused on symptomatic and respiratory support. Two critically ill patients underwent invasive mechanical ventilation. Up to February 24, 2020, three patients remained under treatment in ICU, the other five recovered and were discharged home. Conclusion(s): In this series of severe pediatric patients in Wuhan, polypnea was the most common symptom, followed by fever and cough. Common imaging changes included multiple patch-like shadows and ground-glass opacity; and a cytokine storm was found in these patients, which appeared more serious in critically ill patients. Copyright © 2020, Children's Hospital, Zhejiang University School of Medicine.

Sun, K., et al. (2020). "Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study." The Lancet Digital Health **2**(4): e201-e208.
Background: As the outbreak of coronavirus disease 2019 (COVID-19) progresses, epidemiological data are needed to guide situational awareness and intervention strategies. Here we describe efforts to compile and disseminate epidemiological information on COVID-19 from news media and social networks. Methods: In this population-level observational study, we searched DXY.cn, a health-care-oriented social network that is currently streaming news reports on COVID-19 from local and national Chinese health agencies. We compiled a list of individual patients with COVID-19 and daily province-level case counts between Jan 13 and Jan 31, 2020, in China. We also compiled a list of internationally exported cases of COVID-19 from global news media sources (Kyodo News, The Straits Times, and CNN), national governments, and health authorities. We assessed trends in the epidemiology of COVID-19 and studied the outbreak progression across China, assessing delays between symptom onset, seeking care at a hospital or

clinic, and reporting, before and after Jan 18, 2020, as awareness of the outbreak increased. All data were made publicly available in real time. Findings: We collected data for 507 patients with COVID-19 reported between Jan 13 and Jan 31, 2020, including 364 from mainland China and 143 from outside of China. 281 (55%) patients were male and the median age was 46 years (IQR 35–60). Few patients (13 [3%]) were younger than 15 years and the age profile of Chinese patients adjusted for baseline demographics confirmed a deficit of infections among children. Across the analysed period, delays between symptom onset and seeking care at a hospital or clinic were longer in Hubei province than in other provinces in mainland China and internationally. In mainland China, these delays decreased from 5 days before Jan 18, 2020, to 2 days thereafter until Jan 31, 2020 (p=0·0009). Although our sample captures only 507 (5·2%) of 9826 patients with COVID-19 reported by official sources during the analysed period, our data align with an official report published by Chinese authorities on Jan 28, 2020. Interpretation: News reports and social media can help reconstruct the progression of an outbreak and provide detailed patient-level data in the context of a health emergency. The availability of a central physician-oriented social network facilitated the compilation of publicly available COVID-19 data in China. As the outbreak progresses, social media and news reports will probably capture a diminishing fraction of COVID-19 cases globally due to reporting fatigue and overwhelmed health-care systems. In the early stages of an outbreak, availability of public datasets is important to encourage analytical efforts by independent teams and provide robust evidence to guide interventions. Funding: Fogarty International Center, US National Institutes of Health.

Sun, W. W., et al. (2020). "Epidemiological characteristics of 2019 novel coronavirus family clustering in Zhejiang Province. [Chinese]." Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine] **54**: E027.

Objective: Family clusters of Novel coronavirus pneumonia in Zhejiang province were analyzed to provide epidemiological basis for disease control. Method(s): The data of family clusters occurred from January 20 to February 10 in Zhejiang Province were collected. Descriptive analysis was used to analyze the clinical symptoms and the serial interval between the subsequent cases and the index cases. Chi-square test was used to analyze the age distribution, gender distribution and the relationship between the subsequent cases and the index cases. Result(s): 391 cases including 148 family index cases, 189 subsequent cases and 54 asymptomatic infected cases. The clinical symptoms between family index cases and subsequent cases are similar, fever is the most common symptoms in the two groups 114 (77.03%) and 92 (48.68%) respectively, the cases with diarrhea symptoms accounted for the least proportion, which were 7 (4.73%) and 5 (2.65%). The serial interval between the family index cases and the subsequent cases [M (P(25), P(75))] was 3.00 (1.00, 6.00) days. Family secondary attack rate for subsequent cases and asymptomatic infected cases are 31.61% and 43.20% respectively, the family secondary attack rate of the spouses of the family index cases is 63.87%, and are higher than that of their children (30.53%), parents (28.37%) and other family members (20.93%), the difference was statistically significant. Conclusion(s): 2019 novel coronavirus has shorter serial interval and higher family secondary attack rate, the secondary attack rate of spouses is higher than other family members.

Sundaram, M., et al. (2020). "Novel Coronavirus 2019 (2019-nCoV) Infection: Part II - Respiratory Support in the Pediatric Intensive Care Unit in Resource-limited Settings." Indian Pediatrics **57**(4): 335-342.

The 2019-novel coronavirus predominantly affects the respiratory system with manifestations ranging from upper respiratory symptoms to full blown acute respiratory distress syndrome (ARDS). It is important to recognize the risk factors, categorize severity and provide early treatment. Use of high flow devices and non-invasive ventilation has been discouraged due to high chances of aerosol generation. Early intubation and mechanical ventilation areessential to prevent complications and worsening, especially in resource-limited settings with very few

centers having expertise to manage critical cases. Hydrophobic viral filter in the ventilator circuit minimizes chances of transmission of virus. Strategies to manage ARDS in COVID-19 include low tidal volume ventilation with liberal sedation-analgesia. At the same time, prevention of transmission of the virus to healthcare workers is extremely important in the intensive care setting dealing with severe cases and requiring procedures generating aerosol. We, herein, provide guidance on non-invasive respiratory support, intubation and management of ARDS in a child with COVID-19. Copyright © 2020, Indian Academy of Pediatrics.

Tan, R. M. R., et al. (2020). "Dynamic adaptation to COVID-19 in a Singapore paediatric emergency department." Emergency Medicine Journal **37**(5): 252-254.
Singapore was one of the earliest countries affected by the coronavirus disease 2019 (COVID-19) pandemic, with more laboratory-confirmed COVID-19 cases in early February 2020 than any other country outside China. This short report is a narrative review of our tertiary paediatric emergency department (ED) perspective and experience managing the evolving outbreak situation. Logistic considerations included the segregation of the ED into physically separate high-risk, intermediate-risk and low-risk areas, with risk-adapted use of personal protective equipment (PPE) for healthcare personnel in each ED area. Workflow considerations included the progressive introduction of outpatient COVID-19 testing in the ED for enhanced surveillance; adapting the admissions process particularly for high-risk and intermediate-risk cases; and the management of unwell accompanying adult caregivers. Manpower considerations included the reorganisation of medical manpower into modular teams to mitigate the risk of hospital transmission of COVID-19. Future plans for a tiered isolation facility should include structural modifications for the permanent isolation facility such as anterooms for PPE donning/doffing; replication of key ED functions in the tent facility such as a separate resuscitation room and portable X-ray room; and refresher PPE training. Dynamic reassessment of ED workflow processes, in conjunction with the hospital and national public health response, may help in managing this novel disease entity.

Tan, X., et al. (2020). "[Clinical features of children with SARS-CoV-2 infection: an analysis of 13 cases from Changsha, China]." Zhongguo Dangdai Erke Zazhi **22**(4): 294-298.
OBJECTIVE: To study the clinical features of children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
METHODS: A retrospective analysis was performed for the clinical data of 13 children with SARS-CoV-2 infection who hospitalized in a Changsha hospital.
RESULTS: All 13 children had the disease onset due to family aggregation. Of the 13 children, 2 had no symptoms, and the other 11 children had the clinical manifestations of fever, cough, pharyngeal discomfort, abdominal pain, diarrhea, convulsions, or vomiting. As for clinical typing, 7 had mild type, 5 had common type, and 1 had severe type. The median duration of fever was 2 days in 6 children. All 13 children had normal levels of peripheral blood lymphocyte counts, immunoglobulins, CD4, CD8, and interleukin-6. The median time to clearance of SARS-CoV-2 was 13 days in the nasopharyngeal swabs of the 13 children. Three children presented false negatives for RT-PCR of SARS-CoV-2. SARS-CoV-2 RNA remained detectable in stools for 12 days after the nasopharyngeal swab test yielded a negative result. Abnormal CT findings were observed in 6 children. All 13 children were cured and discharged and they were normal at 2 weeks after discharge.
CONCLUSIONS: Intra-family contact is the main transmission route of SARS-CoV-2 infection in children, and there is also a possibility of fecal-oral transmission. Mild and common types are the major clinical types in children with SARS-CoV-2 infection, and cytokine storm is not observed. Children with SARS-CoV-2 infection tend to have a good short-term prognosis, and follow-up is needed to observe their long-term prognosis. Multiple nucleic acid tests should be performed for patients with SARS-CoV-2 infection and their close contacts by multiple site sampling.

Tan, Y. P., et al. (2020). "Epidemiologic and clinical characteristics of 10 children with coronavirus disease

2019 in Changsha, China." Journal of Clinical Virology **127 (no pagination)**(104353).
Background: The outbreak of a new coronavirus, first reported in Wuhan, China, is spreading around the world. Information on the characteristics of children with Coronavirus Disease 2019 (COVID-19) is limited. Method(s): In this retrospective study, we recruited 10 children infected with SARS-COV-2 from January 27 to March 10, 2020, in Changsha, China. We report the epidemiological, clinical, laboratory, and high-resolution CT findings for these children. Qualitative descriptive analysis was used to describe the key results. Result(s): Ten children were included. Three were male and seven were female. Three were from Wuhan, Hubei Province, and seven were from Changsha. All had a history of close contact with adults with COVID-19 before the onset of disease. Clinical manifestations included fever in four cases, respiratory symptoms in three cases, febrile convulsions in one case, vomiting in one case, abdominal pain in one case, and asymptomatic infection in two cases. All the children tested positive for nucleic acid in throat swabs at admission. Stool swabs of three cases were positive for nucleic acid after several days of fever. In nine children, blood routine results were normal, whereas in one case the white blood cell count was elevated. In four cases, CT findings of the lungs showed light ground-glass opacities, one case showed changes similar to bronchopneumonia, and the remaining cases were normal. All were treated with symptomatic support without complications. Conclusion(s): Our findings indicate that intrafamily transmission may be the main form of transmission of COVID-19 in children, and persistent intestinal excretion of virus is another characteristic among children. The results of stool swab tests should be considered for discharge and release from isolation. Copyright © 2020 The Author(s)

Tang, A., et al. (2020). "Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China." Emerging Infectious Diseases **26**(6).
We report an asymptomatic child who was positive for a 2019 novel coronavirus by reverse transcription PCR in a stool specimen 17 days after the last virus exposure. The child was virus positive in stool specimens for at least an additional 9 days. Respiratory tract specimens were negative by reverse transcription PCR.

Tang, B., et al. (2020). "Adjuvant herbal therapy for targeting susceptibility genes to Kawasaki disease: An overview of epidemiology, pathogenesis, diagnosis and pharmacological treatment of Kawasaki disease." Phytomedicine **70**: 153208.
BACKGROUND: Kawasaki disease (KD) is a self-limiting acute systemic vasculitis occur mainly in infants and young children under 5 years old. Although the use of acetylsalicylic acid (AAS) in combination with intravenous immunoglobulin (IVIG) remains the standard therapy to KD, the etiology, genetic susceptibility genes and pathogenic factors of KD are still un-elucidated.
PURPOSE: Current obstacles in the treatment of KD include the lack of standard clinical and genetic markers for early diagnosis, possible severe side effect of AAS (Reye's syndrome), and the refractory KD cases with resistance to IVIG therapy, therefore, this review has focused on introducing the current advances in the identification of genetic susceptibility genes, environmental factors, diagnostic markers and adjuvant pharmacological intervention for KD.
RESULTS: With an overall update in the development of KD from different aspects, our current bioinformatics data has suggested CASP3, CD40 and TLR4 as the possible pathogenic factors or diagnostic markers of KD. Besides, a list of herbal medicines which may work as the adjunct therapy for KD via targeting different proposed molecular targets of KD have also been summarized.
CONCLUSION: With the aid of modern pharmacological research and technology, it is anticipated that novel therapeutic remedies, especially active herbal chemicals targeting precise clinical markers of KD could be developed for accurate diagnosis and treatment of the disease.

Tang, D., et al. (2020). "Prevention and control strategies for emergency, limited-term, and elective operations in pediatric surgery during the epidemic period of COVID-19." World Journal of Pediatric Surgery **3 (1) (no pagination)**(e000122).

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to more than 100 countries. Children approved to be susceptible to SARS-CoV-2 infection. Preventing and controlling the epidemic while ensuring orderly flows of pediatric surgery clinical work has proven to be a big challenge for both patients and clinicians during the epidemic. Based on the transmission characteristics of SARS-CoV-2 and the requirements for prevention and control of COVID-19, the authors proposed some concrete measures and practical strategies of managing emergency, limited-term, and elective pediatric surgeries during the epidemic period. Copyright © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Team, C.-N. I. R. S. (2020). "COVID-19, Australia: Epidemiology Report 7 (Reporting week ending 19:00 AEDT 14 March 2020)." Communicable Diseases Intelligence **44**: 19.
This is the seventh epidemiological report for coronavirus disease 2019 (COVID-19), reported in Australia as at 19:00 Australian Eastern Daylight Time [AEDT] 14 March 2020. It includes data on COVID-19 cases diagnosed in Australia, the international situation and a review of current evidence.

Terenziani, M., et al. (2020). "SARS-CoV-2 disease and children under treatment for cancer." Pediatric Blood & Cancer: e28346.

Tesarik, J. (2020). "After corona: there is life after the pandemic." Reproductive BioMedicine Online.
The current pandemic of Coronavirus Disease 2019 (COVID-19) has focused the attention of medical-care providers away from non-life-threatening diseases, including infertility. Although infertility does not jeopardize the physical survival of infertile couples, it does jeopardize their future quality of life. Human infertility can be caused by a number of factors, some of which are age-dependent, and their effects may become irreversible if appropriate measures are not taken in time to prevent irreversible childlessness. Accordingly, each case of infertility should be evaluated comprehensively to establish its position of priority. Assisted reproductive technology (ART) makes it possible to separate fertilization and pregnancy in time. Whereas pregnant women infected with coronavirus may have an increased risk of adverse neonatal outcomes, gametes do not transmit COVID-19. Thus, performing ovarian stimulation and fertilization without delay, freezing the resulting embryos and delaying embryo transfer until the end of the pandemic appears to be the best strategy at present. Copyright © 2020 Reproductive Healthcare Ltd.

Tezer, H. and T. Bedir Demirdag (2020). "Novel coronavirus disease (COVID-19) in children." Turkish Journal of Medical Sciences **50**(SI-1): 592-603.
Coronavirus disease (COVID-19) was firstly reported at the end of 2019. The disease rapidly spread all around the world in a few months and was declared a worldwide pandemic by WHO in March 2020. By April 9, there were 1,436,198 confirmed COVID-19 cases in the world, nearly with 6% mortality rate. This novel infectious disease causes respiratory tract illness that may generally occur as mild upper respiratory tract disease or pneumonia. In older patients and/or patients with underlying conditions, it may result in acute respiratory distress syndrome, multi organ failure and even death. According to the current literature, children account approximately for 1%-5% of diagnosed COVID-19 cases. Generally, COVID-19 seems to be a less severe disease for children than adults. Approximately 90% of pediatric patients are diagnosed as asymptomatic, mild, or moderate disease. However, up to 6.7% of cases may be severe. Severe illness is generally seen in patients smaller than 1 year of age and patients who have underlying disesases. The epidemiological and clinical patterns of COVID-19 and treatment approaches in pediatric patients still remain unclear although many pediatric reports are published. This review aims to summarize the current epidemics, clinical presentations, diagnosis, and treatment of COVID-19 in pediatric patients.

Tian, S., et al. (2020). "Characteristics of COVID-19 infection in Beijing." Journal of Infection **80**(4): 401-406.

BACKGROUND: Since the first case of a novel coronavirus (COVID-19) infection pneumonia was detected in Wuhan, China, a series of confirmed cases of the COVID-19 were found in Beijing. We analyzed the data of 262 confirmed cases to determine the clinical and epidemiological characteristics of COVID-19 in Beijing.

METHODS: We collected patients who were transferred by Beijing Emergency Medical Service to the designated hospitals. The information on demographic, epidemiological, clinical, laboratory test for the COVID-19 virus, diagnostic classification, cluster case and outcome were obtained. Furthermore we compared the characteristics between severe and common confirmed cases which including mild cases, no-pneumonia cases and asymptomatic cases, and we also compared the features between COVID-19 and 2003 SARS.

FINDINGS: By Feb 10, 2020, 262 patients were transferred from the hospitals across Beijing to the designated hospitals for special treatment of the COVID-19 infected by Beijing emergency medical service. Among of 262 patients, 46 (17.6%) were severe cases, 216 (82.4%) were common cases, which including 192 (73.3%) mild cases, 11(4.2%) non-pneumonia cases and 13 (5.0%) asymptomatic cases respectively. The median age of patients was 47.5 years old and 48.5% were male. 192 (73.3%) patients were residents of Beijing, 50 (26.0%) of which had been to Wuhan, 116 (60.4%) had close contact with confirmed cases, 21 (10.9%) had no contact history. The most common symptoms at the onset of illness were fever (82.1%), cough (45.8%), fatigue (26.3%), dyspnea (6.9%) and headache (6.5%). The median incubation period was 6.7 days, the interval time from between illness onset and seeing a doctor was 4.5 days. As of Feb 10, 17.2% patients have discharged and 81.7% patients remain in hospital in our study, the fatality of COVID-19 infection in Beijing was 0.9%.

INTERPRETATION: On the basis of this study, we provided the ratio of the COVID-19 infection on the severe cases to the mild, asymptomatic and non-pneumonia cases in Beijing. Population was generally susceptible, and with a relatively low fatality rate. The measures to prevent transmission was very successful at early stage, the next steps on the COVID-19 infection should be focused on early isolation of patients and quarantine for close contacts in families and communities in Beijing.

FUNDING: Beijing Municipal Science and Technology Commission and Ministry of Science and Technology.

Tian, Y., et al. (2020). "Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission." Alimentary Pharmacology & Therapeutics **51**(9): 843-851.

BACKGROUND: There is little published evidence on the gastrointestinal features of COVID-19.

AIMS: To report on the gastrointestinal manifestations and pathological findings of patients with COVID-19, and to discuss the possibility of faecal transmission.

METHODS: We have reviewed gastrointestinal features of, and faecal test results in, COVID-19 from case reports and retrospective clinical studies relating to the digestive system published since the outbreak.

RESULTS: With an incidence of 3% (1/41)-79% (159/201), gastrointestinal symptoms of COVID-19 included anorexia 39.9% (55/138)-50.2% (101/201), diarrhoea 2% (2/99)-49.5% (146/295), vomiting 3.6% (5/138)-66.7% (4/6), nausea 1% (1/99)-29.4% (59/201), abdominal pain 2.2% (3/138)-6.0% (12/201) and gastrointestinal bleeding 4% (2/52)-13.7% (10/73). Diarrhoea was the most common gastrointestinal symptom in children and adults, with a mean duration of 4.1 +/- 2.5 days, and was observed before and after diagnosis. Vomiting was more prominent in children. About 3.6% (5/138)-15.9% (32/201) of adult and 6.5% (2/31)-66.7% (4/6) of children patients presented vomiting. Adult and children patients can present with digestive symptoms in the absence of respiratory symptoms. The incidence of digestive manifestations was higher in the later than in the early stage of the epidemic, but no differences in digestive symptoms among different regions were found. Among the group of patients with a higher proportion of severe cases, the proportion of gastrointestinal symptoms in severe patients was higher than that in

nonsevere patients (anorexia 66.7% vs 30.4%; abdominal pain 8.3% vs 0%); while in the group of patients with a lower severe rate, the proportion with gastrointestinal symptoms was similar in severe and nonsevere cases (nausea and vomiting 6.9% vs 4.6%; diarrhoea 5.8% vs 3.5%). Angiotensin converting enzyme 2 and virus nucleocapsid protein were detected in gastrointestinal epithelial cells, and infectious virus particles were isolated from faeces. Faecal PCR testing was as accurate as respiratory specimen PCR detection. In 36% (5/14)-53% (39/73) faecal PCR became positive, 2-5 days later than sputum PCR positive. Faecal excretion persisted after sputum excretion in 23% (17/73)-82% (54/66) patients for 1-11 days.

CONCLUSIONS: Gastrointestinal symptoms are common in patients with COVID-19, and had an increased prevalence in the later stage of the recent epidemic in China. SARS-CoV-2 enters gastrointestinal epithelial cells, and the faeces of COVID-19 patients are potentially infectious.

Tirelli, F., et al. (2020). "One year in review: Kawasaki disease." Current Opinion in Rheumatology **32**(1): 15-20.

Purpose of review Kawasaki disease is a childhood vasculitis of unknown origin, whose major complication is the development of coronary artery aneurysms (CAA). The purpose of this review is to provide an overview on the most recent evidence on the pathogenesis, diagnosis and treatment options of Kawasaki disease summarizing the most relevant studies published in the last year.Recent findingsSeveral genetic polymorphisms leading to Kawasaki disease susceptibility have been identified, mostly related to immune system regulation; potential external triggers are being investigated by environmental epidemiology studies. A new diagnostic test based on trascriptomics has been tested with promising preliminary results. With regards to first-line treatments, the real effectiveness of high-dose aspirin remains a matter of debate. For refractory cases, the ones at the highest risk for developing CAA, promising results come from the use of biologic agents, especially TNF and IL-1 blockers.SummaryRecent literature has provided interesting insights on the various factors involved in the complex scenario behind the pathogenesis of Kawasaki disease, especially genetic ones. Novel diagnostic tests and new evidence on the use of biologic agents in Kawasaki disease are emerging, but further evidence is needed to permit early diagnosis and effective treatment of this condition.

Tolia, V. M., et al. (2020). "Preliminary Results of Initial Testing for Coronavirus (COVID-19) in the Emergency Department." The Western Journal of Emergency Medicine **03**: 27.

INTRODUCTION: On March 10, 2020, the World Health Organization declared a global pandemic due to widespread infection of the novel coronavirus 2019 (COVID-19). We report the preliminary results of a targeted program of COVID-19 infection testing in the ED in the first 10 days of its initiation at our institution.

METHODS: We conducted a review of prospectively collected data on all ED patients who had targeted testing for acute COVID-19 infection at two EDs during the initial 10 days of testing (March 10-19, 2020). During this initial period with limited resources, testing was targeted toward high-risk patients per Centers for Disease Control and Prevention guidelines. Data collected from patients who were tested included demographics, clinical characteristics, and test qualifying criteria. We present the data overall and by test results with descriptive statistics.

RESULTS: During the 10-day study period, the combined census of the study EDs was 2157 patient encounters. A total of 283 tests were ordered in the ED. The majority of patients were 18-64 years of age, male, non-Hispanic white, had an Emergency Severity Index score of three, did not have a fever, and were discharged from the ED. A total of 29 (10.2%) tested positive. Symptoms-based criteria most associated with COVID-19 were the most common criteria identified for testing (90.6%). All other criteria were reported in 5.51-43.0% of persons being tested. Having contact with a person under investigation was significantly more common in those who tested positive compared to those who tested negative (63% vs 24.5%, respectively). The majority of patients in both results groups had at least two qualifying criteria for testing (75.2%).

CONCLUSION: In this review of prospectively collected data on all ED patients who had targeted testing

for acute COVID-19 infection at two EDs in the first 10 days of testing, we found that 10.2% of those tested were identified as positive. The continued monitoring of testing and results will help providers understand how COVID-19 is progressing in the community.

Tong, Z. D., et al. (2020). "Potential Presymptomatic Transmission of SARS-CoV-2, Zhejiang Province, China, 2020." Emerging Infectious Diseases **26**(5): 1052-1054.
We report a 2-family cluster of persons infected with severe acute respiratory syndrome coronavirus 2 in the city of Zhoushan, Zhejiang Province, China, during January 2020. The infections resulted from contact with an infected but potentially presymptomatic traveler from the city of Wuhan in Hubei Province.

Trabacca, A. and L. Russo (2020). "Covid-19 and child disabilities: whom to protect and how." European journal of physical and rehabilitation medicine. **24**.

Tsai, Y. C., et al. (2020). "Antiviral Action of Tryptanthrin Isolated from Strobilanthes cusia Leaf against Human Coronavirus NL63." Biomolecules **10**(3): 27.
Strobilanthes cusia (Nees) Kuntze is a Chinese herbal medicine used in the treatment of respiratory virus infections. The methanol extract of S. cusia leaf contains chemical components such as beta-sitosterol, indirubin, tryptanthrin, betulin, indigodole A, and indigodole B that have diverse biological activities. However, the antiviral action of S. cusia leaf and its components against human coronavirus remains to be elucidated. Human coronavirus NL63 infection is frequent among immunocompromised individuals, young children, and in the elderly. This study investigated the anti-Human coronavirus NL63 (HCoV-NL63) activity of the methanol extract of S. cusia leaf and its major components. The methanol extract of S. cusia leaf effectively inhibited the cytopathic effect (CPE) and virus yield (IC₅₀ = 0.64 mug/mL) in HCoV-NL63-infected cells. Moreover, this extract potently inhibited the HCoV-NL63 infection in a concentration-dependent manner. Among the six components identified in the methanol extract of S. cusia leaf, tryptanthrin and indigodole B (5aR-ethyltryptanthrin) exhibited potent antiviral activity in reducing the CPE and progeny virus production. The IC₅₀ values against virus yield were 1.52 muM and 2.60 muM for tryptanthrin and indigodole B, respectively. Different modes of time-of-addition/removal assay indicated that tryptanthrin prevented the early and late stages of HCoV-NL63 replication, particularly by blocking viral RNA genome synthesis and papain-like protease 2 activity. Notably, tryptanthrin (IC₅₀ = 0.06 muM) and indigodole B (IC₅₀ = 2.09 muM) exhibited strong virucidal activity as well. This study identified tryptanthrin as the key active component of S. cusia leaf methanol extract that acted against HCoV-NL63 in a cell-type independent manner. The results specify that tryptanthrin possesses antiviral potential against HCoV-NL63 infection.

Tsou, P., et al. (2020). "Association between multiple respiratory viral infections and pediatric intensive care unit admission among infants with bronchiolitis." Archives de Pediatrie **27**(1): 39-44.
Background: It is unclear whether multiple respiratory viral infections are associated with more severe bronchiolitis requiring pediatric intensive care unit (PICU) admission. We aimed to identify the association between multiple respiratory viral infections and PICU admission among infants with bronchiolitis. Method(s): We performed a 1:1 case-control study enrolling previously healthy full-term infants (<=12 months) with bronchiolitis admitted to the PICU as cases and those to the general pediatric ward as controls from 2015 to 2017. Multiplex polymerase chain reaction (PCR) was used for detection of the respiratory viruses. We summarized the characteristics of infants admitted to the PICU and the general pediatric unit. Multivariable logistic regression analysis was used to fit the association between multiple respiratory viral infections (>=2 strains) and PICU admission. Result(s): A total of 135 infants admitted to the PICU were compared with 135 randomly selected control infants admitted to the general pediatric unit. The PICU patients were younger (median: 2.2 months, interquartile range: 1.3-4.2) than the general ward patients (median: 3.2 months, interquartile range: 1.6-6.4). Respiratory syncytial virus (74.1%),

rhinovirus (28.9%), and coronavirus (5.9%) were the most common viruses for bronchiolitis requiring PICU admission. Patients with bronchiolitis admitted to the PICU tended to have multiple viral infections compared with patients on the general ward (23.0% vs. 10.4%, P < 0.001). In the multivariable logistic regression analysis, bronchiolitis with multiple viral infections was associated with higher odds of PICU admission (adjusted odds ratio: 2.56, 95% confidence interval: 1.17-5.57, P = 0.02). Conclusion(s): Infants with multiviral bronchiolitis have higher odds of PICU admission compared with those with a single or nondetectable viral infection.

Tsuda, E., et al. (2020). "Cardiac Valvular Lesions due to Kawasaki Disease: A Japanese Nationwide Survey." Journal of Pediatrics **218**: 78-84.e72.
Objectives: To clarify the characteristics of valvular lesions after Kawasaki disease with a Japanese nationwide survey. Study design: Among 137 026 patients in the nationwide Japanese surveys between 2007 and 2016, 290 (0.2%) with valvular sequelae were investigated by questionnaires. Result(s): Among the 290 patients with valvular sequelae, mitral regurgitation (MR), tricuspid regurgitation, aortic regurgitation, and pulmonary regurgitation were present 1 month after the development of Kawasaki disease in 183 (63%), 112 (39%), 39 (13%), and 49 (17%) patients, respectively. The numbers of patients with MR during the acute phase and 1 year after developing Kawasaki disease were 208 (72%) and 95 (33%), respectively. MR improved significantly during the late period (P < .0001). Although aortic regurgitation and tricuspid regurgitation also improved significantly (P < .001), pulmonary regurgitation did not change. Ruptured mitral valves chordae tendineae occurred in 6 infants by 6 months of age, within 4 months after the onset of Kawasaki disease. Three patients needed mitral valve plasty, and 1 patient died of acute heart failure. Another 4-month-old girl died of an acute myocardial infarction with MR. In the acute phase, there was a significant difference in the MR severity between the intravenous immunoglobulin-responder group and the intravenous immunoglobulin-resistant group (P < .05). Conclusion(s): The inflammation caused by acute Kawasaki disease affects the function of the mitral valves. Most cases of MR improve with the alleviation of inflammation. Severe MR may have decreased with the development of treatment for acute vasculitis. However, ruptured mitral valves chordae tendineae rarely occurs in infants younger than 6 months old, within 4 months after Kawasaki disease.

Tummers, J., et al. (2020). "Coronaviruses and people with intellectual disability: an exploratory data analysis." Journal of Intellectual Disability Research.
Background: Corona virus disease 2019 (COVID-19) has been announced as a new coronavirus disease by the World Health Organization. At the time of writing this article (April 2020), the world is drastically influenced by the COVID-19. Recently, the COVID-19 Open Research Dataset (CORD-19) was published. For researchers on ID such as ourselves, it is of key interest to learn whether this open research dataset may be used to investigate the virus and its consequences for people with an ID. Method(s): From CORD-19, we identified full-text articles containing terms related to the ID care and applied a text mining technique, specifically the term frequency-inverse document frequency analysis in combination with K-means clustering. Result(s): Two hundred fifty-nine articles contained one or more of our specified terms related to ID. We were able to cluster these articles related to ID into five clusters on different topics, namely: mental health, viral diseases, diagnoses and treatments, maternal care and paediatrics, and genetics. Conclusion(s): The CORD-19 open research dataset consists of valuable information about not only COVID-19 disease but also ID and the relationship between them. We suggest researchers investigate literature-based discovery approaches on the CORD-19 and develop a new dataset that addresses the intersection of these two fields for further research.

Turkistani, K. A. (2020). "Precautions and recommendations for orthodontic settings during the COVID-19 outbreak: A review." American Journal of Orthodontics & Dentofacial Orthopedics **13**: 13.
Introduction: Coronavirus disease 2019 (COVID-19) is contagious disease caused by the SARS-CoV-2 virus. It emerged as a global pandemic early in 2020, affecting more than 2000 countries and territories. The infection is highly contagious with disease transmission reported from asymptomatic carriers, including children. It spreads through person-to-person contact, via aerosol and droplets. The practice of social distancing - maintaining a distance of 1 - 2 meters or 6 feet -- between people has been widely recommended to slow or halt the spread. This places orthodontists at high risk of acquiring and transmitting the infection. The objective of this review is to report to orthodontists on the emergence, epidemiology, risks, and precautions during disease crisis. This should help increase awareness, reinforce infection control and prevent cross-transmission within the orthodontic facility.
Methods: A comprehensive literature review of English and non-English articles was performed in March, 2020 using (CORD-19 2020) dataset, PubMed, MEDLINE, Scopus, and Google Scholar to search for infection control and disease transmission in orthodontics.
Results: This review emphasizes minimizing aerosol production and reinforcing strict infection control measures. Compliance with highest level of personal protection and restriction of treatment to emergency cases is recommended during the outbreak. Surface disinfection, adequate ventilation, and decontamination of instruments and supplies following the guidelines is required.
Conclusion: Reinforcing strict infection control measures and minimizing personal contact and aerosol production are keys to prevent contamination within the orthodontic settings. Although no cases of COVID-19 cross-transmission within a dental facility have been reported, the risk exists and the disease is still emerging. Further studies are required.

Turner, D., et al. (2020). "COVID-19 and Paediatric Inflammatory Bowel Diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto group of ESPGHAN." Journal of Pediatric Gastroenterology & Nutrition **31**: 31.
INTRODUCTION: With the current COVID-19 pandemic, concerns have been raised about the risk to children with inflammatory bowel diseases (IBD). We aimed to collate global experience and provide provisional guidance for managing paediatric IBD (PIBD) in the era of COVID-19.
METHODS: An electronic reporting system of children with IBD infected with SARS-CoV-2 has been circulated among 102 PIBD centres affiliated with the Porto and Interest-group of ESPGHAN. A survey has been completed by major PIBD centres in China and South-Korea to explore management during the pandemic. A third survey collected current practice of PIBD treatment. Finally guidance points for practice have been formulated and voted upon by 37 PIBD authors and Porto group members.
RESULTS: Eight PIBD children had COVID-19 globally, all with mild infection without needing hospitalization despite treatment with immunomodulators and/or biologics. No cases have been reported in China and South Korea but biologic treatment has been delayed in 79 children, of whom 17 (22%) had exacerbation of their IBD. Among the Porto group members, face-to-face appointments were often replaced by remote consultations but almost all did not change current IBD treatment. Ten guidance points for clinicians caring for PIBD patients in epidemic areas have been endorsed with consensus rate of 92-100%.
CONCLUSIONS: Preliminary data for PIBD patients during COVID-19 outbreak are reassuring. Standard IBD treatments including biologics should continue at present through the pandemic, especially in children who generally have more severe IBD course on one hand, and milder SARS-CoV-2 infection on the other.

Valk, S. J., et al. (2020). "Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review." Cochrane Database of Systematic Reviews **5**: CD013600.
BACKGROUND: Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a

potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required.

SEARCH METHODS: The protocol was pre-published with the Center for Open Science and can be accessed here: osf.io/dwf53 We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trials registries to identify ongoing studies and results of completed studies on 23 April 2020 for case-series, cohort, prospectively planned, and randomised controlled trials (RCTs).

SELECTION CRITERIA: We followed standard Cochrane methodology and performed all steps regarding study selection in duplicate by two independent review authors (in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group). We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of disease severity, age, gender or ethnicity. We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulins.

DATA COLLECTION AND ANALYSIS: We followed recommendations of the Cochrane Rapid Reviews Methods Group regarding data extraction and assessment. To assess bias in included studies, we used the assessment criteria tool for observational studies, provided by Cochrane Childhood Cancer. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events, and serious adverse events. MAIN RESULTS: We included eight studies (seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised. Overall risk of bias of the eight included studies was high, due to: study design; small number of participants; poor reporting within studies; and varied type of participants with different severities of disease, comorbidities, and types of previous or concurrent treatments, including antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support. We rated all outcomes as very low certainty, and we were unable to summarise numerical data in any meaningful way. As we identified case-series studies only, we reported results narratively. Effectiveness of convalescent plasma for people with COVID-19 The following reported outcomes could all be related to the underlying natural history of the disease or other concomitant treatment, rather than convalescent plasma. All-cause mortality at hospital discharge All studies reported mortality. All participants were alive at the end of the reporting period, but not all participants had been discharged from hospital by the end of the study (15 participants discharged, 6 still hospitalised, 11 unclear). Follow-up ranged from 3 days to 37 days post-transfusion. We do not know whether convalescent plasma therapy affects mortality (very low-certainty evidence). Improvement of clinical symptoms (assessed by respiratory support) Six studies, including 28 participants, reported the level of respiratory support required; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some participants. We do not know whether convalescent plasma improves clinical symptoms (very low-certainty evidence). Time to discharge from hospital Six studies reported time to discharge from hospital for at least some participants, which ranged from four to 35 days after convalescent plasma therapy. Admission on the intensive care unit (ICU) Six studies included patients who were critically ill. At final follow-up the majority of these patients were no longer on the ICU or no longer required mechanical ventilation. Length of stay on the ICU Only one study (1 participant) reported length of stay on the ICU. The individual was discharged from the ICU 11 days after plasma transfusion. Safety of convalescent plasma for people with COVID-19 Grade 3 or 4 adverse events The studies did not report the grade of adverse events after convalescent plasma transfusion. Two studies reported data relating to participants who had experienced adverse events, that were presumably grade 3 or 4. One case study reported a participant who had moderate fever (38.9 degreeC). Another study (3 participants) reported a case of severe anaphylactic shock. Four studies reported the absence of moderate or severe

adverse events (19 participants). We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence). Serious adverse events One study (3 participants) reported one serious adverse event. As described above, this individual had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether or not convalescent plasma therapy affec

van Boheemen, S., et al. (2020). "Retrospective Validation of a Metagenomic Sequencing Protocol for Combined Detection of RNA and DNA Viruses Using Respiratory Samples from Pediatric Patients." Journal of Molecular Diagnostics **22**(2): 196-207.
Viruses are the main cause of respiratory tract infections. Metagenomic next-generation sequencing (mNGS) enables unbiased detection of all potential pathogens. To apply mNGS in viral diagnostics, sensitive and simultaneous detection of RNA and DNA viruses is needed. Herein, were studied the performance of an in-house mNGS protocol for routine diagnostics of viral respiratory infections with potential for automated pan-pathogen detection. The sequencing protocol and bioinformatics analysis were designed and optimized, including exogenous internal controls. Subsequently, the protocol was retrospectively validated using 25 clinical respiratory samples. The developed protocol using Illumina NextSeq 500 sequencing showed high repeatability. Use of the National Center for Biotechnology Information's RefSeq database as opposed to the National Center for Biotechnology Information's nucleotide database led to enhanced specificity of classification of viral pathogens. A correlation was established between read counts and PCR cycle threshold value. Sensitivity of mNGS, compared with PCR, varied up to 83%, with specificity of 94%, dependent on the cutoff for defining positive mNGS results. Viral pathogens only detected by mNGS, not present in the routine diagnostic workflow, were influenza C, KI polyomavirus, cytomegalovirus, and enterovirus. Sensitivity and analytical specificity of this mNGS protocol were comparable to PCR and higher when considering off-PCR target viral pathogens. One single test detected all potential viral pathogens and simultaneously obtained detailed information on detected viruses.

Verdoni, L., et al. (2020). "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study." Lancet **13**: 13.
Background: The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic.
Methods: All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki- like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.
Findings: Group 1 comprised 19 patients (seven boys, 12 girls; aged 3.0 years [SD 2.5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7.5 years [SD 3.5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 vs group 2, 0.3 vs ten per month), mean age (3.0 vs 7.5 years), cardiac involvement (two of 19 vs six of ten), KDSS (zero of 19 vs five of ten), MAS (zero of 19 vs five of ten), and need for adjunctive steroid treatment (three of 19 vs eight of ten; all $p<0.01$).

Interpretation: In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic.
Funding: None.

Verma, S., et al. (2020). "Neonatal Intensive Care Unit Preparedness for the Novel Coronavirus Disease-2019 Pandemic: A New York City Hospital Perspective." Current Problems in Pediatric & Adolescent Health Care: 100795.
In January 2020, China reported a cluster of cases of pneumonia associated with a novel pathogenic coronavirus provisionally named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). Since then, Coronavirus Disease 2019 (COVID-19) has been reported in more than 180 countries with approximately 3 million known infections and more than 210,000 deaths attributed to this disease. The majority of confirmed COVID-19 cases have been reported in adults, especially older individuals with co-morbidities. Children have had a relatively lower rate and a less serious course of infection as reported in the literature to date. One of the most vulnerable pediatric patient populations is cared for in the neonatal intensive care unit. There is limited data on the effect of COVID-19 in fetal life, and among neonates after birth. Therefore there is an urgent need for proactive preparation, and planning to combat COVID-19, as well as to safeguard patients, their families, and healthcare personnel. This review article is based on the Centers for Disease Control and Prevention's (CDC) current recommendations for COVID-19 and its adaptation to our local resources. The aim of this article is to provide basic consolidated guidance and checklists to clinicians in the neonatal intensive care units in key aspects of preparation needed to counter exposure or infection with COVID-19. We anticipate that CDC will continue to update their guidelines regarding COVID-19 as the situation evolves, and we recommend monitoring CDC's updates for the most current information.

Verscheijden, L. F. M., et al. (2020). "Chloroquine dosing recommendations for pediatric COVID-19 supported by modeling and simulation." Clinical Pharmacology & Therapeutics **22**: 22.
As chloroquine (CHQ) is part of the Dutch Centre for Infectious Disease Control COVID-19 experimental treatment guideline, pediatric dosing guidelines are needed. Recent pediatric data suggest that existing WHO dosing guidelines for children with malaria are suboptimal. The aim of our study was to establish best-evidence to inform pediatric CHQ doses for children infected with COVID-19. A previously developed physiologically-based pharmacokinetic (PBPK) model for CHQ was used to simulate exposure in adults and children and verified against published pharmacokinetic data. The COVID-19 recommended adult dosage regimen of 44mg/kg total was tested in adults and children to evaluate the extent of variation in exposure. Based on differences in AUC_{0-70h} the optimal CHQ dose was determined in children of different ages compared to adults. Revised doses were re-introduced into the model to verify that overall CHQ exposure in each age band was within 5% of the predicted adult value. Simulations showed differences in drug exposure in children of different ages and adults when the same body-weight based dose is given. As such, we propose the following total cumulative doses: 35 mg/kg (CHQ base) for children 0-1 month, 47 mg/kg for 1-6 months, 55 mg/kg for 6 months-12 years and 44 mg/kg for adolescents and adults, not to exceed 3300 mg in any patient. Our study supports age-adjusted CHQ dosing in children with COVID-19 in order to avoid suboptimal or toxic doses. The knowledge-driven, model-informed dose selection paradigm can serve as a science-based alternative to recommend pediatric dosing when pediatric clinical trial data is absent.

Vetter, P., et al. (2020). "Clinical features of covid-19." BMJ **369**: m1470.

Victor, G. (2020). "COVID-19 admissions calculators: General population and paediatric cohort." Early

Human Development **145 (no pagination)**(105043).
The world is in the grip of pandemic COVID-19 (SARS-CoV-2). Children appear to be only mildly affected but for those countries that are still preparing for their first wave of infections, it is salutary to have some estimates with which to plan for eventual contingencies. These assessments would include acute hospital admission requirements, intensive care admissions and deaths per given population. It is also useful to have an estimate of how many paediatric admissions to expect per given population. However it is only very recently that paediatric epidemiological data has become available. This paper will create an interactive spreadsheet model to estimate population and paediatric admissions for a given population, with the author's country, Malta, as a worked example for both. Copyright © 2020 Elsevier B.V.

Wagner, K. D. (2020). "Addressing the Experience of Children and Adolescents During the COVID-19 Pandemic." The Journal of clinical psychiatry **81**(3).

Wampler Muskardin, T. L. (2020). "Intravenous Anakinra for Macrophage Activation Syndrome May Hold Lessons for Treatment of Cytokine Storm in the Setting of Coronavirus Disease 2019." ACR Open Rheumatology **08**: 08.
Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are increasingly recognized as being on a continuum of cytokine storm syndromes, with different initiating pathways culminating in cytotoxic dysfunction and uncontrolled activation and proliferation of T lymphocytes and macrophages. The activated immune cells produce large amounts of proinflammatory cytokines, including interleukin 1beta (IL)-1beta. Management depends on the recognized diagnosis. In the setting of a cytokine storm syndrome and infection, collaborative involvement of specialists, including infectious disease and rheumatology is ideal. Anakinra, a recombinant IL-1 receptor antagonist, has been used subcutaneously and intravenously in pediatric patients and is considered a first-line treatment for MAS and secondary HLH (sHLH) among many pediatric rheumatologists. Previous reports of anakinra used in adults for treatment of MAS or sHLH are limited to subcutaneous administration. In this issue, Moneagudo et al. present a series of adult patients with sHLH treated with intravenous anakinra, including patients in whom subcutaneous anakinra was insufficient. As the authors suggest, there is a potential therapeutic use for anakinra in sHLH or the cytokine storm syndrome triggered by COVID19. Trial design will be key, with the patient subpopulation, timing of intervention, and doses tested important.

Wan, S., et al. (2020). "Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients." British Journal of Haematology **189**(3): 428-437.
We explored the relationships between lymphocyte subsets, cytokines, pulmonary inflammation index (PII) and disease evolution in patients with (corona virus disease 2019) COVID-19. A total of 123 patients with COVID-19 were divided into mild and severe groups. Lymphocyte subsets and cytokines were detected on the first day of hospital admission and lung computed tomography results were quantified by PII. Difference analysis and correlation analysis were performed on the two groups. A total of 102 mild and 21 severe patients were included in the analysis. There were significant differences in cluster of differentiation 4 (CD4⁺ T), cluster of differentiation 8 (CD8⁺ T), interleukin 6 (IL-6), interleukin 10 (IL-10) and PII between the two groups. There were significant positive correlations between CD4⁺ T and CD8⁺ T, IL-6 and IL-10 in the mild group ($r^2 = 0.694$, $r^2 = 0.633$, respectively; $P < 0.01$). After 'five-in-one' treatment, all patients were discharged with the exception of the four who died. Higher survival rates occurred in the mild group and in those with IL-6 within normal values. CD4⁺ T, CD8⁺ T, IL-6, IL-10 and PII can be used as indicators of disease evolution, and the PII can be used as an independent indicator for disease progression of COVID-19.

Wang, D., et al. (2020). "Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**(4): E011.
Objective: To analyze the epidemiological history, clinical manifestations, treatment and the short-term prognosis of 31 cases of 2019 novel coronavirus(2019-nCoV) infection in children from six provinces (autonomous region) in northern China. Method(s): A retrospective analysis of the epidemiological history, clinical symptoms, signs, laboratory examinations, chest imaging, treatment and the short-term prognosis of 31 cases of 2019-nCoV was conducted. The patients were diagnosed between January 25th, 2020 and February 21st, 2020 in 21 hospitals in 17 cities of six provinces(autonomous region) of Shaanxi, Gansu, Ningxia, Hebei, Henan and Shandong. Result(s): The age of the 31 children with 2019-nCoV infection was 7 years and 1 month (6 months -17 years). Nine cases (29%) were imported cases. Other 21 cases (68%) had contact with confirmed infected adults. One case (3%) had contact with asymptomatic returnees from Wuhan. Among the 31 children, 28 patients (90%) were family cluster cases. The clinical types were asymptomatic type in 4 cases (13%), mild type in 13 cases (42%), and common type in 14 cases (45%). No severe or critical type existed. The most common symptom was fever (n=20, 65%), including 1 case of high fever, 9 cases of moderate fever, 10 cases of low fever. Fever lasted from 1 day to 9 days. The fever of fifteen cases lasted for <=3 d, while in other 5 cases lasted > 3 d. Other symptoms included cough (n=14, 45%), fatigue (n=3, 10%) and diarrhea (n=3, 9%). Pharyngalgia, runny nose, dizziness, headache and vomiting were rare. In the early stage, the total leukocytes count in peripheral blood decreased in 2 cases (6%), the lymphocytes count decreased in 2 cases (6%), and the platelet count increased in 2 cases (6%).Elevation of C-reactive protein (10%, 3/30), erythrocyte sedimentation rate(19%,4/21), procalcitonin(4%,1/28), liver enzyme(22%, 6/27) and muscle enzyme (15%, 4/27) occurred in different proportions. Renal function and blood glucose were normal. There were abnormal chest CT changes in 14 cases, including 9 cases with patchy ground glass opacities and nodules, mostly located in the lower lobe of both lungs near the pleural area. After receiving supportive treatment, the viral nucleic acid turned negative in 25 cases within 7-23 days. Among them, 24 children (77%) recovered and were discharged from hospital. No death occurred. Conclusion(s): In this case series, 2019-nCoV infections in children from six provinces (autonomous region) in northern China are mainly caused by close family contact. Clinical types are asymptomatic, mild and common types. Clinical manifestations and laboratory examination results are nonspecific. Close contact history of epidemiology, nucleic acid detection and chest imaging are important bases for diagnosis. After general treatment, the short-term prognosis is good.

Wang, D., et al. (2020). "[Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]." Zhonghua Erke Zazhi **58**(4): 269-274.
Objective: To analyze the epidemiological history, clinical manifestations, treatment and the short-term prognosis of 31 cases of 2019 novel coronavirus (2019-nCoV) infection in children from six provinces (autonomous region) in northern China.

Wang, G., et al. (2020). "Mitigate the effects of home confinement on children during the COVID-19 outbreak." The Lancet **395**(10228): 945-947.

Wang, H., et al. (2020). "Rehospitalization of a Recovered Coronavirus Disease 19 (COVID-19) Child With Positive Nucleic Acid Detection." The Pediatric infectious disease journal. **09**.
Since December 2019, novel coronavirus-infected pneumonia (coronavirus disease 19) occurred in Wuhan and rapidly spread throughout China and beyond. During this period, increasing of reports found that several recovered patients from different hospitals showed positive results of nucleic acid test again soon after discharge. However, little attention has been paid to recovered children. Herein, we reported a case of 8-year-old recovered child, who was rehospitalized again

because of unexplained fever.

Wang, J., et al. (2020). "SARS-CoV-2 infection with gastrointestinal symptoms as the first manifestation in a neonate. [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(3): 211-214.
Since December 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has occurred in Wuhan, Hubei Province, China. The infected cases were noted mostly in adults, but rarely reported in children, especially neonates. Most children with SARS-CoV-2 infection present mainly with respiratory symptoms, but less commonly with gastrointestinal symptoms, and tend to have mild clinical symptoms. A neonate with SARS-CoV-2 infection, who had vomiting and milk refusal as the first symptom, was recently admitted to Wuhan Children's Hospital. After two weeks of treatment, the patient recovered gradually and was discharged. Here, this case is reported to improve the understanding of SARS-CoV-2 infection in neonates.

Wang, J., et al. (2020). "[SARS-CoV-2 infection with gastrointestinal symptoms as the first manifestation in a neonate]." Zhongguo Dangdai Erke Zazhi **22**(3): 211-214.
Since December 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has occurred in Wuhan, Hubei Province, China. The infected cases were noted mostly in adults, but rarely reported in children, especially neonates. Most children with SARS-CoV-2 infection present mainly with respiratory symptoms, but less commonly with gastrointestinal symptoms, and tend to have mild clinical symptoms. A neonate with SARS-CoV-2 infection, who had vomiting and milk refusal as the first symptom, was recently admitted to Wuhan Children's Hospital. After two weeks of treatment, the patient recovered gradually and was discharged. Here, this case is reported to improve the understanding of SARS-CoV-2 infection in neonates.

Wang, L., et al. (2020). "The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China." European Respiratory Journal **55**(4): 04.

Wang, L., et al. (2020). "Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (First edition)." Annals of Translational Medicine **8 (3) (no pagination)**(47).
Since December 2019, there has been an outbreak of novel coronavirus (2019-nCoV) infection in China. Two cases of neonates with positive 2019-nCoV tests have been reported. Due to the immature immune system and the possibility of vertical transmission from mother to infant, neonates have become a high-risk group susceptible to 2019-nCoV, which emphasize a close cooperation from both perinatal and neonatal pediatrics. In neonatal intensive care unit (NICU), to prevent and control infection, there should be practical measures to ensure the optimal management of children potentially to be infected. According to the latest 2019-nCoV national management plan and the actual situation, the Chinese Neonatal 2019-nCoV expert working Group has put forward measures on the prevention and control of neonatal 2019-nCoV infection. Copyright © Annals of Translational Medicine. All rights reserved.

Wang, S., et al. (2020). "A case report of neonatal COVID-19 infection in China." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. **12**.
In December 2019, the 2019 novel coronavirus disease (COVID-19) caused by SARS-CoV-2 emerged in China and now has spread in many countries. Pregnant women are susceptible population of COVID-19 which are more likely to have complications and even progresse to severe illness. We report a case of neonatal COVID-19 infection in China with pharyngeal swabs tested positive by rRT-PCR assay 36 hours after birth. However, whether the case is a vertical transmission from mother to child remains to be confirmed. Copyright © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights

Wang, S., et al. (2020). "Sleep disturbances among medical workers during the outbreak of COVID-2019." Occupational medicine **06**.
BACKGROUND: The outbreak of Corona Virus Disease-2019 (COVID-19) has posed unprecedented pressure and threats to healthcare workers in Wuhan and the entire country. AIMS: To assess the effect of the COVID-19 outbreak on the sleep quality of healthcare workers in a children's healthcare centre in Wuhan. METHOD(S): A cross-sectional, anonymized, self-reported questionnaire survey was conducted at the Children's Healthcare Centre of Renmin Hospital, Wuhan University, Wuhan, China. The questionnaire consisted of three parts, including socio-demographic characteristics and COVID-19 epidemic-related factors, the Pittsburgh sleep quality index (PSQI), and Zung's self-rating anxiety scale (SAS) and self-rating depression scale (SDS). RESULT(S): In total, 47 out of 123 (38%) participants with PSQI scores > 7 were identified as having sleep disturbance. A logistic regression analysis showed that sleep disturbance was independently associated with being an only child (adjusted odds ratio (OR) and 95% confidence interval (CI) 3.40 (1.21-9.57), P < 0.05), exposure to COVID-19 patients (adjusted OR and 95% CI 2.97 (1.08-8.18), P < 0.05) and depression (adjusted OR and 95% CI 2.83 (1.10-7.27), P < 0.05). CONCLUSION(S): We observed that, during the outbreak of COVID-19, sleep disturbance was highly prevalent among paediatric healthcare workers, and sleep disturbance was independently associated with being an only child, exposure to COVID-19 patients and depression. Therefore, more mental health services are required for front-line paediatric healthcare workers in Wuhan. Copyright © The Author(s) 2020. Published by Oxford University Press on behalf of the Society of Occupational Medicine. All rights reserved. For Permissions, please email: journals.permissions@oup.com.

Wang, S. S., et al. (2020). "Experience of Clinical Management for Pregnant Women and Newborns with Novel Coronavirus Pneumonia in Tongji Hospital, China." Current medical science **40**(2): 285-289.
Based on the New Diagnosis and Treatment Scheme for Novel Coronavirus Infected Pneumonia (Trial Edition 5), combined with our current clinical treatment experience, we recently proposed a revision of the first edition of "Guidance for maternal and fetal management during pneumonia epidemics of novel coronavirus infection in the Wuhan Tongji Hospital". This article focused on the issues of greatest concern of pregnant women including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection diagnostic criteria, inspection precautions, drug treatment options, indications and methods of termination of pregnancy, postpartum fever, breastfeeding considerations, mode of mother-to-child transmission, neonatal isolation and advice on neonatal nursing, to provide valuable experience for better management of SARS-CoV-2 infection in pregnant women and newborns.

Wang, X. F., et al. (2020). "Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen. [Chinese]." Zhonghua er ke za zhi = Chinese journal of pediatrics **58**: E008.
Objective: To describe the characteristics of clinical manifestations and epidemiology of children with 2019 novel coronavirus (2019-nCoV) infection. Method(s): All 34 children with laboratory-confirmed 2019-nCoV infection by quantitative real-time reverse transcription-PCR through nasopharyngeal swab specimens were admitted to the Third People's Hospital of Shenzhen from January 19 to Febuary 7, 2020. Clinical data and epidemiological history of these patients were retrospectively collected and analyzed. Result(s): Among the 34 cases, 14 were males, and 20 were females. The median age was 8 years and 11 months. No patients had underlying diseases. There were 28 children (82%) related with a family cluster outbreak. There were 26 children (76%) with a travel or residence history in Hubei Province. These patients could be categorized into different clinical types, including 22 (65%) common cases, 9 (26%) mild cases and 3 (8.8%) asymptomatic cases. No severe or critical cases were identified. The most

common symptoms were fever (17 cases, 50%) and cough (13 cases, 38%). In the 34 cases, the white blood cell counts of 28 cases (82%) were normal. Five cases had white blood cell counts more than 10x10(9)/L. One case had white blood cell counts less than 4x10(9)/L. Neutropenia and lymphopenia was found in one case, respectively. C-reactive protein levels and erythrocyte sedimentation rates were elevated in 1 and 5 case, respectively. Elevated procalcitonin was found in 1 case and D-Dimer in 3 cases. The levels of lactic dehydrogenase (LDH) were more than 400 U/L in 10 cases. The CT images of these patients showed bilateral multiple patchy or nodular ground-glass opacities and/or infiltrating shadows in middle and outer zone of the lung or under the pleura. Twenty patients were treated with lopinavir and ritonavir. Glucocorticoids and immunoglobulin were not used in any cases. All the cases improved and were discharged from hospital. Further following up was need. Conclusion(s): The clinical manifestations in children with 2019-nCoV infection are non-specific and are milder than that in adults. Chest CT scanning is heplful for early diagnosis. Children's infection is mainly caused by family cluster outbreak and imported cases. Family daily prevention is the main way to prevent 2019-nCoV infection.

Wang, Y., et al. (2020). "Discovery of a subgenotype of human coronavirus NL63 associated with severe lower respiratory tract infection in China, 2018." Emerging Microbes and Infections **9**(1): 246-255.

Human coronavirus NL63 (HCoV-NL63) is primarily associated with common cold in children, elderly and immunocompromised individuals. Outbreaks caused by HCoV-NL63 are rare. Here we report a cluster of HCoV-NL63 cases with severe lower respiratory tract infection that arose in Guangzhou, China, in 2018. Twenty-three hospitalized children were confirmed to be HCoV-NL63 positive, and most of whom were hospitalized with severe pneumonia or acute bronchitis. Whole genomes of HCoV-NL63 were obtained using next-generation sequencing. Phylogenetic and single amino acid polymorphism analyses showed that this outbreak was associated with two subgenotypes (C3 and B) of HCoV-NL63. Half of patients were identified to be related to a new subgenotype C3. One unique amino acid mutation at I507 L in spike protein receptor binding domain (RBD) was detected, which segregated this subgenotype C3 from other known subgenotypes. Pseudotyped virus bearing the I507 L mutation in RBD showed enhanced entry into host cells as compared to the prototype virus. This study proved that HCoV-NL63 was undergoing continuous mutation and has the potential to cause severe lower respiratory disease in humans.

Wang, Y., et al. (2020). "Oral Health Management of Children during the Epidemic Period of Coronavirus Disease 2019. [Chinese]." Sichuan da xue xue bao **Yi xue ban = Journal of Sichuan University. Medical science edition. 51**(2): 151-154.

Coronavirus disease 2019 (COVID-19) is becoming a major public health event affecting China and even the whole world. During the epidemic period of corona virus disease, appropriate oral health management and disease prevention of children is very important for children's oral and general health. In order to prevent the occurrence of cross-infection and epidemic spreading of COVID-19 during dental practice, the recommendations to parents include: not only training children to maintain hand hygiene at home, exercise appropriately, strengthen physical resistance, but also helping children develop good oral and diet habit such as effective brushing and flossing to avoid oral diseases and emergency. If non-emergency oral situation occur, parents could assist their child to take home based care such as rinsing to relieve the symptoms. When oral emergencies such as acute pulpitis, periapical periodontitis, dental trauma, oral and maxillofacial infections happen, parents and children should visit dental clinic in time with correct personal protection. During the epidemic period, children's oral emergencies should be treated in accordance with current guidelines and control of COVID-19.

Wang, Y., et al. (2020). "[Oral Health Management of Children during the Epidemic Period of Coronavirus Disease 2019]." Sichuan da Xue Xue Bao. Yi Xue Ban/Journal of Sichuan University. Medical Science Edition **51**(2): 151-154.
Coronavirus disease 2019 (COVID-19) is becoming a major public health event affecting China and even the whole world. During the epidemic period of corona virus disease, appropriate oral health management and disease prevention of children is very important for children's oral and general health. In order to prevent the occurrence of cross-infection and epidemic spreading of COVID-19 during dental practice, the recommendations to parents include: not only training children to maintain hand hygiene at home, exercise appropriately, strengthen physical resistance, but also helping children develop good oral and diet habit such as effective brushing and flossing to avoid oral diseases and emergency. If non-emergency oral situation occur, parents could assist their child to take home based care such as rinsing to relieve the symptoms. When oral emergencies such as acute pulpitis, periapical periodontitis, dental trauma, oral and maxillofacial infections happen, parents and children should visit dental clinic in time with correct personal protection. During the epidemic period, children's oral emergencies should be treated in accordance with current guidelines and control of COVID-19.

Wang, Y., et al. (2020). "The Risk of Children Hospitalized With Severe COVID-19 in Wuhan." The Pediatric infectious disease journal. **06**.
BACKGROUND: Novel coronavirus disease (COVID-19) is spreading globally. Little is known about the risk factors for the clinical outcomes of COVID-19 in children. METHOD(S): A retrospective case-control study was taken in children with severe acute respiratory syndrome coronary virus-2 infection in Wuhan Children's Hospital. Risk factors associated with the development of COVID-19 and progression were collected and analyzed. RESULT(S): Eight out of 260 children diagnosed with severe COVID-19 pneumonia were included in the study. Thirty-five children with COVID-19 infection matched for age, sex and date of admission, and who classified as non-severe type, were randomly selected from the hospital admissions. For cases with severe pneumonia caused by COVID-19, the most common symptoms were dyspnea (87.5%), fever (62.5%) and cough (62.5%). In laboratory, white blood cells count was significantly higher in severe children than non-severe children. Levels of inflammation bio-makers such as hsCRP, IL-6, IL-10 and D-dimer elevated in severe children compared with non-severe children on admission. The level of total bilirubin and uric acid clearly elevated in severe children compared with non-severe children on admission. All of severe children displayed the lesions on chest CT, more lung segments were involved in severe children than in non-severe children, which was only risk factor associated with severe COVID-19 pneumonia in multivariable analysis. CONCLUSION(S): More than 3 lung segments involved were associated with greater risk of development of severe COVID-19 in children. Moreover, the possible risk of the elevation of IL-6, high total bilirubin and D-dimer with univariable analysis could identify patients to be severe earlier.

Wang, Y. and L. Q. Zhu (2020). "Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019." World Journal of Pediatrics **12**: 12.

Weinkove, R., et al. (2020). "Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance." Medical Journal of Australia **13**: 13.
INTRODUCTION: A pandemic coronavirus, SARS-CoV-2, causes COVID-19, a potentially life-threatening respiratory disease. Patients with cancer may have compromised immunity due to their malignancy and/or treatment, and may be at elevated risk of severe COVID-19. Community transmission of COVID-19 could overwhelm health care services, compromising delivery of cancer care. This interim consensus guidance provides advice for clinicians managing patients with cancer during the pandemic.
MAIN RECOMMENDATIONS: During the COVID-19 pandemic: In patients with cancer with fever and/or respiratory symptoms, consider causes in addition to COVID-19, including other infections and therapy-related pneumonitis. For suspected or confirmed COVID-19, discuss temporary cessation

of cancer therapy with a relevant specialist. Provide information on COVID-19 for patients and carers. Adopt measures within cancer centres to reduce risk of nosocomial SARS-CoV-2 acquisition; support population-wide social distancing; reduce demand on acute services; ensure adequate staffing; and provide culturally safe care. Measures should be equitable, transparent and proportionate to the COVID-19 threat. Consider the risks and benefits of modifying cancer therapies due to COVID-19. Communicate treatment modifications, and review once health service capacity allows. Consider potential impacts of COVID-19 on the blood supply and availability of stem cell donors. Discuss and document goals of care, and involve palliative care services in contingency planning.

CHANGES IN MANAGEMENT AS A RESULT OF THIS STATEMENT: This interim consensus guidance provides a framework for clinicians managing patients with cancer during the COVID-19 pandemic. In view of the rapidly changing situation, clinicians must also monitor national, state, local and institutional policies, which will take precedence.

ENDORSED BY: Australasian Leukaemia and Lymphoma Group; Australasian Lung Cancer Trials Group; Australian and New Zealand Children's Haematology/Oncology Group; Australia and New Zealand Society of Palliative Medicine; Australasian Society for Infectious Diseases; Bone Marrow Transplantation Society of Australia and New Zealand; Cancer Council Australia; Cancer Nurses Society of Australia; Cancer Society of New Zealand; Clinical Oncology Society of Australia; Haematology Society of Australia and New Zealand; National Centre for Infections in Cancer; New Zealand Cancer Control Agency; New Zealand Society for Oncology; and Palliative Care Australia.

Wilson, J. M., et al. (2020). "Doing Our Part to Conserve Resources: Determining Whether All Personal Protective Equipment Is Mandatory for Closed Reduction and Percutaneous Pinning of Supracondylar Humeral Fractures." Journal of Bone & Joint Surgery American **2020**: 04.

BACKGROUND: Closed reduction and percutaneous pinning (CRPP) of supracondylar humeral fractures is one of the most common procedures performed in pediatric orthopaedics. The use of full, standard preparation and draping with standard personal protective equipment (PPE) may not be necessary during this procedure. This is of particular interest in the current climate as we face unprecedented PPE shortages due to the current COVID-19 pandemic.

METHODS: This is a retrospective chart review of 1,270 patients treated with CRPP of a supracondylar humeral fracture at 2 metropolitan pediatric centers by 10 fellowship-trained pediatric orthopaedic surgeons. One surgeon in the group did not wear a mask when performing CRPP of supracondylar humeral fractures, and multiple surgeons in the group utilized a semisterile preparation technique (no sterile gown or drapes). Infectious outcomes were compared between 2 groups: full sterile preparation and semisterile preparation. We additionally analyzed a subgroup of patients who had semisterile preparation without surgeon mask use. Hospital cost data were used to estimate annual cost savings with the adoption of the semisterile technique.

RESULTS: In this study, 1,270 patients who underwent CRPP of a supracondylar humeral fracture and met inclusion criteria were identified. There were 3 deep infections (0.24%). These infections all occurred in the group using full sterile preparation and surgical masks. No clinically relevant pin-track infections were noted. There were no known surgeon occupational exposures to bodily fluid. It is estimated that national adoption of this technique in the United States could save between 18,612 and 22,162 gowns and masks with costs savings of $3.7 million to $4.4 million annually.

CONCLUSIONS: We currently face critical shortages of PPE due to the COVID-19 pandemic. Data from this large series suggest that a semisterile technique during CRPP of supracondylar humeral fractures is a safe practice. We anticipate that this could preserve approximately 20,000 gowns and masks in the United States over the next year. Physicians are encouraged to reevaluate their daily practice to identify safe opportunities for resource preservation.

LEVEL OF EVIDENCE: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Woo Baidal, J. A., et al. (2020). "Zooming Towards a Telehealth Solution for Vulnerable Children with Obesity During COVID-19." Obesity **30**.
Health inequities exist throughout the life course, resulting in racial/ethnic and socioeconomic disparities in obesity and obesity-related health complications. Obesity and its co-morbidities appear linked to COVID-19 mortality. Approaches to reduce obesity in the time of COVID-19 closures are urgently needed and should start early in life. In New York City, we developed a telehealth pediatric weight management collaborative spanning NewYork-Presbyterian, Columbia University Vagelos College of Physicians and Surgeons, and Weill Cornell Medicine during COVID-19 with show rates 76-89%. To stave off the impending exacerbation of health disparities related to obesity risk factors in the aftermath of the COVID-19 pandemic, effective interventions that can be delivered remotely are urgently needed among vulnerable children with obesity. Challenges in digital technology access, social and linguistic differences, privacy security, and reimbursement must be overcome to realize the full potential of telehealth for pediatric weight management among low-income and racial/ethnic minority children. Copyright This article is protected by copyright. All rights reserved.

Working Group for the, P. and V. I. i. t. P. P. o. t. E. C. o. C. J. o. C. P. Control of Neonatal -nCo (2020). "[Perinatal and neonatal management plan for prevention and control of 2019 novel coronavirus infection (1st Edition)]." Zhongguo Dangdai Erke Zazhi **22**(2): 87-90.
Since December 2019, the novel coronavirus (2019-nCoV) infection has been prevalent in China. Due to immaturity of immune function and the possibility of mother-fetal vertical transmission, neonates are particularly susceptible to 2019-nCoV. The perinatal-neonatal departments should cooperate closely and take integrated approaches, and the neonatal intensive care unit should prepare the emergency plan for 2019-nCoV infection as far as possible, so as to ensure the optimal management and treatment of potential victims. According to the latest 2019-nCoV national management plan and the actual situation, the Working Group for the Prevention and Control of Neonatal 2019-nCoV Infection in the Perinatal Period of the Editorial Committee of Chinese Journal of Contemporary Pediatrics puts forward recommendations for the prevention and control of 2019-nCoV infection in neonates.

Wu, G. (2020). "Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health." Amino Acids **52**(3): 329-360.
Taurine (a sulfur-containing beta-amino acid), creatine (a metabolite of arginine, glycine and methionine), carnosine (a dipeptide; beta-alanyl-l-histidine), and 4-hydroxyproline (an imino acid; also often referred to as an amino acid) were discovered in cattle, and the discovery of anserine (a methylated product of carnosine; beta-alanyl-1-methyl-l-histidine) also originated with cattle. These five nutrients are highly abundant in beef, and have important physiological roles in anti-oxidative and anti-inflammatory reactions, as well as neurological, muscular, retinal, immunological and cardiovascular function. Of particular note, taurine, carnosine, anserine, and creatine are absent from plants, and hydroxyproline is negligible in many plant-source foods. Consumption of 30 g dry beef can fully meet daily physiological needs of the healthy 70-kg adult human for taurine and carnosine, and can also provide large amounts of creatine, anserine and 4-hydroxyproline to improve human nutrition and health, including metabolic, retinal, immunological, muscular, cartilage, neurological, and cardiovascular health. The present review provides the public with the much-needed knowledge of nutritionally and physiologically significant amino acids, dipeptides and creatine in animal-source foods (including beef). Dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline are beneficial for preventing and treating obesity, cardiovascular dysfunction, and ageing-related disorders, as well as inhibiting tumorigenesis, improving skin and bone health, ameliorating neurological abnormalities, and promoting well being in infants, children and adults. Furthermore, these nutrients may promote the immunological defense of humans against infections by bacteria, fungi, parasites, and viruses (including coronavirus) through enhancing the metabolism and functions of monocytes, macrophages, and other cells of the immune system. Red meat (including beef) is a functional

food for optimizing human growth, development and health. Copyright © 2020, The Author(s).

Wu, J. T., et al. (2020). "Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China." Nature Medicine **26**(4): 506-510.
As of 29 February 2020 there were 79,394 confirmed cases and 2,838 deaths from COVID-19 in mainland China. Of these, 48,557 cases and 2,169 deaths occurred in the epicenter, Wuhan. A key public health priority during the emergence of a novel pathogen is estimating clinical severity, which requires properly adjusting for the case ascertainment rate and the delay between symptoms onset and death. Using public and published information, we estimate that the overall symptomatic case fatality risk (the probability of dying after developing symptoms) of COVID-19 in Wuhan was 1.4% (0.9-2.1%), which is substantially lower than both the corresponding crude or naive confirmed case fatality risk (2,169/48,557 = 4.5%) and the approximator¹ of deaths/deaths + recoveries (2,169/2,169 + 17,572 = 11%) as of 29 February 2020. Compared to those aged 30-59 years, those aged below 30 and above 59 years were 0.6 (0.3-1.1) and 5.1 (4.2-6.1) times more likely to die after developing symptoms. The risk of symptomatic infection increased with age (for example, at ~4% per year among adults aged 30-60 years).

Wu, P. and J. Wang (2020). "Changes and significance of serum sB7-H3 and cytokines in children with mycoplasma pneumonae pneumonia." Journal of the College of Physicians and Surgeons Pakistan **30**(3): 268-271.
Objective: To explore the relationship between serum sB7-H3 and cytokines (TNF-a, IL-1beta and IL-6) and to evaluate the development of Mycoplasma pneumonae pneumonia (MPP) through analysis of the expression levels of above indices in serum of children with MPP. Study Design: An experimental study. Place and Duration of Study: Department of Clinical Laboratory, Renmin Hospital of Wuhan University, China, from January 2018 to August 2019. Methodology: One hundred and eight children with MPP were divided into severe MPP group (53 cases) and mild MPP group (55 cases) according to children's condition. Fifty children who received hernia or selective operation due to redundant prepuce were included in control group. Serum sB7-H3, TNF-a, IL-1beta and IL-6 were compared. Result(s): Serum sB7-H3, TNF-a, IL-1beta, and IL-6 levels in MPP group were higher than those in control group (all p<0.001); above indices in severe MPP group were higher than those in mild MPP group (all p<0.001). Pearson's linear correlation analysis results revealed that sB7-H3 had positive correlation with TNF-a, IL-1beta, and IL-6 in MPP group (r=0.986, p<0.001; r=0.987, p<0.001; and r=0.991, p<0.001, respectively). Conclusion(s): Detection of SB7-H3, TNF-a, IL-1beta and IL-6 levels may be conducive to early diagnosis of MPP and the judgement of the severity of this disease. Copyright © 2020 College of Physicians and Surgeons Pakistan. All rights reserved.

Xia, H., et al. (2020). "Emergency Caesarean delivery in a patient with confirmed COVID-19 under spinal anaesthesia." British Journal of Anaesthesia **124**(5): e216-e218.

Xia, W., et al. (2020). "Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults." Pediatric Pulmonology **55**(5): 1169-1174.
PURPOSE: To discuss the different characteristics of clinical, laboratory, and chest computed tomography (CT) in pediatric patients from adults with 2019 novel coronavirus (COVID-19) infection.
METHODS: The clinical, laboratory, and chest CT features of 20 pediatric inpatients with COVID-19 infection confirmed by pharyngeal swab COVID-19 nucleic acid test were retrospectively analyzed during 23 January and 8 February 2020. The clinical and laboratory information was obtained from inpatient records. All the patients were undergone chest CT in our hospital.
RESULTS: Thirteen pediatric patients (13/20, 65%) had an identified history of close contact with COVID-19 diagnosed family members. Fever (12/20, 60%) and cough (13/20, 65%) were the most common symptoms. For laboratory findings, procalcitonin elevation (16/20, 80%) should be

pay attention to, which is not common in adults. Coinfection (8/20, 40%) is common in pediatric patients. A total of 6 patients presented with unilateral pulmonary lesions (6/20, 30%), 10 with bilateral pulmonary lesions (10/20, 50%), and 4 cases showed no abnormality on chest CT (4/20, 20%). Consolidation with surrounding halo sign was observed in 10 patients (10/20, 50%), ground-glass opacities were observed in 12 patients (12/20, 60%), fine mesh shadow was observed in 4 patients (4/20, 20%), and tiny nodules were observed in 3 patients (3/20, 15%). CONCLUSION: Procalcitonin elevation and consolidation with surrounding halo signs were common in pediatric patients which were different from adults. It is suggested that underlying coinfection may be more common in pediatrics, and the consolidation with surrounding halo sign which is considered as a typical sign in pediatric patients.

Xiao, H. H., et al. (2020). "[Research advances in cardiovascular system damage caused by SARS-CoV-2 in children]." Zhongguo Dangdai Erke Zazhi **22**(4): 299-304.
The outbreak of coronavirus disease 2019 (COVID-19) started in December 2019 in China and the epidemic is still going on at present. Since children are the susceptible population, the number of cases is gradually increasing. In addition to the typical respiratory symptoms, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection also has the clinical symptoms of cardiovascular system damage. Based on a literature review, this article discusses the possible cardiovascular system damage caused by SARS-CoV-2 in children and related mechanisms, in order to provide help for the timely treatment and prevention of cardiovascular system damage caused by SARS-CoV-2 in children.

Xie, G., et al. (2020). "Corona virus disease 2019 in infant: Case report. [Chinese]." Chinese Journal of Medical Imaging Technology **36**(3): 381.

Xie, Z. (2020). "Pay attention to SARS-CoV-2 infection in children." Pediatric Investigation **4**(1): 1-4.

Xing, Y. H., et al. (2020). "Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019." Journal of Microbiology, Immunology and Infection.
Objective: To determine the dynamic changes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in respiratory and fecal specimens in children with coronavirus disease 2019 (COVID-19). Method(s): From January 17, 2020 to February 23, 2020, three paediatric cases of COVID-19 were reported in Qingdao, Shandong Province, China. Epidemiological, clinical, laboratory, and radiological characteristics and treatment data were collected. Patients were followed up to March 10, 2020, and dynamic profiles of nucleic acid testing results in throat swabs and fecal specimens were closely monitored. Result(s): Clearance of SARS-CoV-2 in respiratory tract occurred within two weeks after abatement of fever, whereas viral RNA remained detectable in stools of pediatric patients for longer than 4 weeks. Two children had fecal SARS-CoV-2 undetectable 20 days after throat swabs showing negative, while that of another child lagged behind for 8 days. Conclusion(s): SARS-CoV-2 may exist in children's gastrointestinal tract for a longer time than respiratory system. Persistent shedding of SARS-CoV-2 in stools of infected children raises the possibility that the virus might be transmitted through contaminated fomites. Massive efforts should be made at all levels to prevent spreading of the infection among children after reopening of kindergartens and schools. Copyright © 2020

Xiong, Z., et al. (2020). "Construction and evaluation of a novel diagnosis process for 2019-Corona Virus Disease. [Chinese]." Zhonghua yi xue za zhi **100**: E019.
Objective: To construct and evaluate a diagnosis process for 2019-Corona Virus Disease (COVID-19). Method(s): A continuous cohort of adults and adolescent (>=12 years) who screened COVID-19 was included in Xiangya Hospital of Central South University from January 23 to February 3, 2020 in which cases were divided the test library and the verification library. Their gender, age, onset time were recorded. Take epidemiological history, fever, and the blood lymphocytes decline as clinical indicators, used CT to evaluate the possibility of COVID-19 and

range of lung involvement. According to the current national standards, throat swabs of suspected cases were collected and the nucleic acid of COVID-19 was detected by reverse transcription-polymerase chain reaction (RT-PCR). The Xiangya process was constructed according to multi-index, compared with clinical indicators, CT results and national standards, the efficiency of detecting confirmed cases were verified in the test and verification library. Result(s): A continuous cohort of 382 adults who screened COVID-19 was included in which 261 cases were in the test library and 121 cases were in the verification library. In the 382 cases, 192 were males (50.3%) and 190 were females (49.7%), with a median age of 35 years (range: 15-92 years). There were 183 cases (47.9%) with epidemiological history, 275 cases (72.0%) with fever, 212 cases (55.5%) with decreased hemolytic lymphocytes, CT positive 114 cases (29.8%), 43 cases (11.3%) with positive CT-COVID-19, and 30 cases (7.9%) with positive throat swab nucleic acid. Compared with clinical indicators, the sensitivity and specificity of CT were 0.950 and 0.704, respectively. The accuracy of CT to make a definite diagnosis was higher than that of epidemiological history, fever, and blood lymph count decline (0.809 vs 0.660, 0.532, 0.596, P=0.001, 0.002, 0.003, respectively). The sensitivity of this process and the program recommended by the Health Commission all were high (all were 1.000) , and the specificity and accuracy of the process were higher than the program recommended by the Health Commission (0.872 vs 0.765, 0.778 vs 0.592, both P<0.001). The CT-COVID-19 would have reduced the missed diagnosis rate caused by false negative of nucleic acid test (31 vs 64, difference rate 51.6%), the positive rate of nucleic acid test was 64.5% (20/31). In validation library, the specificity and accuracy of the Xiangya process was 0.967, the positive rate of nucleic acid test was 76.9% (10/13). Conclusion(s): The Xiangya process can predict the nucleic acid test results of COVID-19 well, and can be applied as a reliable basis for confirmed cases detection in adults and adolescent (>=12 years) in areas other than Hubei during the epidemic period of COVID-19. The cohort size needs to be increased for further validation.

Xu, G., et al. (2020). "Clinical Pathway for Early Diagnosis of COVID-19: Updates from Experience to Evidence-Based Practice." Clinical Reviews in Allergy and Immunology.
The COVID-19 pandemic is a significant global event in the history of infectious diseases. The SARS-CoV-2 appears to have originated from bats but is now easily transmissible among humans, primarily through droplet or direct contact. Clinical features of COVID-19 include high fever, cough, and fatigue which may progress to ARDS. Respiratory failure can occur rapidly after this. The primary laboratory findings include lymphopenia and eosinopenia. Elevated D-dimer, procalcitonin, and CRP levels may correlate with disease severity. Imaging findings include ground-glass opacities and patchy consolidation on CT scan. Mortality is higher in patients with hypertension, cardiac disease, diabetes mellitus, cancer, and COPD. Elderly patients are more susceptible to severe disease and death, while children seem to have lower rates of infection and lower mortality. Diagnostic criteria and the identification of persons under investigation have evolved as more data has emerged. However, the approach to diagnosis is still very variable from region to region, country to country, and even among different hospitals in the same city. The importance of a clinical pathway to implement the most effective and relevant diagnostic strategy is of critical importance to establish the control of this virus that is responsible for more and more deaths each day.

Xu, X., et al. (2020). "Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2." European Journal of Nuclear Medicine & Molecular Imaging **47**(5): 1275-1280.
BACKGROUND: The pneumonia caused by the 2019 novel coronavirus (SARS-CoV-2, also called 2019-nCoV) recently break out in Wuhan, China, and was named as COVID-19. With the spread of the disease, similar cases have also been confirmed in other regions of China. We aimed to report the imaging and clinical characteristics of these patients infected with SARS-CoV-2 in Guangzhou, China.
METHODS: All patients with laboratory-identified SARS-CoV-2 infection by real-time polymerase chain

reaction (PCR) were collected between January 23, 2020, and February 4, 2020, in a designated hospital (Guangzhou Eighth People's Hospital). This analysis included 90 patients (39 men and 51 women; median age, 50 years (age range, 18-86 years). All the included SARS-CoV-2-infected patients underwent non-contrast enhanced chest computed tomography (CT). We analyzed the clinical characteristics of the patients, as well as the distribution characteristics, pattern, morphology, and accompanying manifestations of lung lesions. In addition, after 1-6 days (mean 3.5 days), follow-up chest CT images were evaluated to assess radiological evolution.
FINDINGS: The majority of infected patients had a history of exposure in Wuhan or to infected patients and mostly presented with fever and cough. More than half of the patients presented bilateral, multifocal lung lesions, with peripheral distribution, and 53 (59%) patients had more than two lobes involved. Of all included patients, COVID-19 pneumonia presented with ground glass opacities in 65 (72%), consolidation in 12 (13%), crazy paving pattern in 11 (12%), interlobular thickening in 33 (37%), adjacent pleura thickening in 50 (56%), and linear opacities combined in 55 (61%). Pleural effusion, pericardial effusion, and lymphadenopathy were uncommon findings. In addition, baseline chest CT did not show any abnormalities in 21 patients (23%), but 3 patients presented bilateral ground glass opacities on the second CT after 3-4 days.
CONCLUSION: SARS-CoV-2 infection can be confirmed based on the patient's history, clinical manifestations, imaging characteristics, and laboratory tests. Chest CT examination plays an important role in the initial diagnosis of the novel coronavirus pneumonia. Multiple patchy ground glass opacities in bilateral multiple lobular with periphery distribution are typical chest CT imaging features of the COVID-19 pneumonia.

Xu, X. W., et al. (2020). "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series." BMJ **368**: m606.
OBJECTIVE: To study the clinical characteristics of patients in Zhejiang province, China, infected with the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) responsible for coronavirus disease 2019 (covid-2019).
DESIGN: Retrospective case series.
SETTING: Seven hospitals in Zhejiang province, China.
PARTICIPANTS: 62 patients admitted to hospital with laboratory confirmed SARS-Cov-2 infection. Data were collected from 10 January 2020 to 26 January 2020.
MAIN OUTCOME MEASURES: Clinical data, collected using a standardised case report form, such as temperature, history of exposure, incubation period. If information was not clear, the working group in Hangzhou contacted the doctor responsible for treating the patient for clarification.
RESULTS: Of the 62 patients studied (median age 41 years), only one was admitted to an intensive care unit, and no patients died during the study. According to research, none of the infected patients in Zhejiang province were ever exposed to the Huanan seafood market, the original source of the virus; all studied cases were infected by human to human transmission. The most common symptoms at onset of illness were fever in 48 (77%) patients, cough in 50 (81%), expectoration in 35 (56%), headache in 21 (34%), myalgia or fatigue in 32 (52%), diarrhoea in 3 (8%), and haemoptysis in 2 (3%). Only two patients (3%) developed shortness of breath on admission. The median time from exposure to onset of illness was 4 days (interquartile range 3-5 days), and from onset of symptoms to first hospital admission was 2 (1-4) days.
CONCLUSION: As of early February 2020, compared with patients initially infected with SARS-Cov-2 in Wuhan, the symptoms of patients in Zhejiang province are relatively mild.

Xu, Y., et al. (2020). "Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding." Nature Medicine **26**(4): 502-505.
We report epidemiological and clinical investigations on ten pediatric SARS-CoV-2 infection cases confirmed by real-time reverse transcription PCR assay of SARS-CoV-2 RNA. Symptoms in these cases were nonspecific and no children required respiratory support or intensive care. Chest X-rays lacked definite signs of pneumonia, a defining feature of the infection in adult cases. Notably, eight children persistently tested positive on rectal swabs even after nasopharyngeal

testing was negative, raising the possibility of fecal-oral transmission.

Xu, Y. H., et al. (2020). "Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2." Journal of Infection **80**(4): 394-400.
PURPOSE: To investigate the clinical and imaging characteristics of computed tomography (CT) in novel coronavirus pneumonia (NCP) caused by SARS-CoV-2.
MATERIALS AND METHODS: A retrospective analysis was performed on the imaging findings of patients confirmed with COVID-19 pneumonia who had chest CT scanning and treatment after disease onset. The clinical and imaging data were analyzed.
RESULTS: Fifty patients were enrolled, including mild type in nine, common in 28, severe in 10 and critically severe in the rest three. Mild patients (29 years) were significantly (P<0.03) younger than either common (44.5 years) or severe (54.7) and critically severe (65.7 years) patients, and common patients were also significantly (P<0.03) younger than severe and critically severe patients. Mild patients had low to moderate fever (<39.1degreeC), 49 (98%) patients had normal or slightly reduced leukocyte count, 14 (28%) had decreased counts of lymphocytes, and 26 (52%) patients had increased C-reactive protein. Nine mild patients were negative in CT imaging. For all the other types of NCP, the lesion was in the right upper lobe in 30 cases, right middle lobe in 22, right lower lobe in 39, left upper lobe in 33 and left lower lobe in 36. The lesion was primarily located in the peripheral area under the pleura with possible extension towards the pulmonary hilum. Symmetrical lesions were seen in 26 cases and asymmetrical in 15. The density of lesion was mostly uneven with ground glass opacity as the primary presentation accompanied by partial consolidation and fibrosis.
CONCLUSION: CT imaging presentations of NCP are mostly patchy ground glass opacities in the peripheral areas under the pleura with partial consolidation which will be absorbed with formation of fibrotic stripes if improved. CT scanning provides important bases for early diagnosis and treatment of NCP.

Yadav, U. and R. Pal (2020). "Challenging Times for Children With Transfusion-dependent Thalassemia Amid the COVID-19 Pandemic." Indian pediatrics. **07**.

Yang, P., et al. (2020). "Clinical characteristics and risk assessment of newborns born to mothers with COVID-19." Journal of Clinical Virology **127 (no pagination)**(104356).
Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is causing an outbreak of pneumonia in Wuhan, Hubei Province, China, and other international areas. Objective(s): Here, we report the clinical characteristics of the newborns delivered by SARS-CoV-2 infected pregnant women. Method(s): We prospectively collected and analyzed the clinical features, laboratory data and outcomes of 7 newborns delivered by SARS-CoV-2 infected pregnant women in Zhongnan Hospital of Wuhan University during January 20 to January 29, 2020. Result(s): 4 of the 7 newborns were late preterm with gestational age between 36 weeks and 37 weeks, and the other 3 were full-term infants. The average birth weight was 2096 +/- 660 g. All newborns were born without asphyxia. 2 premature infants performed mild grunting after birth, but relieved rapidly with non-invasive continuous positive airway pressure (nCPAP) ventilation. 3 cases had chest X-ray, 1 was normal and 2 who were supported by nCPAP presented mild neonatal respiratory distress syndrome (NRDS). Samples of pharyngeal swab in 6 cases, amniotic fluid and umbilical cord blood in 4 cases were tested by qRT-PCR, and there was no positive result of SARS-CoV-2 nucleic acid in all cases. Conclusion(s): The current data show that the infection of SARS-CoV-2 in late pregnant women does not cause adverse outcomes in their newborns, however, it is necessary to separate newborns from mothers immediately to avoid the potential threats. Copyright © 2020 Elsevier B.V.

Yarimkaya, E. and O. K. Esenturk (2020). "Promoting physical activity for children with autism spectrum disorders during Coronavirus outbreak: benefits, strategies, and examples." International Journal of Developmental Disabilities.

Described as a global outbreak (pandemic) by the World Health Organization, Coronavirus disease (COVID-19) raises great concern with more than 2 million infected patients worldwide. A series of measures are taken by governments worldwide to prevent the spread of the outbreak. As new cases increase, people are asked to stay at home. Active living areas such as sports centers, parks and schools are closed in most countries. In this process, staying at home for a long time makes it difficult for individuals with special needs such as Autism Spectrum Disorders (ASD) to stay physically active as well as typically developing individuals. The education process of children with ASD is disrupted, especially due to closed special education schools and rehabilitation centers. Online learning environments are often not suitable for children with ASD. It is predicted that excessive weight, obesity and sedentary life, which are high in children with ASD, may increase even more due to COVID-19. This article outlines the benefits of physical activity for children with ASD and provides strategies and examples of physical activity for children with ASD during the COVID-19 outbreak. The article is thought to be a guide for encouraging children with ASD in the home environment to physical activity. Copyright © 2020, © The British Society of Developmental Disabilities 2020.

Yasri, S. and V. Wiwanitkit (2020). "Clinical features in pediatric COVID-19." Pediatric Pulmonology **55**(5): 1097.

Ye, X. T., et al. (2020). "Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019." European Review for Medical & Pharmacological Sciences **24**(6): 3390-3396.
OBJECTIVE: The Coronavirus disease 2019 (COVID-19) which outbroke in December 2019 is highly contagious with a low cure rate. In view of this, there is an urgent need to find a more appropriate therapeutic scheme against COVID-19. The study aimed to investigate whether lopinavir/ritonavir (LPV/r) in combination with other pneumonia-associated adjuvant drugs has a better therapeutic effect on COVID-19.
PATIENTS AND METHODS: Totally 47 patients with COVID-19 infection who were admitted to Rui'an People's Hospital between January 22 and January 29, 2020 were collected. The patients were divided into the test group and the control group according to whether they had been treated with LPV/r or not during hospitalization. Patients in the test group were treated with LPV/r combined with adjuvant medicine, while those in the control group were just treated with adjuvant medicine. The changes of body temperature, blood routine and blood biochemistry between the two groups were observed and compared.
RESULTS: Both groups achieved good therapeutic effect with the body temperature of patients decreased gradually from admission to the 10th day of treatment. But the body temperature of patients in the test group decreased faster than that of the control group. Blood routine indexes showed that compared with the control group, the abnormal proportion of white blood cells, lymphocytes and C-reactive protein of the test group could be reduced to some extent. Blood biochemical indexes exhibited that the proportion of patients with abnormal alanine aminotransferase and aspartate aminotransferase in the test group were lower than the control group. The number of days for nCoV-RNA turning negative after treatment was significantly decreased in the test group than that in the control group.
CONCLUSIONS: Compared with the treatment of pneumonia-associated adjuvant drugs alone, the combination treatment with LPV/r and adjuvant drugs has a more evident therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects. In view of these conclusions, we suggested that the use of LPV/r combined with pneumonia-associated adjuvant drugs in the clinical treatment for patients with COVID-19 should be promoted.

Yesil, E. and M. Hacimustafaoglu (2020). "Novel coronavirus 2019 infections current status. [Turkish]." Guncel Pediatri **18**(1): 134-139.
Coronaviruses are enveloped RNA viruses that take their name from the thorny protrusions (Corona; Crown) on their surface in electron microscopy.They can cause

respiratory,enteric,hepatic, and neurological diseases in humans and animals.Human infections are usually caused by Alpha and Beta types. Human Coronaviruses (HCoV) were first described in the 1960s,and these are mainly 229E,NL63,OC43 and HKU1 Coronaviruses, causing typical mild/moderate respiratory diseases in humans.In addition,occasional outbreaks of different severe Coronavirus infections (MERS-CoV,SARS-CoV) have been reported.Apart from these,new(novel) Coronavirus infections (2019-nCoV,SARS-CoV-2 or COVID-19) have been reported which started in Wuhan,Hubei,China in December 2019 and tend to spread all over the world.In this review,it is aimed to present the epidemiological course,genetic factors,transmission,prevention of this novel Coronavirus infections with the clinical findings in adults and children,diagnosis,treatment,prevention methods and current information in our country.As of February 12,2020, 45.171 proven cases have been reported in the world and 25 different countries have been affected by this epidemic.The average incubation period of COVID-19 infection was 5.2days (1-14 days).The fatality rate was 2.5% on average in all cases,but 4.3-15% in severe or hospitalized patients.In adult cases,it begins clinically with non-specific upper respiratory tract infections such as fever,cough and weakness.In severe cases,symptoms such as pneumonia and severe respiratory failure develop within days.In laboratory findings;lymphopenia was observed in hospitalized patients,lung involvement was in almost all cases with bilateral and multilobuler and/or subsegmental consolidation. Pediatric cases were usually asymptomatic or with mild upper respiratory tract infection findings. Pneumonia has been rarely seen.Mortality has not been reported in pediatric cases.Treatment of COVID-19 mainly consists of supportive therapy. Droplet isolation measures and hand hygiene play an important role in protection.Rigorous application of infection control measures is expected to be helpful in breaking the epidemics and pandemics. Copyright © 2020, Galenos Yayincilik,. All rights reserved.

Yi, L., et al. (2020). "Elevated Levels of Platelet Activating Factor and Its Acetylhydrolase Indicate High Risk of Kawasaki Disease." Journal of Interferon and Cytokine Research **40**(3): 159-167. Kawasaki disease (KD) is a systemic vasculitis in children, which is related to inflammation and abnormal activation of immune system. Platelet activating factor (PAF) and its acetylhydrolase (PAF-AH) may play an important role in the pathogenesis of KD. This study aimed to investigate diagnosis and prognostic value of serum PAF and PAF-AH in KD. One hundred thirteen KD children were divided into coronary artery lesion (CAL) KD, noncoronary artery lesion (NCAL) KD, intravenous immunoglobulin (IVIG)-responsive KD, and IVIG-nonresponsive KD group. Seventy cases of fever control (F) group and 71 cases of normal control (N) group were set up. Peripheral venous blood was collected to detect serum PAF and PAF-AH levels, combined with other inflammatory mediators. Results showed that the serum levels of PAF and PAF-AH were significantly elevated in the KD group compared with F group and N group ($P < 0.05$). And the levels of conventional inflammatory mediators in KD group were significantly higher than those of F group ($P < 0.05$). In children with fever (KD group and F group), the area under the receiver operating characteristic curve (AUC) for PAF in prediction of KD was 0.804, and the estimated sensitivity and specificity were 79.6% and 74.3% with a cutoff of PAF >201.77 ng/mL, respectively; the AUC for PAF-AH in prediction of KD was 0.587, and the estimated sensitivity and specificity were 61.9% and 55.7% with a cutoff of PAF-AH >0.153 μmol/min/mL, respectively. Compared with NCAL group, PAF and C-reactive protein were higher in CAL group ($P < 0.05$). The AUC for PAF in prediction of CAL KD was 0.679, and the estimated sensitivity and specificity were 96.0% and 40.9% with a cutoff of PAF >225.52 ng/mL, respectively. Thus, serum levels of PAF and PAF-AH were significantly elevated in the acute phase of KD. Serum PAF and PAF-AH contributed to the diagnosis of KD, and serum PAF has a greater diagnostic value for KD. At the same time, elevated serum PAF has a certain predictive value for the occurrence of coronary artery lesions in Kawasaki disease rather than IVIG-nonresponsive KD. © Mary Ann Liebert, Inc., publishers 2020.

Yin, X., et al. (2020). "A mild type of childhood Covid-19 - A case report." Radiology of Infectious

Diseases.
This case is about a 9-year-old child diagnosed with COVID-19, with a history of epidemiology; SARS-CoV-2 nucleic acids testing was positive, while chest CT examination was negative. The clinical classification was light. Nonetheless, isolation measures should still be taken to avoid infecting others. Copyright © 2020 Beijing You'an Hospital affiliated to Capital Medical University

Yongchen, Z., et al. (2020). "Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients." Emerging Microbes & Infections **9**(1): 833-836.
Effective strategy to mitigate the ongoing pandemic of 2019 novel coronavirus (COVID-19) require a comprehensive understanding of humoral responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the emerging virus causing COVID-19. The dynamic profile of viral replication and shedding along with viral antigen specific antibody responses among COVID-19 patients started to be reported but there is no consensus on their patterns. Here, we conducted a serial investigation on 21 individuals infected with SARS-CoV-2 in two medical centres from Jiangsu Province, including 11 non-severe COVID-19 patients, and 5 severe COVID-19 patients and 5 asymptomatic carriers based on nucleic acid test and clinical symptoms. The longitudinal swab samples and sera were collected from these people for viral RNA testing and antibody responses, respectively. Our data revealed different pattern of seroconversion among these groups. All 11 non-severe COVID-19 patients and 5 severe COVID-19 patients were seroconverted during hospitalization or follow-up period, suggesting that serological testing is a complementary assay to nucleic acid test for those symptomatic COVID-19 patients. Of note, immediate antibody responses were identified among severe cases, compared to non-severe cases. On the other hand, only one were seroconverted for asymptomatic carriers. The SARS-CoV-2 specific antibody responses were well-maintained during the observation period. Such information is of immediate relevance and would assist COVID-19 clinical diagnosis, prognosis and vaccine design.

Yonker, L. M., et al. (2020). "Lessons unfolding from pediatric cases of COVID-19 disease caused by SARS-CoV-2 infection." Pediatric Pulmonology **55**(5): 1085-1086.

Yoshizato, R. and H. Koga (2020). "Comparison of initial and final diagnoses in children with acute febrile illness: A retrospective, descriptive study: Initial and final diagnoses in children with acute fever." Journal of Infection and Chemotherapy **26**(3): 251-256.
Background: This study aimed to elucidate the etiologies and diagnostic errors of early-phase pediatric fever without an obvious cause. Methods: This single-center, retrospective, descriptive study included 1334 febrile children hospitalized at Beppu Medical Center in Japan between 2014 and 2018. Eligibility criteria were age ≤12 years, axillary temperature ≥38.0°C, and fever duration ≤7 days at admission. Initial diagnoses on the day of admission and final diagnoses at defervescence were divided into initial fever with identified source (FIS) and initial fever without source (FWS) and final FIS and final FWS, respectively. The etiology of initial FWS and diagnostic discordance between initial FIS and final FIS were investigated. Results: Of the 1334 participants, 94 (7.0%) were diagnosed with initial FWS. Among patients with initial FWS, final diagnoses were confirmed in 40 (43%), including Kawasaki disease in 17, urinary tract infection in 5, bacteremia in 4, exanthem subitum in 3, and the others in 11. Among the 1275 patients diagnosed with final FIS, diagnostic discordances between initial and final diagnoses were observed in 131 patients (10%). The multiple logistic regression analysis identified increased serum C-reactive protein value at admission (odds ratio [OR]: 1.09; 95% confidence interval [CI]: 1.06–1.13), exanthem subitum (OR: 409; 95% CI: 119–1399), and Kawasaki disease (OR: 14.3; 95% CI: 8.7–23.3) as independent risk factors for diagnostic discordance. Conclusion: Exanthem subitum and Kawasaki disease may be undiagnosed or misdiagnosed in febrile children with fever duration ≤7 days. © 2019 Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases

Yuan, R., et al. (2020). "Psychological status of parents of hospitalized children during the COVID-19 epidemic in China." Psychiatry Research **288 (no pagination)**(112953).
A series of unexplained pneumonia appeared in Wuhan, Hubei Province, China, which is highly contagious. The virus is prone to nervous and anxious psychological reactions. In the objective environment of complex and densely populated hospitals, it is a high-risk area for virus-transmitted infections and children generally have lower immunity who are more likely to develop infections. The results showed that the mental health problems of parents of hospitalized children during the epidemic were more serious, and the anxiety and depression were more obvious. Copyright © 2020 Elsevier B.V.

Yuki, K., et al. (2020). "COVID-19 pathophysiology: A review." Clinical Immunology **215**: 108427.
In December 2019, a novel coronavirus, now named as SARS-CoV-2, caused a series of acute atypical respiratory diseases in Wuhan, Hubei Province, China. The disease caused by this virus was termed COVID-19. The virus is transmittable between humans and has caused pandemic worldwide. The number of death tolls continues to rise and a large number of countries have been forced to do social distancing and lockdown. Lack of targeted therapy continues to be a problem. Epidemiological studies showed that elder patients were more susceptible to severe diseases, while children tend to have milder symptoms. Here we reviewed the current knowledge about this disease and considered the potential explanation of the different symptomatology between children and adults.

Zhang, G. X., et al. (2020). "Twin girls infected with SARS-CoV-2. [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(3): 221-225.
This article reports the diagnosis and treatment of twin girls who were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Hunan Province, China. The twin girls, aged 1 year and 2 months, were admitted on January 29, 2020 due to fever for one day and cough and sneezing for two days respectively. Both recovered after symptomatic treatment. The two girls had mild symptoms and rapid recovery, suggesting that children with SARS-CoV-2 infection may be mild and have a good prognosis. There were differences in the clinical symptoms and imaging findings between the twin girls, suggesting that SARS-CoV-2 infection has diverse clinical features in children.

Zhang, G. X., et al. (2020). "[Twin girls infected with SARS-CoV-2]." Zhongguo Dangdai Erke Zazhi **22**(3): 221-225.
This article reports the diagnosis and treatment of twin girls who were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Hunan Province, China. The twin girls, aged 1 year and 2 months, were admitted on January 29, 2020 due to fever for one day and cough and sneezing for two days respectively. Both recovered after symptomatic treatment. The two girls had mild symptoms and rapid recovery, suggesting that children with SARS-CoV-2 infection may be mild and have a good prognosis. There were differences in the clinical symptoms and imaging findings between the twin girls, suggesting that SARS-CoV-2 infection has diverse clinical features in children.

Zhang, J., et al. (2020). "Acute stress, behavioural symptoms and mood states among school-age children with attention-deficit/hyperactive disorder during the COVID-19 outbreak." Asian Journal of Psychiatry **51 (no pagination)**(102077).

Zhang, L., et al. (2020). "An analysis of global research on SARS-CoV-2. [Chinese]." Sheng wu yi xue gong cheng xue za zhi = Journal of biomedical engineering = Shengwu yixue gongchengxue zazhi **37**(2): 236-245.
The SARS-CoV-2 has been spread to 26 countries around the world since its outbreak. By February 16, 2020, more than 68 000 people had been diagnosed with COVID-19. Researchers from all over the world have carried out timely studies on this public health emergency and

produced a number of scientific publications. This review aims to re-analyze and summarize the current research findings in a timely manner to guide scholars in relevant fields to further SARS-CoV-2 research and assist healthcare professionals in their work and decision-making. The SARS-CoV-2 related terms were selected in both English and Chinese and were searched in several major databases, including Pubmed, Web of Science, CNKI, Wanfang, and VIP databases. The reference list of each search result was screened for relevance, which was further supplemented to the search results. The included studies were categorized by topics with key characteristics extracted, re-analyzed, and summarized. A total of 301 articles were finally included with 136 in Chinese and 165 in English. The number of publications has rapidly increased since mid-January, 2020, and a peak day was 6th February on which 50 articles were published. The top three countries publishing articles were China, the United States and the United Kingdom. The Lancet and its specialty journals have published the most articles, with contribution also from journals such as New England Journal of Medicine (NEJM), The Journal of the American Medical Association (JAMA), and Nature. All articles were categorized into epidemiology, clinical diagnosis and treatment, basic research, pregnant women and children, mental health, epidemic prevention & control, and others. The literatures related to SARS-CoV-2 are emerging rapidly. It is necessary to sort out and summarize the research topic in time, which has a good reference value for staff in different positions. At the same time, it is necessary to strengthen the judgment of the quality of literatures.

Zhang, L., et al. (2020). "[An analysis of global research on SARS-CoV-2]." Shengwu Yixue Gongchengxue Zazhi/Journal of Biomedical Engineering **37**(2): 236-245.
The SARS-CoV-2 has been spread to 26 countries around the world since its outbreak. By February 16, 2020, more than 68 000 people had been diagnosed with COVID-19. Researchers from all over the world have carried out timely studies on this public health emergency and produced a number of scientific publications. This review aims to re-analyze and summarize the current research findings in a timely manner to guide scholars in relevant fields to further SARS-CoV-2 research and assist healthcare professionals in their work and decision-making. The SARS-CoV-2 related terms were selected in both English and Chinese and were searched in several major databases, including Pubmed, Web of Science, CNKI, Wanfang, and VIP databases. The reference list of each search result was screened for relevance, which was further supplemented to the search results. The included studies were categorized by topics with key characteristics extracted, re-analyzed, and summarized. A total of 301 articles were finally included with 136 in Chinese and 165 in English. The number of publications has rapidly increased since mid-January, 2020, and a peak day was 6th February on which 50 articles were published. The top three countries publishing articles were China, the United States and the United Kingdom. The Lancet and its specialty journals have published the most articles, with contribution also from journals such as New England Journal of Medicine (NEJM), The Journal of the American Medical Association (JAMA), and Nature. All articles were categorized into epidemiology, clinical diagnosis and treatment, basic research, pregnant women and children, mental health, epidemic prevention & control, and others. The literatures related to SARS-CoV-2 are emerging rapidly. It is necessary to sort out and summarize the research topic in time, which has a good reference value for staff in different positions. At the same time, it is necessary to strengthen the judgment of the quality of literatures.

Zhang, L. and Y. Liu (2020). "Potential interventions for novel coronavirus in China: A systematic review." Journal of Medical Virology **92**(5): 479-490.
An outbreak of a novel coronavirus (COVID-19 or 2019-CoV) infection has posed significant threats to international health and the economy. In the absence of treatment for this virus, there is an urgent need to find alternative methods to control the spread of disease. Here, we have conducted an online search for all treatment options related to coronavirus infections as well as some RNA-virus infection and we have found that general treatments, coronavirus-specific treatments, and antiviral treatments should be useful in fighting COVID-19. We suggest that the

nutritional status of each infected patient should be evaluated before the administration of general treatments and the current children's RNA-virus vaccines including influenza vaccine should be immunized for uninfected people and health care workers. In addition, convalescent plasma should be given to COVID-19 patients if it is available. In conclusion, we suggest that all the potential interventions be implemented to control the emerging COVID-19 if the infection is uncontrollable.

Zhang, M. Q., et al. (2020). "[Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing]." Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases **43**(3): 215-218.
Objective: To summarize and analyze the clinical and imaging characteristics of patients with 2019 novel coronavirus pneumonia in the early stage in Beijing.

Zhang, T., et al. (2020). "Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia." Journal of Medical Virology **29**: 29.
Coronavirus Disease 2019 (COVID-19) is a newly emerging infectious disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After its first occurrence in Wuhan of China from December 2019, COVID-19 rapidly spread around the world. According to the World Health Organization statement on 13 March 2020, there had been over 132 500 confirmed cases globally. Nevertheless, the case reports of children are rare, which results in the lack of evidence for preventing and controlling of children's infection. Here, we report three cases of SARS-CoV-2 infected children diagnosed from 3 February to 17 February 2020 in Tianjin, China. All of these three cases experienced mild illness and recovered soon after the treatment, with the nucleic acid of throat swab turning negative within 14, 11, and 7 days after diagnosis, respectively. However, after been discharged, all three cases were tested SARS-CoV-2 positive in the stool samples within 10 days, in spite of their remained negative nucleic acid in throat swab specimens. Therefore, it is necessary to be aware of the possibility of fecal-oral transmission of SARS-CoV-2 infection, especially for children cases.

Zhang, Z. J., et al. (2020). "Novel Coronavirus Infection in Newborn Babies Under 28 Days in China." The European respiratory journal. **08**.
Previous studies described the clinical features of Covid-19 in adults and infants under 1 year of age. Little is known about features, outcomes and intrauterine transmission potential in newborn babies aged 28 days or less. Through systematical searching, we identified 4 infections in newborn babies in China as of March 13. The age range was 30 h to 17 days old. Three were male. Two newborn babies had fever, 1 had shortness of breath, 1 had cough and 1 had no syndromes. Supportive treatment was provided for all 4 newborn babies. None required intensive unit care or mechanical ventilation. None had any severe complications. Three newborn babies recovered by the end of this study and had been discharged with 16, 23, and 30 days of hospital stay. All 4 mothers were infected by SARS-CoV-2, 3 showing symptoms before and 1 after delivery. Cesarean section was used for all 4 mothers, 3 at level III hospitals and 1 at a level II hospital. Three newborn babies were separated from mothers right after being born and were not breastfed. In summary, newborn babies are susceptible to SARS-CoV-2 infection. The symptoms in newborn babies were milder and outcomes were less severe as compared to adults. Intrauterine vertical transmission is possible but direct evidence is still lacking. Copyright ©ERS 2020.

Zhao, S., et al. (2020). "Anesthetic Management of Patients with COVID 19 Infections during Emergency Procedures." Journal of Cardiothoracic and Vascular Anesthesia **34**(5): 1125-1131.
Objectives: The aim of the present study was to prevent cross-infection in the operating room during emergency procedures for patients with confirmed or suspected 2019 novel coronavirus (2019-nCoV) by following anesthesia management protocols, and to document clinical- and anesthesia-related characteristics of these patients. Design(s): This was a retrospective,

multicenter clinical study. Setting(s): This study used a multicenter dataset from 4 hospitals in Wuhan, China. Participant(s): Patients and health care providers with confirmed or suspected 2019-nCoV from January 23 to 31, 2020, at the Wuhan Union Hospital, the Wuhan Children's Hospital, The Central Hospital of Wuhan, and the Wuhan Fourth Hospital in Wuhan, China. Intervention(s): Anesthetic management and infection control guidelines for emergency procedures for patients with suspected 2019-nCoV were drafted and applied in 4 hospitals in Wuhan. Measurements and Main Results: Cross-infection in the operating rooms of the 4 hospitals was effectively reduced by implementing the new measures and procedures. The majority of patients with laboratory-confirmed 2019-nCoV infection or suspected infection were female (23 [62%] of 37), and the mean age was 41.0 years old (standard deviation 19.6; range 4-78). 10 (27%) patients had chronic medical illnesses, including 4 (11%) with diabetes, 8 (22%) with hypertension, and 8 (22%) with digestive system disease. Twenty-five (68%) patients presented with lymphopenia, and 23 (62%) patients exhibited multiple mottling and ground-glass opacity on computed tomography scanning. Conclusion(s): The present study indicates that COVID 19-specific guidelines for emergency procedures for patients with confirmed or suspected 2019-nCoV may effectively prevent cross-infection in the operating room. Most patients with confirmed or suspected COVID 19 presented with fever and dry cough and demonstrated bilateral multiple mottling and ground-glass opacity on chest computed tomography scans. Copyright © 2020 Elsevier Inc.

Zhao, Y., et al. (2020). "First Case of Coronavirus Disease 2019 in Childhood Leukemia in China." Pediatric Infectious Disease Journal **12**: 12.
We report the first case of coronavirus disease 2019 (COVID-19) comorbid with leukemia in a patient hospitalized in Beijing, China. The patient showed a prolonged manifestation of symptoms and a protracted diagnosis period of COVID-19. It is necessary to extend isolation time, increase the number of nucleic acid detections and conduct early symptomatic treatment for children with both COVID-19 and additional health problems.

Zhen-Dong, Y., et al. (2020). "Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: A review." Journal of Infection.
Objective: Chinese pediatricians are working on the front line to fight COVID-19. They have published a great amount of first-hand clinical data. Collecting their data and forming a large sample for analysis is more conducive to the recognition, prevention and treatment of coronavirus disease 2019 in children. The epidemic prevention and control experience of Chinese pediatricians should be shared with the world. Method(s): By searching Chinese and English literature, the data of 406 children with COVID-19 in China were analyzed. Result(s): It was found that the clustered incidence of children's families is a dynamic transmission feature; the incidence is low; asymptomatic infections and mild cases account for 44.8%, with only 7 cases of critical illness; laboratory examination of lymphocyte counts is not reduced, as it is for adults; chest CT findings are less severe than those for adults. These presentations are the clinical features of COVID-19 in children. Only 55 of the 406 cases were tested by anal swab for virus nucleic acid, 45 of which were positive, accounting for 81.8% of stool samples. Conclusion(s): There are more children than adults with asymptomatic infections, milder conditions, faster recovery, and a better prognosis. Some concealed morbidity characteristics also bring difficulties to the early identification, prevention and control of COVID-19. COVID-19 screening is needed in the pediatric fever clinic, and respiratory and digestive tract nucleic acid tests should be performed. Efforts should be made to prevent children from becoming a hidden source of transmission in kindergartens, schools or families. Furthermore, China's experience in treating COVID-19 in children has led to faster recovery of sick children. Copyright © 2020 The British Infection Association

Zheng, F., et al. (2020). "Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China." Current medical science **40**(2): 275-280.

Since December 2019, COVID-19 has occurred unexpectedly and emerged as a health problem worldwide. Despite the rapidly increasing number of cases in subsequent weeks, the clinical characteristics of pediatric cases are rarely described. A cross-sectional multicenter study was carried out in 10 hospitals across Hubei province. A total of 25 confirmed pediatric cases of COVID-19 were collected. The demographic data, epidemiological history, underlying diseases, clinical manifestations, laboratory and radiological data, treatments, and outcomes were analyzed. Of 25 hospitalized patients with COVID-19, the boy to girl ratio was 1.27:1. The median age was 3 years. COVID-19 cases in children aged <3 years, 3.6 years, and ≥6-years patients were 10 (40%), 6 (24%), and 9 (36%), respectively. The most common symptoms at onset of illness were fever (13 [52%]), and dry cough (11 [44%]). Chest CT images showed essential normal in 8 cases (33.3%), unilateral involvement of lungs in 5 cases (20.8%), and bilateral involvement in 11 cases (45.8%). Clinical diagnoses included upper respiratory tract infection (n=8), mild pneumonia (n=15), and critical cases (n=2). Two critical cases (8%) were given invasive mechanical ventilation, corticosteroids, and immunoglobulin. The symptoms in 24 (96%) of 25 patients were alleviated and one patient had been discharged. It was concluded that children were susceptible to COVID-19 like adults, while the clinical presentations and outcomes were more favorable in children. However, children less than 3 years old accounted for majority cases and critical cases lied in this age group, which demanded extra attentions during home caring and hospitalization treatment. © 2020, Huazhong University of Science and Technology.

Zhong, Z., et al. (2020). "Chest CT findings and clinical features of coronavirus disease 2019 in children." Zhong nan da xue xue bao **Yi xue ban = Journal of Central South University. Medical sciences. 45**(3): 236-242.

Zhou, F., et al. (2020). "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." Lancet **395**(10229): 1054-1062.
BACKGROUND: Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

METHODS: In this retrospective, multicentre cohort study, we included all adult inpatients (>=18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.

FINDINGS: 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95% CI 1.03-1.17, per year increase; p=0.0043), higher Sequential Organ Failure Assessment (SOFA) score (5.65, 2.61-12.23; p<0.0001), and d-dimer greater than 1 mug/mL (18.42, 2.64-128.55; p=0.0033) on admission. Median duration of viral shedding was 20.0 days (IQR 17.0-24.0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

INTERPRETATION: The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 mug/mL could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

FUNDING: Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences; National Science

Grant for Distinguished Young Scholars; National Key Research and Development Program of China; The Beijing Science and Technology Project; and Major Projects of National Science and Technology on New Drug Creation and Development.

Zhou, M. Y., et al. (2020). "From SARS to COVID-19: What we have learned about children infected with COVID-19." International Journal of Infectious Diseases **07**: 07.
Coronaviruses, both SARS-CoV and SARS-CoV-2 were firstly appeared in China. They have certain similarities in biological, epidemiological and pathological. To data, the researches have shown that their gene exhibit 79% of identical sequence and the receptor-binding domain structure is also very similar. There have been extensive research performed on SARS, however, the understanding of pathophysiology impact of Corona Virus Disease 2019(COVID-19) is still limited. In the review, we draw upon the lessons learnt from SARS in the epidemiology, clinical characteristics and pathogenesis for further understand the features of COVID-19. By comparing these two diseases, we found, COVID-19 has quicker and wider transmission, obvious family agglomeration, higher morbidity and mortality. Newborns, asymptomatic children and normal chest imaging cases were emerged in COVID-19. Children started with gastrointestinal symptoms may progress to severe condition and newborn whose mother was infected with COVID-19 could have severe complications. The laboratory test data showed, the percentage of neutrophils and the level of LDH is higher, otherwise the number of CD4+ and CD8+T cells is decreased in children's COVID-19 cases. Based on these early observations, as pediatrician, we put forward some thoughts on children's COVID-19 and give some recommendations to contain the disease.

Zhou, Y., et al. (2020). "Clinical features and chest CT findings of coronavirus disease 2019 in infants and young children. [Chinese]." Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics **22**(3): 215-220.
OBJECTIVE: To study the clinical features and chest CT findings of coronavirus disease 2019 (COVID-19) in infants and young children. METHOD(S): A retrospective analysis was performed for the clinical data and chest CT images of 9 children, aged 0 to 3 years, who were diagnosed with COVID-19 by nucleic acid detection between January 20 and February 10, 2020. RESULT(S): All 9 children had an epidemiological history, and family clustering was observed for all infected children. Among the 9 children with COVID-19, 5 had no symptoms, 4 had fever, 2 had cough, and 1 had rhinorrhea. There were only symptoms of the respiratory system. Laboratory examination showed no reductions in leukocyte or lymphocyte count. Among the 9 children, 6 had an increase in lymphocyte count and 2 had an increase in leukocyte count. CT examination showed that among the 9 children, 8 had pulmonary inflammation located below the pleura or near the interlobar fissure and 3 had lesions distributed along the bronchovascular bundles. As for the morphology of the lesions, 6 had nodular lesions and 7 had patchy lesions; ground glass opacity with consolidation was observed in 6 children, among whom 3 had halo sign, and there was no typical paving stone sign. CONCLUSION(S): Infants and young children with COVID-19 tend to have mild clinical symptoms and imaging findings not as typical as those of adults, and therefore, the diagnosis of COVID-19 should be made based on imaging findings along with epidemiological history and nucleic acid detection. Chest CT has guiding significance for the early diagnosis of asymptomatic children.

Zhu, H., et al. (2020). "Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia." Translational Pediatrics **9**(1): 51-60.
Background: The newly identified 2019-nCoV, which appears to have originated in Wuhan, the capital city of Hubei province in central China, is spreading rapidly nationwide. A number of cases of neonates born to mothers with 2019-nCoV pneumonia have been recorded. However, the clinical features of these cases have not been reported, and there is no sufficient evidence for the proper prevention and control of 2019- nCoV infections in neonates. Method(s): The clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals from January 20 to February 5, 2020 were retrospectively

analyzed. Result(s): Among these 9 pregnant women with confirmed 2019-nCoV infection, onset of clinical symptoms occurred before delivery in 4 cases, on the day of delivery in 2 cases, and after delivery in 3 cases. In most cases, fever and a cough were the first symptoms experienced, and 1 patient also had diarrhea. Of the newborns born to these mothers, 8 were male and 2 were female; 4 were full-term infants and 6 were born premature; 2 were small-for-gestational-age (SGA) infants and 1 was a large-for-gestational-age (LGA) infant; there were 8 singletons and 2 twins. Of the neonates, 6 had a Pediatric Critical Illness Score (PCIS) score of less than 90. Clinically, the first symptom in the neonates was shortness of breath (n=6), but other initial symptoms such as fever (n=2), thrombocytopenia accompanied by abnormal liver function (n=2), rapid heart rate (n=1), vomiting (n=1), and pneumothorax (n=1) were observed. Up to now, 5 neonates have been cured and discharged, 1 has died, and 4 neonates remain in hospital in a stable condition. Pharyngeal swab specimens were collected from 9 of the 10 neonates 1 to 9 days after birth for nucleic acid amplification tests for 2019-nCoV, all of which showed negative results. Conclusion(s): Perinatal 2019-nCoV infection may have adverse effects on newborns, causing problems such as fetal distress, premature labor, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death. However, vertical transmission of 2019-nCoV is yet to be confirmed. Copyright © 2020 Translational Pediatrics.

Zhu, L., et al. (2020). "Clinical characteristics of a case series of children with coronavirus disease 2019." Pediatric Pulmonology **55**(6): 1430-1432.
We reported the clinical characteristics of a case series of 10 patients with coronavirus disease 2019 (COVID-19) aged from 1 year to 18 years. Seven patients had contact with confirmed COVID-19 family members before onset. Fever (4 [40.0%]) and cough (3 [30.0%]) were the most common symptoms. No patient showed leucopenia and lymphopenia on admission. Pneumonia was observed in chest CT images in 5 (50.0%) patients. Five (50.0%) patients received antiviral treatment. No patient had severe complications or developed a severe illness in our study. Our study indicated that COVID-19 children present less severe symptoms and have better outcomes.

Zimmermann, P. and N. Curtis (2020). "Coronavirus infections in children including COVID-19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children." Pediatric Infectious Disease Journal: 355-368.
Coronaviruses (CoVs) are a large family of enveloped, single-stranded, zoonotic RNA viruses. Four CoVs commonly circulate among humans: HCoV2-229E,-HKU1,-NL63 and-OC43. However, CoVs can rapidly mutate and recombine leading to novel CoVs that can spread from animals to humans. The novel CoVs severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The 2019 novel coronavirus (SARS-CoV-2) is currently causing a severe outbreak of disease (termed COVID-19) in China and multiple other countries, threatening to cause a global pandemic. In humans, CoVs mostly cause respiratory and gastrointestinal symptoms. Clinical manifestations range from a common cold to more severe disease such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure and even death. SARS-CoV, MERS-CoV and SARS-CoV-2 seem to less commonly affect children and to cause fewer symptoms and less severe disease in this age group compared with adults, and are associated with much lower case-fatality rates. Preliminary evidence suggests children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms. However, the importance of children in transmitting the virus remains uncertain. Children more often have gastrointestinal symptoms compared with adults. Most children with SARS-CoV present with fever, but this is not the case for the other novel CoVs. Many children affected by MERS-CoV are asymptomatic. The majority of children infected by novel CoVs have a documented household contact, often showing symptoms before them. In contrast, adults more often have a nosocomial exposure. In this review, we summarize epidemiologic, clinical and diagnostic findings, as well as

treatment and prevention options for common circulating and novel CoVs infections in humans with a focus on infections in children. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Zwald, M. L., et al. (2020). "Rapid Sentinel Surveillance for COVID-19 - Santa Clara County, California, March 2020." MMWR - Morbidity & Mortality Weekly Report **69**(14): 419-421.
On February 27, 2020, the Santa Clara County Public Health Department (SCCPHD) identified its first case of coronavirus disease 2019 (COVID-19) associated with probable community transmission (i.e., infection among persons without a known exposure by travel or close contact with a patient with confirmed COVID-19). At the time the investigation began, testing guidance recommended focusing on persons with clinical findings of lower respiratory illness and travel to an affected area or an epidemiologic link to a laboratory-confirmed COVID-19 case, or on persons hospitalized for severe respiratory disease and no alternative diagnosis (1). To rapidly understand the extent of COVID-19 in the community, SCCPHD, the California Department of Public Health (CDPH), and CDC began sentinel surveillance in Santa Clara County. During March 5-14, 2020, four urgent care centers in Santa Clara County participated as sentinel sites. For this investigation, county residents evaluated for respiratory symptoms (e.g., fever, cough, or shortness of breath) who had no known risk for COVID-19 were identified at participating urgent care centers. A convenience sample of specimens that tested negative for influenza virus was tested for SARS-CoV-2 RNA. Among 226 patients who met the inclusion criteria, 23% had positive test results for influenza. Among patients who had negative test results for influenza, 79 specimens were tested for SARS-CoV-2, and 11% had evidence of infection. This sentinel surveillance system helped confirm community transmission of SARS-CoV-2 in Santa Clara County. As a result of these data and an increasing number of cases with no known source of transmission, the county initiated a series of community mitigation strategies. Detection of community transmission is critical for informing response activities, including testing criteria, quarantine guidance, investigation protocols, and community mitigation measures (2). Sentinel surveillance in outpatient settings and emergency departments, implemented together with hospital-based surveillance, mortality surveillance, and serologic surveys, can provide a robust approach to monitor the epidemiology of COVID-19.

COVID-19 PMIS Articles < 2020

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Agrawal, H. and A. M. Qureshi (2019). "Cardiac Catheterization in Assessment and Treatment of Kawasaki Disease in Children and Adolescents." Children **6**(2): 21.
Cardiac catheterization has become a promising tool to assess and treat coronary artery lesions in patients with Kawasaki disease. Significant coronary artery lesions can now be treated via transcatheter route even in small children. Further development and miniaturization of this technology will help to promote widespread use to the benefit of small children suffering from coronary artery disease. The role of diagnostic and interventional coronary artery procedures in children and adolescents are discussed in this article.

Altman, M. C., et al. (2019). "Transcriptome networks identify mechanisms of viral and nonviral asthma exacerbations in children." Nature Immunology **20**(5): 637-651.
Respiratory infections are common precursors to asthma exacerbations in children, but molecular immune responses that determine whether and how an infection causes an exacerbation are poorly understood. By using systems-scale network analysis, we identify repertoires of cellular transcriptional pathways that lead to and underlie distinct patterns of asthma exacerbation. Specifically, in both virus-associated and nonviral exacerbations, we demonstrate a set of core exacerbation modules, among which epithelial-associated SMAD3 signaling is upregulated and lymphocyte response pathways are downregulated early in exacerbation, followed by later upregulation of effector pathways including epidermal growth factor receptor signaling, extracellular matrix production, mucus hypersecretion, and eosinophil activation. We show an additional set of multiple inflammatory cell pathways involved in virus-associated exacerbations, in contrast to squamous cell pathways associated with nonviral exacerbations. Our work introduces an in vivo molecular platform to investigate, in a clinical setting, both the mechanisms of disease pathogenesis and therapeutic targets to modify exacerbations. Copyright © 2019, The Author(s), under exclusive licence to Springer Nature America, Inc.

Aoki, Y., et al. (2019). "Propylthiouracil-induced anti-neutrophil cytoplasmic antibody-associated vasculitis mimicking Kawasaki disease." Paediatrics and International Child Health **39**(2): 142-145.
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is rare in children and is characterised as necrotising vasculitis predominantly affecting small and medium-sized vessels. Propylthiouracil (PTU), an antithyroid drug, has been implicated in drug-induced AAV. In contrast, Kawasaki disease (KD) is a common systemic vasculitis, typically observed in children, which affects the medium-sized vessels, including the coronary arteries. An 11-year-old girl who developed AAV while receiving PTU therapy for Graves' disease is described. She was admitted to hospital following a 2-day history of fever, cervical adenopathy, cheilitis and papular rash, 3 weeks after an increase in the PTU dose. Despite discontinuation of PTU and the administration of intravenous antibiotic therapy, her clinical condition deteriorated and over the next 2 days she developed severe diarrhoea, conjunctival injection and swelling and redness of the right index finger. Additional findings included liver dysfunction, hydrops of the gallbladder, coagulopathy and urine abnormalities, suggesting glomerulonephritis. She met the diagnostic criteria for KD and received intravenous immunoglobulin (IVIG) combined with prednisolone, with rapid resolution of clinical and laboratory parameters. Peeling of the right index fingertip became evident on Day 12 of admission. Serial ultrasound cardiography demonstrated no evidence of cardiac involvement. A high titre of myeloperoxidase ANCA was detected in the patient's serum on admission, and the titre decreased during the convalescent stage. This case demonstrates that children with PTU-associated AAV may present with clinical features mimicking KD, and that IVIG along with corticosteroid therapy may be effective in treating patients with drug-induced

severe systemic AAV. © 2018, © 2018 Informa UK Limited, trading as Taylor & Francis Group.

Arslanoglu Aydin, E., et al. (2019). "Pleural effusion as an atypical presentation of Kawasaki disease: a case report and review of the literature." Journal of Medical Case Reports [Electronic Resource] **13**(1): 344.
BACKGROUND: Kawasaki disease is an acute, febrile vasculitis of childhood that affects medium-sized arteries, predominantly the coronary arteries. It is a multisystem disease; therefore, it may present with non-cardiac findings of disease.
CASE PRESENTATION: Here, we report the case of 7-year-old Turkish girl who presented with symptoms of fever, chest pain, and vomiting, who was diagnosed as having Kawasaki disease. We also present a literature review on pulmonary involvement due to Kawasaki disease.
CONCLUSION: Pediatricians should consider the diagnosis of Kawasaki disease in the presence of pneumonia and pleural effusion that is nonresponsive to antibiotic therapy. This will prevent delay in diagnosis and the adverse consequences of the disease.

Ball, J. D., et al. (2019). "Clinical and Epidemiologic Patterns of Chikungunya Virus Infection and Coincident Arboviral Disease in a School Cohort in Haiti, 2014-2015." Clinical Infectious Diseases **68**(6): 919-926.
Background Beginning in December 2013, an epidemic of chikungunya virus (CHIKV) infection spread across the Caribbean and into virtually all countries in the Western hemisphere, with >2.4 million cases reported through the end of 2017. Methods We monitored a cohort of school children in rural Haiti from May 2014, through February 2015, for occurrence of acute undifferentiated febrile illness, with clinical and laboratory data available for 252 illness episodes. Results Our findings document passage of the major CHIKV epidemic between May and July 2014, with 82 laboratory-confirmed cases. Subsequent peaks of febrile illness were found to incorporate smaller outbreaks of dengue virus serotypes 1 and 4 and Zika virus, with identification of additional infections with Mayaro virus, enterovirus D68, and coronavirus NL63. CHIKV and dengue virus serotype 1 infections were more common in older children, with a complaint of arthralgia serving as a significant predictor for infection with CHIKV (odds ratio, 16.2; 95% confidence interval, 8.0-34.4; positive predictive value, 66%; negative predictive value, 80%). Conclusions Viral/arboviral infections were characterized by a pattern of recurrent outbreaks and case clusters, with the CHIKV epidemic representing just one of several arboviral agents moving through the population. Although clinical presentations of these agents are similar, arthralgias are highly suggestive of CHIKV infection. Copyright © The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America.

Baron, S., et al. (2019). "Cloning antibodies against kawasaki disease from acute plasmablast responses." Open Forum Infectious Diseases **6 (Supplement 2)**: S206-S207.
Background. Kawasaki Disease (KD) is a childhood vasculitis, marked by prolonged fevers and coronary artery inflammation/aneurysms in near one-quarter of those untreated. The cause remains unknown; however, epidemiologic and demographic data support a single preceding infectious agent may lead to KD. Plasmablasts (PBs) are a stage of transitional B-cells that lead to plasma cells, the long-lived antibody-producing cells of the bone marrow. After initial infection, peripherally circulating PB populations are enriched for cells with antibodies against the preceding infection. We have recently published data showing children with KD have similar PB responses to children with infections. We sought to define the antibody characteristics, including clonality, of these PBs during KD. Methods. We used antibody repertoire next-generation sequencing to characterize memory and PB populations. Additionally, pairing of heavy and light chains was performed with Chromium Single Cell Gene Expression (10x Genomics, Pleasanton, CA) using the Human B cell Single Cell V(D)J Enrichment Kit. Results. From subject 24, antibody sequences using VH4-34 and a 19 amino acid length complementarity determining region 3 showed a massive expansion between day 4 and 6 of fever. Chromium single-cell sequencing produced over 946 heavy and light chain paired sequences. Sequence comparison showed 40% of

sequences demonstrated markers of clonal expansion, which represented 100 clonal groups. Seven other KD subjects are being processed and comparative analysis will be presented. Conclusion. This clonal expansion within plasmablast populations supports that Kawasaki disease is caused by an infection. Antigen targeting of these monoclonal antibodies is currently being explored. (Figure Presented) .

Benavides-Nieto, M., et al. (2019). "The role of respiratory viruses in children with humoral immunodeficiency on immunoglobulin replacement therapy." Pediatric Pulmonology **54**(2): 194-199.
Background: The role of viruses in children with respiratory tract infections and humoral immunodeficiencies has hardly been studied. We have evaluated these infections in children with humoral immunodeficiencies who required immunoglobulin replacement therapy, considering their relationship with symptoms, lung function, bacterial co-infection, and outcomes. Method(s): We conducted a prospective case-control study during a 1-year period, including children with humoral immunodeficiencies receiving immunoglobulin replacement therapy. For each patient, at least one healthy family member was included. Respiratory samples for viral detection were taken every 1-3 months, and in case of respiratory tract infections. Symptoms questionnaires were filled biweekly. Spirometry and sputum culture were performed in every episode. Result(s): Sixty-six episodes were analyzed in 14 patients (median age 12 years; IQR 7-17), identifying 18 respiratory viruses (27.3%), being rhinovirus the most frequently isolated one (12/18; 66%). Positive viral episodes were associated with clinical symptoms (89% vs 43%), more frequent antibiotic treatment (44% vs 15%) or hospital admission (22% vs 0%) than negative ones. Patients with positive viral detection showed impaired lung function, with lower FEV1 and FVC values. Conclusion(s): In our experience, viral respiratory tract infections can cause significant respiratory symptoms and impaired lung function, in children with HID, despite immunoglobulin replacement therapy. These patients could benefit from the monitoring of viral infections, as these may be a gateway for ongoing lung damage.

Bettiol, A., et al. (2019). "Unveiling the Efficacy, Safety, and Tolerability of Anti-Interleukin-1 Treatment in Monogenic and Multifactorial Autoinflammatory Diseases." International Journal of Molecular Sciences **20**(8): 17.
Autoinflammatory diseases (AIDs) are heterogeneous disorders characterized by dysregulation in the inflammasome, a large intracellular multiprotein platform, leading to overproduction of interleukin-1(IL-1)beta that plays a predominant pathogenic role in such diseases. Appropriate treatment is crucial, also considering that AIDs may persist into adulthood with negative consequences on patients' quality of life. IL-1beta blockade results in a sustained reduction of disease severity in most AIDs. A growing experience with the human IL-1 receptor antagonist, Anakinra (ANA), and the monoclonal anti IL-1beta antibody, Canakinumab (CANA), has also been engendered, highlighting their efficacy upon protean clinical manifestations of AIDs. Safety and tolerability have been confirmed by several clinical trials and observational studies on both large and small cohorts of AID patients. The same treatment has been proposed in refractory Kawasaki disease, an acute inflammatory vasculitis occurring in children before 5 years, which has been postulated to be autoinflammatory for its phenotypical and immunological similarity with systemic juvenile idiopathic arthritis. Nevertheless, minor concerns about IL-1 antagonists have been raised regarding their employment in children, and the development of novel pharmacological formulations is aimed at minimizing side effects that may affect adherence to treatment. The present review summarizes current findings on the efficacy, safety, and tolerability of ANA and CANA for treatment of AIDs and Kawasaki vasculitis with a specific focus on the pediatric setting.

Boonyaratanakornkit, J., et al. (2019). "Early Respiratory Viral Acquisition after Allogeneic Hematopoietic Cell Transplant (HCT)." Biology of Blood and Marrow Transplantation **25 (3 Supplement)**: S346-S347.
Introduction: Respiratory infections after HCT lead to significant morbidity, mortality, and health

care costs due to pulmonary complications. In up to a third of patients following allogeneic HCT, infection can progress from an upper to a lower respiratory tract infection. Without vaccines or effective therapeutics for most viruses, very little can be done beyond supportive care. Objective(s): There is a need to identify risk factors for virus acquisition in HCT recipients in order to develop and implement better preventative interventions. Method(s): In a prospective study, 471 HCT patients enrolled between 2005 and 2010 underwent weekly PCR-based surveillance for RSV, metapneumovirus, parainfluenza virus 1-4, influenza A and B, rhinovirus, coronavirus, and adenovirus. Detailed weekly surveys were collected from subjects for up to 1 year post-transplant on symptoms and exposures to children under 10 years or sick contacts (within 3 feet for more than 1 hour total in the past week). We performed multivariable Cox regression analysis to identify risk factors associated with the time to first positive respiratory viral detection by PCR (asymptomatic and symptomatic) within the first 100 days HCT. Result(s): In this cohort, 211 patients (45%) acquired a respiratory virus in the first 100 days after transplant. Of those infected, 88 (42%) were symptomatic with at least 2 respiratory symptoms. We found significantly higher risk of acquiring any respiratory viral infection for patients with underlying chronic leukemia compared with other hematologic malignancies [hazard ratio (HR) 1.79 (1.16 - 2.77)], exposure to children under or over 4 years [HR 1.84 (1.36 - 2.48)], exposure to contacts with cold symptoms [HR 1.47 (1.02 - 2.12)], exposure to systemic steroids [HR 1.49 (1.07 - 2.08)], and absolute monocyte counts < 100/micro L [HR 1.81 (1.12 - 2.94)]. Age, age of child exposure, gender, smoking history, season, conditioning regimen, donor relationship, cell source, presence of acute GVHD, albumin level, total IgG level, lymphocyte counts, and neutrophil counts were not associated with risk for acquisition. We also analyzed the association of these same variables with the time to first positive respiratory viral detection with symptomatic respiratory disease. We found that exposure to children [HR 1.56 (1.03 - 2.35)] and exposure to steroids [HR 1.59 (1.01 - 2.52)] remained associated with acquisition of symptomatic respiratory viral infection. Conclusion(s): These data support the contribution of both exposure and immunologic determinants to the risk of respiratory viral acquisition with and without development of symptoms. Although many infections were asymptomatic, patients receiving steroids and those in close proximity to children may benefit from closer monitoring and counseling in the early post-transplant period. Copyright © 2018

Brini Khalifa, I., et al. (2019). "Demographic and seasonal characteristics of respiratory pathogens in neonates and infants aged 0 to 12 months in the Central-East region of Tunisia." Journal of Medical Virology **91**(4): 570-581.
Background: This study aimed to characterize the epidemiology of pathogenic respiratory agents in patients aged 0 to 12 months and hospitalized for acute respiratory infections in Tunisia between 2013 and 2014. Method(s): A total of 20 pathogens, including viruses, Mycoplasma pneumoniae, and Streptococcus pneumoniae, were detected using molecular sensitive assays, and their associations with the patient's demographic data and season were analyzed. Result(s): Viral infectious agents were found in 449 (87.2%) of 515 specimens. Dual and multiple infectious agents were detected in 31.4% and 18.6% of the samples, respectively. Viral infection was predominant in the pediatric environment (90.8%, P < 0.001), male patients (88.0%), and spring (93.8%). Rhinovirus was the most detected virus (51.8%) followed by respiratory syncytial virus A/B (34.4%), coronavirus group (18.5%), adenovirus (17.9%), and parainfluenza viruses 1-4 (10.9%). Respiratory Syncytial virus A/B was significantly associated with gender (38.0% male cases vs 28.3% female cases, P = 0.02). Infections by Adenovirus, Bocavirus, and Metapneumovirus A/B increased with increasing age of patients (predominated cases aged 6-12 months, P < 0.001). S. pneumoniae was detected in 30.9% of th tested samples. In 18.2% of the negative viral infections, only S. pneumoniae was identified. Conclusion(s): A predominance of the rhinovirus infection was observed in this study. Coronavirus subtypes were described for the first time in Tunisia. The observed different pathogenic profiles across age groups could be helpful to avoid the misclassification of patients presenting with ARIs at the triage level when no standardized protocol is available. This study will provide clues for physicians informing decisions

regarding preventive strategies and medication in Tunisia. Copyright © 2018 The Authors. Journal of Medical Virology Published by Wiley Periodicals, Inc.

Bunthi, C., et al. (2019). "Enhanced surveillance for severe pneumonia, Thailand 2010-2015." BMC Public Health **19**(Suppl 3): 472.
BACKGROUND: The etiology of severe pneumonia is frequently not identified by routine disease surveillance in Thailand. Since 2010, the Thailand Ministry of Public Health (MOPH) and US CDC have conducted surveillance to detect known and new etiologies of severe pneumonia.
METHODS: Surveillance for severe community-acquired pneumonia was initiated in December 2010 among 30 hospitals in 17 provinces covering all regions of Thailand. Interlinked clinical, laboratory, pathological and epidemiological components of the network were created with specialized guidelines for each to aid case investigation and notification. Severe pneumonia was defined as chest-radiograph confirmed pneumonia of unknown etiology in a patient hospitalized <=48 h and requiring intubation with ventilator support or who died within 48 h after hospitalization; patients with underlying chronic pulmonary or neurological disease were excluded. Respiratory and pathological specimens were tested by reverse transcription polymerase chain reaction for nine viruses, including Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and 14 bacteria. Cases were reported via a secure web-based system.
RESULTS: Of specimens from 972 cases available for testing during December 2010 through December 2015, 589 (60.6%) had a potential etiology identified; 399 (67.8%) were from children aged < 5 years. At least one viral agent was detected in 394 (40.5%) cases, with the most common of single vial pathogen detected being respiratory syncytial virus (RSV) (110/589, 18.7%) especially in children under 5 years. Bacterial pathogens were detected in 341 cases of which 67 cases had apparent mixed infections. The system added MERS-CoV testing in September 2012 as part of Thailand's outbreak preparedness; no cases were identified from the 767 samples tested.
CONCLUSIONS: Enhanced surveillance improved the understanding of the etiology of severe pneumonia cases and improved the MOPH's preparedness and response capacity for emerging respiratory pathogens in Thailand thereby enhanced global health security. Guidelines for investigation of severe pneumonia from this project were incorporated into surveillance and research activities within Thailand and shared for adaption by other countries.

Cameron, S. A., et al. (2019). "Coronary artery aneurysms are more severe in infants than in older children with Kawasaki disease." Archives of Disease in Childhood **104**(5): 451-455.
Objective We aimed to compare the severity of coronary artery abnormalities in Kawasaki disease between infants and older children. Methods We retrospectively reviewed and compared coronary artery dilation and aneurysm severity in infants <1 year of age with Kawasaki disease at our centre over a 10-year period with that observed in children ≥1 year of age in the Pediatric Heart Network Trial of Pulse Steroid Therapy in Kawasaki Disease. Coronary artery abnormalities were defined by z-scores according to American Heart Association guidelines. Results Of the 93 infants identified during the study period, 80 were treated with intravenous gamma globulin within the first 10 days of illness and were included for comparison to 170 children ≥1 year of age treated in the same time frame from the Pediatric Heart Network public database. The mean maximum z-score was significantly higher in infants compared with older children (3.37 vs 2.07, p<0.001). A higher incidence of medium and giant aneurysms was observed in infants compared with children ≥1 year of age (11% vs 3% for medium aneurysms, p=0.015; 8% vs <1% for giant aneurysms, p=0.005). Conclusions Infants with Kawasaki disease have more severe coronary artery dilation compared with older children, and a higher prevalence of medium and giant aneurysms. Because adverse outcomes are closely linked to the maximal coronary artery diameter in Kawasaki disease, patients diagnosed as infants require very close long-term monitoring for cardiac complications. © Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

Carman, K. B., et al. (2019). "Viral etiological causes of febrile seizures for respiratory pathogens (EFES

Study)." Human Vaccines and Immunotherapeutics **15**(2): 496-502.
Background: Febrile seizure is the most common childhood neurological disorder, is an important health problem with potential short- and long-term complications, also leading to economic burden and increased parental anxiety about fevers and seizures occurring in their children. There are no routine recommendation to detect etiological causes of FS for neurological perspective, further knowledge about the etiological causes of FS in children will support preventive measures and follow-up strategies. The aim of this study is to evaluate the percentage of respiratory viruses in children with FS. Method(s): This prospective multicenter study, entitled "Viral etiological causes of febrile seizures for respiratory pathogens (EFES Study)" examined representative populations in eight different cities in Turkey between March 1, 2016 and April 1, 2017. Nasopharyngeal swabs were taken from all children at presentation. A respiratory multiplex array was performed to detect for influenza A and B; respiratory syncytial virus A and B; human parainfluenza virus 1-2-3 and 4; human coronavirus 229E and OC43; human rhinovirus; human enterovirus; human adenovirus; human bocavirus; human metapneumovirus. Result(s): During the study period, at least one virus was detected in 82.7% (144/174) of children with FS. The most frequently detected virus was adenovirus, followed by influenza A and influenza B. Detection of more than one virus was present in 58.3% of the children with FS, and the most common co-existence was the presence of adenovirus and influenza B. In children younger than 12 months, Coronavirus OC43 was the most common, while influenza A was most frequently observed in children older than 48 months ($p < 0.05$). Human bocavirus was common in children who experienced complex FS, while respiratory syncytial virus (RSV) A was more common in children who experienced simple FS. Influenza B virus was the most common virus identified in children who were experiencing their first incidence of FS ($p < 0.05$). Conclusion(s): This study indicates that respiratory viruses are important in the etiology of FS in children. The results show that antibiotics must be prescribed carefully in children with FS since the majority of cases are related to viral causes. Widespread use of the existing quadrivalent influenza vaccine might be useful for the prevention of FS related to the flu. Further vaccine candidates for potential respiratory pathogens, including RSV, might be helpful for the prevention of FS. Copyright © 2018, © 2018 Taylor & Francis Group, LLC.

Cattalini, M., et al. (2019). "Sex Differences in Pediatric Rheumatology." Clinical Reviews in Allergy & Immunology **56**(3): 293-307.
Autoimmune diseases affect up to 10% of the world's population and, as a whole, they are far more common in females, although differences exist according to the single disease and also in different age groups. In childhood-onset autoimmune diseases, the sex bias is generally less evident than in adults, probably for the different hormonal milieau, being estrogens strongly implicated in the development of autoimmunity. Still, some rheumatic conditions, such as juvenile idiopathic arthritis (JIA), show a strong predilection for girls (F:M = 3-6.6:1), and differences may coexist between males and females regarding disease outcome. For example, chronic anterior uveitis associated with JIA affects more commonly girls but boys tend to have a more severe course. Systemic lupus erythematosus predominantly affects girls and women (F:M = 3-5:1 in children, F:M = 10-15:1 in adults). Behsigmaet's disease has been reported to be more prevalent in adult males (F:M = 1:1-4); in children, there are no differences. The sex ratio is equal in children and adults for Henoch-Schonlein purpura (F:M = 1:1). A higher male-to-female ratio exists for Kawasaki disease (F:M = 1:1.1-1.6 in children, F:M = 1:1,5 in adults). Juvenile dermatomyositis (F:M = 2-5:1), systemic sclerosis (F:M = 4:1 in children, F:M = 6:1 in adults), and Takayasu arteritis (F:M = 2:1 in children, F:M = 7-9:1 in adults) are more common in girls and women then in boys and men. There is no gender bias for acute rheumatic fever in children, while in adults, the F:M ratio is 2:1. Given that estrogen levels are not different between genders during childhood, pediatric rheumatic diseases could represent good models to study other mechanisms related to the development of autoimmunity. Recently, the levels of miRNA expression, and their variation according to sex chromosomes, have been linked to the development of autoimmune diseases, with different impact among sexes. This review will focus

not only on the sex bias reported in the more common rheumatic conditions of childhood, focusing on differences in incidence, but also on outcome and trying to depict the mechanisms underlying those differences.

Celik, K., et al. (2019). "Prevalence of respiratory pathogens during two consecutive respiratory syncytial virus seasons at a tertiary medical care center." Archivos Argentinos de Pediatria **117**(4): E356-E362.
Aim: To determine the etiological profiles of lower respiratory tract infection (LRI) in neonates during respiratory syncytial virus(RSV) season, and to define the clinical features of RSV-related infection and others. Method(s): The retrospective study included newborn infants who were hospitalized for LRI during the two consecutive RSV seasons, and then tested for possible etiological agent by multiplex real-time polymerase chain reaction. All relevant data were reviewed, and the clinical characteristics of RSV-related infection were compared to those of others. Result(s): Of 224 patients, 160 (71 %) were positive for at least one potentially causative agent. Of them, 65 % had RSV, and 15 % had more than on ecausative agent (co-infection). The RSV group had more the findings of respiratory distress ($p< 0.01$), abnormal chest radiography ($p< 0.01$), need for intensive care ($p< 0.01$), and duration of oxygen requirement ($p< 0.01$) but less fever on admission and duration of antibiotic use (for both, $p< 0.01$), and no longer hospital stay. Need of intensive care nursery was more common in patients with co-infection than others (25 % vs. 6.5 %, $p< 0.01$). Conclusion(s): This study highlighted that RSV was the most frequent agent in neonates hospitalized for LRI during the season, with a more severe clinical course than other detected pathogens. The disease severity of RSV infection may have seemed to be increased by the presence of coinfection and abnormal chest radiography.

Chang, A., et al. (2019). "Spatiotemporal analysis and epidemiology of kawasaki disease in western New York a 16-year review of cases presenting to a single tertiary care center." Pediatric Infectious Disease Journal **38**(6): 582-588.
Background: Kawasaki disease (KD) is one of the leading causes of acquired heart disease in children in developed nations. Epidemiologic evidence suggests that KD is related to an infectious agent; however, the cause remains unknown. Yearly incidence in Japan has been steadily increasing, but few long-term databases of KD cases from North America have been reviewed. Methods: We reviewed the epidemiology of local cases over a 16-year period to study incidence with time and temporal and geographic clustering of cases in a representative cohort in North America. Results: The yearly incidence in cases per population <5 years old per 100,000 was 20.2 and 15.9, using International Classification of Disease, ninth revision and detailed chart review, respectively. Using International Classification of Disease, ninth revision alone overestimates our incidence by 27%. We show a distinct seasonality of cases with winter predominance. Applying Kulldorff 's spatial scan statistic revealed no significant clustering of cases with either purely spatial or space-time analyses. On purely nonconstrained temporal SaTScan analysis, there was a significant clustering of cases in a 67- to 68-week period in 2000-2001. Conclusions: Our analysis reveals an apparent outbreak of KD in our region in 2000-2001. In contrast to Japan, for the last 14 years, the incidence in our region has been stable.

Chanthavanich, P., et al. (2019). "Safety, Tolerability and Immunogenicity of an MF59-adjuvanted, Cell Culture-derived, A/H5N1, Subunit Influenza Virus Vaccine: Results From a Dose-finding Clinical Trial in Healthy Pediatric Subjects." The Pediatric infectious disease journal **38**(7): 757-764.
BACKGROUND: A/H5N1 influenza virus has significant pandemic potential, and vaccination is the main prophylactic measure. This phase 2, randomized, observer-blind, multicenter study evaluated the safety and immunogenicity of two MF59-adjuvanted, cell culture-derived H5N1 (aH5N1c) vaccine formulations in healthy pediatric subjects 6 months to 17 years old. METHOD(S): Subjects (N = 662) received 2 aH5N1c doses 3 weeks apart, containing either 7.5

mug (full dose) or 3.75 mug (half dose) hemagglutinin antigen per dose. Local reactions and adverse events (AEs) were assessed by age. Antibody responses were measured by hemagglutination inhibition assay and assessed as geometric mean titers, geometric mean ratios (GMRs) and percentages of subjects achieving titers >=1:40 and seroconversion (NCT01776554). RESULT(S): No vaccine-related serious AEs occurred. Incidence of solicited local reactions and systemic AEs were similar across vaccine groups. Tenderness and irritability in <6-year olds, and injection site pain, myalgia and fatigue in 6-17-year olds were the most commonly reported reactions in both full- and half-dose recipients. Frequencies of AEs were lower after the second dose than the first dose in all vaccine and age groups. Three weeks after the administration of a second dose, both full- and half-dose formulations met the Center for Biologics Evaluation Research and Review (United States) and Committee for Medicinal Products for Human Use (EU) licensure criteria for titers >=1:40 (full dose 96% subjects; half dose 86%), seroconversion (full dose 96% subjects; half dose 86%), and GMR (full dose GMR 262; half dose 84). Antibody responses were highest in 6-35-month olds. CONCLUSION(S): In pediatric subjects, both aH5N1c vaccine formulations were well tolerated and highly immunogenic, meeting both US and EU licensure criteria for pandemic influenza vaccines.

Chaudhary, H., et al. (2019). "Biomarkers for Kawasaki Disease: Clinical Utility and the Challenges Ahead." Frontiers in Pediatrics **7**: 242.
Kawasaki disease (KD) has replaced acute rheumatic fever as the most common cause of acquired heart disease in children in the developed world and is increasingly being recognized from several developing countries. It is a systemic vasculitis with a predilection for coronary arteries. The diagnosis is based on a constellation of clinical findings that appear in a temporal sequence. Quite understandably, this can become a problem in situations wherein the clinical features are not typical. In such situations, it can be very difficult, if not impossible, to arrive at a diagnosis. Several biomarkers have been recognized in children with acute KD but none of these has reasonably high sensitivity and specificity in predicting the course of the illness. A line up of inflammatory, proteomic, gene expression and micro-RNA based biomarkers has been studied in association with KD. The commonly used inflammatory markers e.g. erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and total leucocyte counts (TLC) lack specificity for KD. Proteomic studies are based on the identification of specific proteins in serum, plasma and urine by gel electrophoresis. A host of genetic studies have identified genes associated with KD and some of these genes can predict the course and coronary outcomes in the affected individuals. Most of these tests are in the early stages of their development and some of these can predict the course, propensity to develop coronary artery sequelae, intravenous immunoglobulin (IVIg) resistance and the severity of the illness in a patient. Development of clinical criteria based on these tests will improve our diagnostic acumen and aid in early identification and prevention of cardiovascular complications.

Claudio, A. M., et al. (2019). "Antibiotic Use and Respiratory Pathogens in Adults With Sickle Cell Disease and Acute Chest Syndrome." Annals of Pharmacotherapy **53**(10): 991-996.
Background: Acute chest syndrome (ACS) is an acute complication of sickle cell disease (SCD). Historically, the most common pathogens were Chlamydophila pneumoniae, Mycoplasma pneumoniae, and respiratory syncytial virus. Pediatric patients receiving guideline-adherent therapy experienced fewer ACS-related and all-cause 30-day readmissions compared with those receiving nonadherent therapy. This has not been evaluated in adults. Objective(s): The primary objectives were to characterize antibiotic use and pathogens. The secondary objective was to assess the occurrence of readmissions associated with guideline-adherent and clinically appropriate treatment compared with regimens that did not meet those criteria. Method(s): A retrospective cohort analysis was conducted for adults with SCD hospitalized between August 1, 2014, and July 31, 2017, with pneumonia (PNA) or ACS. The study was approved by the institutional review board. Result(s): A total of 139 patients with 255 hospitalizations were reviewed. Among 41 respiratory cultures, 3 organisms were isolated: Cryptococcus neoformans,

Pseudomonas aeruginosa, and budding yeast. Respiratory panels were collected on 121 admissions, with 17 positive for 1 virus; all were negative for Chlamydophila pneumoniae and M pneumoniae. There were significantly more ACS-/PNA-related 7-day readmissions from patients on guideline-adherent regimens compared with nonadherent regimens (3.7% vs 0%; P = 0.04). Conclusion and Relevance: These findings challenge existing knowledge regarding the most common pathogens in adults with SCD with ACS or PNA. Routine inclusion of a macrolide may not be necessary. Future studies focused on pathogen characterization with standardized assessment are necessary to determine appropriate empirical therapy in this population.

Coelho, N. H., et al. (2019). "Rare Condition, Unusual Anatomy, Elegant Solution - an Uncommon Manifestation of Kawasaki Disease." EJVES Short Reports **42**: 12-14.
Introduction: Peripheral artery aneurysms are a rare manifestation of Kawasaki disease (KD), with an estimated incidence of approximately 2% of all KD patients. The case of a 14-year-old girl with past clinical history suggestive of KD is reported; she presented with an aneurysm located in the brachial part of a superficial brachioulnoradial artery, still with the genuine brachial artery in place (an anatomical variation with a reported incidence of 0.14-1.3% in general population). Relevant medical data were collected from the hospital database. Report: This is a report of a case of a symptomatic superficial brachioulnoradial artery aneurysm, secondary to KD, treated with aneurysm exclusion and superficial brachioulnoradial to the genuine brachial artery transposition. Uneventful intra- and postoperative course with symptom resolution is reported. Discussion(s): The coexistence of a rare manifestation of KD (peripheral aneurysm) with an even rarer brachial artery variation allowed a simple but elegant solution, making this a unique case.

Darby, J. B., et al. (2019). "Variability in Kawasaki disease practice patterns: A survey of hospitalists at pediatric hospital medicine 2017." Hospital Pediatrics **9**(9): 724-728.
OBJECTIVE: To explore practice variations in the care of patients with Kawasaki disease (KD) among pediatric hospitalist physicians (PHPs). METHOD(S): A 13-item questionnaire was developed by a multi-institutional group of KD experts. The survey was administered via live-audience polling by using smartphone technology during a KD plenary session at the 2017 Pediatric Hospital Medicine National Meeting, and simple descriptive statistics were calculated. RESULT(S): Of the 297 session attendees, 90% responded to at least 1 survey question. Approximately three-quarters of respondents identified as PHPs practicing in the United States. The reported length of inpatient monitoring after initial intravenous immunoglobulin (IVIG) therapy demonstrated a wide time distribution (30% 24 hours, 36% 36 hours, and 31% 48 hours). Similarly, PHP identification of the treatment failure interval, indicated by recrudescent fever after IVIG, demonstrated a broad distribution (56% 24 hours, 27% 36 hours, and 16% 48 hours). Furthermore, there was variation in routine consultation with non-PHP subspecialists. In contrast, PHPs reported little variation in their choice of initial and refractory treatment of patients with KD. CONCLUSION(S): In a convenience sample at a national hospitalist meeting, there was variation in reported KD practice patterns, including observation time after initial treatment, time when the recurrence of fever after initial therapy was indicative of nonresponse to IVIG, and routine consultation of non-PHP subspecialists. These results may guide future study of KD practice patterns and inform efforts to improve evidence-based practices in the care of patients with KD.

De Conto, F., et al. (2019). "Epidemiology of human respiratory viruses in children with acute respiratory tract infection in a 3-year hospital-based survey in Northern Italy." Diagnostic Microbiology and Infectious Disease **94**(3): 260-267.
Acute respiratory tract infections (ARTIs) are among the leading causes of morbidity and mortality in children. The viral etiology of ARTIs was investigated over 3 years (October 2012-September 2015) in 2575 children in Parma, Italy, using indirect immunofluorescent

staining of respiratory samples for viral antigens, cell culture, and molecular assays. Respiratory viruses were detected in 1299 cases (50.44%); 1037 (79.83%) were single infections and 262 (20.17%) mixed infections. The highest infection incidence was in children aged >6 months to <=3 years (57.36%). Human respiratory syncytial virus (27.12%) and human adenovirus (23.58%) were the most common viruses identified. The virus detection rate decreased significantly between the first and third epidemic season (53.9% vs. 43.05%, P < 0.0001). The simultaneous use of different diagnostic tools allowed us to identify a putative viral etiology in half the children examined and to provide an estimate of the epidemiology and seasonality of respiratory viruses associated with ARTIs. Copyright © 2019 Elsevier Inc.

Del Toro Rojas, R., et al. (2019). "Atypical presentation and early recurrence of kawasaki disease in a female infant: Case report." Annals of the Rheumatic Diseases **78 (Supplement 2)**: 1945. Background: Kawasaki Disease (KD) is the second most common vascu-litis in the pediatric population and the leading cause for pediatric acquired heart disease in developed countries. It is commonly diagnosed in the Mexican pediatric population, epidemiology in this country is not established, since cases are not usually reported to the healthcare system. The clinical features are quite variable, but diagnosis and prompt treatment will decrease morbidity and mortality. Coronary artery aneurysms are the most common complication, which represent the leading cause of acute coronary syndrome before 40 years of age. Recurrence of KD is estimated to be around 3% in Japanese patients and 1% in the United States, nevertheless, this data in Latin-American children is unknown. It usually affects patients before reaching 3 years old and within 2 years of the initial attack, presenting with an abrupt onset and higher complication rates, requiring aggressive workup, treatment and follow-up. Objective(s): To review an atypical presentation of KD and early recurrence in a 7-month-old female. Method(s): We present a 7-month-old female diagnosed with KD at 48 days old. She presented to the emergency unit with irritability, high and persistent fever and acholia. During workup, she was found with cholesta-sis and gallbladder hydrops. Negative CSF, blood and urine cultures were documented during hospitalization, and fulfilled the KD criteria. The cardiac ultrasound revealed coronary abnormalities: a RCA of 2.8mm (Z-Score +4.79), LCA of 3.3mm (Z-Score +5.69) and LAD of 2.4mm (Z-SCORE +4.25), which fit into classification 3 and 4, as small and medium aneurysms, according to AHA 2017. Immunoglobulin (2g/kg) and aspirin (80mg/kg) were administered and she was discharged 36 hours after the IVIg infusion, afebrile and with ambulatory follow-up, 30 days later the coronary abnormalities showed RCA of 2.0mm (Z-Score +2.3), LCA of 3.0mm (Z-Score +6), LAD 2.3mm (Z-Score +2.9). Six months later, she presented fever for 6 days, irritability and polymorphous rash. On physical exam BCGitis, non-suppurative conjunctivitis and pallor in hands and feet, elevated CRP and ESR, leukocytosis, thrombocytosis and sterile leukocyturia. Echocardiography reported RCA od 2.4mm (Z-Score +4.8), LCA of 3.1 (Z-Score +4.2) and LAD of 2.3mm (Z-Score +3.2), diagnosing KD recurrence, admitting the patient for IVIg and aspirin administration. Result(s): The patient was treated with IVIg and aspirin. Follow-up by Cardiology determined improvement of Z-Scores. Recurrence occurred with worsening of the cardiac abnormalities. Cardiac prognosis is importantly affected due to the atypical age, vascular abnormalities and repeated vasculitic process. Rheumatologic consult should be considered since disease like Takayasu Arteritis, Polyarteritis Nosa and ADA2 deficiency need to be ruled out. Conclusion(s): KD needs prompt diagnosis and treatment due to the potential consequences when delayed. Clinical suspicion is important due to the possible atypical presentation. As with this patient, age, gender and presentation are not exclusive. Despite adequate treatment, recurrence and worsening of the cardiac abnormalities occurred. Both KD events before 1 year old and with atypical presentations. Rheumatologic and cardiac follow-up need to be stringent through lifetime, to determine pharma-cologic treatment, as ell as physical activity and reproductive counseling.

Derrar, F., et al. (2019). "Virologic study of acute lower respiratory tract infections in children admitted to the paediatric department of Blida University Hospital, Algeria." New Microbes and New

Infections **30 (no pagination)**(100536).
Acute lower respiratory tract infections (ALRTI)such as pneumonia and bronchiolitis are major causes of mortality and morbidity in children under 5 years of age. The main microbial agents responsible for ALRTI are either bacterial agents (Streptococcus pneumoniae, Haemophilus influenzae type b, Mycoplasma pneumoniae)or viruses (respiratory syncytial virus (RSV, also known as human orthopneumovirus), Myxovirus influenzae, Myxovirus parainfluenzae, adenovirus)[1]. More recently, other viruses (rhinovirus, metapneumovirus, coronavirus, bocavirus)have been implicated in ALRTI; their identification has been facilitated by new molecular biology techniques such as real-time PCR. To our knowledge, these emerging viruses have never been the subject of epidemiologic studies in our country. Copyright © 2019 The Authors

Deschamp, A. R., et al. (2019). "Early respiratory viral infections in infants with cystic fibrosis." Journal of Cystic Fibrosis **18**(6): 844-850.
Background: Viral infections contribute to morbidity in cystic fibrosis (CF), but the impact of respiratory viruses on the development of airway disease is poorly understood. Method(s): Infants with CF identified by newborn screening were enrolled prior to 4 months of age to participate in a prospective observational study at 4 centers. Clinical data were collected at clinic visits and weekly phone calls. Multiplex PCR assays were performed on nasopharyngeal swabs to detect respiratory viruses during routine visits and when symptomatic. Participants underwent bronchoscopy with bronchoalveolar lavage (BAL) and a subset underwent pulmonary function testing. We present findings through 8.5 months of life. Result(s): Seventy infants were enrolled, mean age 3.1 +/- 0.8 months. Rhinovirus was the most prevalent virus (66%), followed by parainfluenza (19%), and coronavirus (16%). Participants had a median of 1.5 viral positive swabs (range 0-10). Past viral infection was associated with elevated neutrophil concentrations and bacterial isolates in BAL fluid, including recovery of classic CF bacterial pathogens. When antibiotics were prescribed for respiratory-related indications, viruses were identified in 52% of those instances. Conclusion(s): Early viral infections were associated with greater neutrophilic inflammation and bacterial pathogens. Early viral infections appear to contribute to initiation of lower airway inflammation in infants with CF. Antibiotics were commonly prescribed in the setting of a viral infection. Future investigations examining longitudinal relationships between viral infections, airway microbiome, and antibiotic use will allow us to elucidate the interplay between these factors in young children with CF. Copyright © 2019

Desforges, M., et al. (2019). "Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?" Viruses **12**(1): 20.
Respiratory viruses infect the human upper respiratory tract, mostly causing mild diseases. However, in vulnerable populations, such as newborns, infants, the elderly and immune-compromised individuals, these opportunistic pathogens can also affect the lower respiratory tract, causing a more severe disease (e.g., pneumonia). Respiratory viruses can also exacerbate asthma and lead to various types of respiratory distress syndromes. Furthermore, as they can adapt fast and cross the species barrier, some of these pathogens, like influenza A and SARS-CoV, have occasionally caused epidemics or pandemics, and were associated with more serious clinical diseases and even mortality. For a few decades now, data reported in the scientific literature has also demonstrated that several respiratory viruses have neuroinvasive capacities, since they can spread from the respiratory tract to the central nervous system (CNS). Viruses infecting human CNS cells could then cause different types of encephalopathy, including encephalitis, and long-term neurological diseases. Like other well-recognized neuroinvasive human viruses, respiratory viruses may damage the CNS as a result of misdirected host immune responses that could be associated with autoimmunity in susceptible individuals (virus-induced neuro-immunopathology) and/or viral replication, which directly causes damage to CNS cells (virus-induced neuropathology). The etiological agent of several neurological disorders remains unidentified. Opportunistic human respiratory pathogens could be associated with the triggering

or the exacerbation of these disorders whose etiology remains poorly understood. Herein, we present a global portrait of some of the most prevalent or emerging human respiratory viruses that have been associated with possible pathogenic processes in CNS infection, with a special emphasis on human coronaviruses.

Dionne, A., et al. (2019). "Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis." Pediatrics **143**(6).
BACKGROUND: Coronary artery aneurysms (CAA) are a serious complication of Kawasaki disease. Treatment with intravenous immunoglobulin (IVIg) within 10 days of fever onset reduces the risk of CAA from 25% to,5%. Corticosteroids and infliximab are often used in high-risk patients or those with CAA at diagnosis, but there are no data on their longer-term impact on CAA. METHODS: Retrospective multicenter study including children who had CAA with a z score $2.5 and,10 at time of diagnosis and who received primary therapy with IVIg alone or in combination with either corticosteroids or infliximab within 10 days of onset of fever. RESULTS: Of 121 children, with a median age of 2.8 (range 0.1–15.5) years, 30 (25%) received primary therapy with corticosteroids and IVIg, 58 (48%) received primary therapy with infliximab and IVIg, and 33 (27%) received primary therapy with IVIg only. Median coronary z scores at the time of diagnosis did not differ among treatment groups (P = .39). Primary treatment intensification with either corticosteroids or infliximab were independent protective factors against progression of coronary size on follow-up (coefficient: 21.31 [95% confidence interval: 22.33 to 20.29]; coefficient: 21.07 [95% confidence interval: 21.95 to 20.19], respectively). CONCLUSIONS: Among a high-risk group of patients with Kawasaki disease with CAA on baseline echocardiography, those treated with corticosteroids or infliximab in addition to IVIg had less progression in CAA size compared with those treated with IVIg alone. Prospective randomized trials are needed to determine the best adjunctive treatment of patients who present with CAA. Copyright © 2019 by the American Academy of Pediatrics

Doan, T. T., et al. (2019). "Regadenoson Stress Perfusion Cardiac Magnetic Resonance Imaging in Children With Kawasaki Disease and Coronary Artery Disease." American Journal of Cardiology **124**(7): 1125-1132.
Coronary artery (CA) stenosis and occlusion in convalescent Kawasaki disease (KD) is progressive and may result in myocardial infarction. The use of regadenoson, a strong selective CA vasodilator with low side effect profile, for stress cardiac magnetic resonance (CMR) imaging has not been studied in children with KD. The safety, feasibility, and diagnostic utility of regadenoson stress CMR was assessed in children with KD and CA abnormalities. A retrospective review of regadenoson stress CMR in children with convalescent KD was performed. Hemodynamics changes after regadenoson administration and adverse effects were recorded. First-pass perfusion was evaluated at rest and during pharmacologic stress. The results were compared with anatomic CA imaging. Forty-one stress CMR (18 sedated examinations, 44%) were performed successfully in 32 patients. Median age was 11.2 years (range 2.2 to 18.6) and weight 41 kg (range 13 to 93.4). Heart rate increased 66 ± 25% (p <0.005) after regadenoson. Minor adverse events occurred in 6 sedated and 1 unsedated patients. Hypoperfusion during stress occurred in 16 of 41 (39%), including 5 inducible, 9 inducible and fixed, and 2 fixed lesions. Late gadolinium enhancement was present in 10 of 16 with hypoperfusion and in 1 without hypoperfusion. Stress CMR had 100% positive agreement and >90% negative and overall agreement with moderate-to-severe CA stenoses. Four patients with hypoperfusion underwent revascularization for severe CA stenoses. In conclusion, regadenoson stress CMR is hemodynamically safe and feasible in children with KD and CA disease. It has excellent agreement with CA angiography and aided decision-making to proceed with revascularization. © 2019 Elsevier Inc.

Dogra, M., et al. (2019). "A not so common cold-a case of acute respiratory distress syndrome due to adenovirus-associated pneumonia." American Journal of Respiratory and Critical Care Medicine.

Conference **199**(9).
Adenovirus is a double-stranded DNA virus, and is a common cause of febrile illnesses and upper respiratory tract syndromes in children and infants. Most diseases are self limited. It has rarely been reported to cause severe lower respiratory tract infections in immunocompromised adult patients. We report a rare case of Acute respiratory distress syndrome (ARDS) due to adenovirus-associated pneumonia in an immunocompetent patient. Case Report; A 45 year old healthy male came to the hospital with fever, chills, cough and shortness of breath for 7 days and was requiring supplemental oxygen. Chest X ray on admission showed consolidation in the right upper lobe. He was started on ceftriaxone and azithromycin for suspected community acquired pneumonia. On day 2 of admission, he became increasingly hypoxemic and was transferred to the ICU. He required high flow nasal cannula initially and mechanical ventilation on day 3. Antibiotics were switched to vancomycin, zosyn and oseltamivir for broader coverage. Respiratory panel PCR was positive for Adenovirus and negative for Influenza virus, respiratory syncytial virus, human metapneumovirus, parainfluenza virus, coronavirus, bordetella pertussis, mycoplasma pneumoniae and chlamydia pneumoniae. Sputum and blood bacterial and fungal cultures were negative. On day 4, his PaO2/FiO2 ratio worsened and chest x ray showed worsening diffuse opacities, suggestive of ARDS. Patient was paralyzed, proned and was started on APRV mode of ventilation. Repeat microbiologic cultures including bacterial, AFB and fungal cultures were obtained through bronchoscopic alveolar lavage, which were negative as well. Patient was managed supportively and was successfully extubated on day 10. Subsequently he was transferred to general ward and was discharged home. He was alive and had normal activities at the 1-year follow up assessment. Discussion; ARDS is an acute, diffuse, inflammatory lung injury, associated with increased vascular permeability, diffuse alveolar damage and loss of aerated tissue. It is characterized by non-cardiogenic pulmonary edema with bilateral chest radiograph opacities and hypoxemia refractory to oxygen therapy. Adenovirus is a rare cause of ARDS in immunocompetent patients. Patients initially present with flu-like symptoms, cough, fever and can progress to rapidly worsening hypoxia refractory to oxygen therapy. The management is mostly supportive. Potential agents include brincidofovir and cidofovir, but there use is limited due to potential severe nephrotoxicity and myelosuppression. Conclusion; This case aims to sensitize physicians to consider adenovirus-associated ARDS as a differential in immunocompetent patients.(Figure Presented).

Dominguez, S. R., et al. (2019). "Diagnostic and Treatment Trends in Children with Kawasaki Disease in the United States, 2006-2015." Pediatric Infectious Disease Journal **38**(10): 1010-1014.
Objective: To evaluate variations in treatment practice and compliance with national guidelines for the diagnostic evaluation of children with Kawasaki disease (KD). Study Design: We used the Pediatric Hospital Information System database to analyze demographic, laboratory and treatment data from patients admitted with KD between January 1, 2006, and December 31, 2015. Results: During the study period, 12,089 children with KD were diagnosed. Nearly all patients had a complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein ordered. Fewer patients had alanine aminotransferase (48.6%) or a urinalysis (75.3%). A small percentage of children had abdominal imaging (11.5%), neck imaging (5.9%), and lumbar punctures (4.5%), and 36.0% of patients received antibiotic therapy. Obtaining echocardiograms pretreatment and the use of steroids and infliximab significantly increased over the study period ($P < 0.001$). For patients who failed initial intravenous immunoglobulin (IVIG) monotherapy, 82.0% received a second dose of IVIG, 7.7% received steroids, 6.5% received infliximab, and 3.9% received combination therapy. Patients receiving infliximab or steroids as second therapy had a higher response rate than those who received only a second IVIG dose (87.9% versus 83.0% versus 73.3%, $P < 0.001$). Conclusions: KD remains a challenging diagnosis. Opportunities exist for earlier use of echocardiograms in the evaluation of children with potential KD. Significant variations in practice exist surrounding second-line therapy. Our data suggest superiority of second-line therapy use of infliximab or steroids over IVIG in terms of reducing need for additional therapies. Prospective, controlled studies are needed to confirm this finding.

Duignan, S., et al. (2019). "Refractory Kawasaki disease: diagnostic and management challenges." Pediatric Health Medicine & Therapeutics **10**: 131-139.
Kawasaki disease (KD), an acute, self-limiting, medium-sized arterial vasculitis, is now the most common cause of acquired heart disease in childhood in the developed world. In this review, we discuss the diagnosis of KD, predicting resistance to traditional therapy and treatment options in refractory or high-risk disease. We also highlight ongoing clinical trials and other potential avenues of research which may prove beneficial in managing children, especially those with resistant KD.

Emanuels, A., et al. (2019). "Respiratory viral coinfection in a birth cohort of infants in rural Nepal." Open Forum Infectious Diseases **6 (Supplement 2)**: S797-S798.
Background. Acute respiratory illnesses are a leading cause of global morbidity and mortality in children. Coinfection with multiple respiratory viruses is common. Although the effects of each virus have been studied individually, the effects of coinfection on disease severity or healthcare seeking are less well-understood. Methods. A secondary analysis was performed of a maternal influenza vaccine trial conducted between 2011 and 2014 in rural southern Nepal. Prospective weekly active household-based surveillance of infants was conducted from birth to 180 days of age. Mid-nasal swabs were collected and tested for respiratory syncytial virus (RSV), rhinovirus, influenza, human metapneumovirus (HMPV), coronavirus, parainfluenza (HPIV), and bocavirus by RT-PCR. Coinfection was defined as the presence of two or more respiratory viruses simultaneously detected as part of the same illness episode. Maternal vaccination status, infant age, prematurity, and number of children under 5 in the household were adjusted for with multivariate logistic regression. Results. Of 1,730 infants with a respiratory illness, 327 (19%) had at least two respiratory viruses detected on their primary illness episode. Coinfection status did not differ by maternal vaccination status, infant age, premature birth, and number of children under 5 in the household. Of 113 infants with influenza, 23 (20%) had coinfection. Of 214 infants with RSV, 87 (41%) had coinfection. Overall, infants with coinfection had increased occurrence of fever lasting 4 or more days overall (OR 1.4, 95% CI: 1.1, 2.0), and in the subset of infants with influenza (OR 5.8, 95% CI: 1.8, 18.7). Coinfection was not associated with seeking further care (OR 1.1, 95% CI: 0.8, 1.5) or pneumonia (OR 1.2, 95% CI: 1.0, 1.6). Conclusion. A high proportion of infants experiencing their first respiratory illness had multiple viruses detected. Coinfection with influenza was associated with longer duration of fever compared with children with influenza alone, but was not associated with increased illness severity by other measures. (Figure Presented).

Eroglu, C., et al. (2019). "The relation between serum vitamin D levels, viral infections and severity of attacks in children with recurrent wheezing." Allergologia et Immunopathologia **47**(6): 591-597.
Introduction and Objectives: Vitamin D deficiency is associated with increased susceptibility to infections and wheezing. We aimed to evaluate the relation between vitamin D levels, viral infections and severity of attacks in children with recurrent wheezing. Material(s) and Method(s): A total of 52 patients who applied with wheezing, at the ages of 12-60 months with a history of three or more wheezing attacks in the last year and 54 healthy children were included. Sociodemographic data, risk factors for recurrent wheezing, and the severity of the wheezing attacks were recorded. 25(OH)D3, calcium, phosphor, alkaline phosphatase and parathormone levels of all children were measured. Nasopharyngeal samples of the patients for viruses were studied by multiplex polymerase chain reaction. Result(s): For the patient group, being breastfed for six months or less, history of cesarean section, cigarette exposure, humid home environment, and family history of allergic disease were significantly higher compared with the control group. Serum vitamin D levels in the patient group were significantly lower compared to the control group. There was no significant relationship between vitamin D levels and hospitalization, oxygen or steroid therapy. Virus was detected in 38 patients (73%). Rhinovirus (63.2%) was the most

frequently detected virus. Coinfection was found in 14 (36.8%) patients. There was no statistically significant difference between detection of virus and vitamin D levels. Conclusion(s): Cigarette exposure, being breastfed six months or less, humid home environment, history of cesarean section, family history of allergic disease and vitamin D deficiency might be risk factors for recurrent wheezing. Copyright © 2019 SEICAP

Esposito, S., et al. (2019). "The Gut Microbiota-Host Partnership as a Potential Driver of Kawasaki Syndrome." Frontiers in Pediatrics **7**: 124.
Kawasaki syndrome (KS) is a necrotizing vasculitis of small- and medium-sized vessels mostly affecting children under 5 years of age; a host of clinical and epidemiological data supports the notion that KS might result from an infectious disease. However, many efforts have failed to identify a potentially universal trigger of KS. The contribution of the intestinal microbial community-called the "microbiota"-to KS has been evaluated by an increasing number of studies, though limited to small cohorts of patients. Differences in the microbiota composition were found in children with KS, both its acute and non-acute phase, with abnormal colonization by Streptococcus species in the intestinal tract and a wider presence of Gram-positive cocci in jejunal biopsies. In particular, a higher number of Gram-positive cocci (of the genera Streptococcus and Staphylococcus), Eubacterium, Peptostreptococcus, and HSP60-producing Gram-negative microbes have been found in the stools of KS children, and their effects on the antigenic repertoire of specific T cells and Vbeta2 T cell expansion have been assessed. Conversely, Lactobacilli were lacking in most children with KS compared with other febrile illnesses and healthy controls. All studies available to date have confirmed that an imbalance in the gut microbiota might indirectly interfere with the normal function of innate and adaptive immunity, and that variable microbiota interactions with environmental factors, mainly infectious agents, might selectively drive the development of KS in genetically susceptible children. Further investigations of the intestinal microflora in larger cohorts of KS patients will provide clues to disentangle the pathogenesis of this disease and probably indicate disease-modifying agents or more rational KS-specific therapies.

Eugenie, G., et al. (2019). "Epidemiology of the Kawasaki disease in children in Switzerland." Swiss Medical Weekly **149 (Supplement 235)**: 2S.
Introduction: Kawasaki disease (KD) was first described in 1967 and is now the leading cause of acquired heart disease in children in developed countries. It is an acute febrile illness of unknown aetiology occurring predominantly in infants and young children and most commonly affect-ing coronary arteries. The epidemiology of KD is unknown in Switzerland, therefore we conducted a national study to investigate the demography, diagnosis and treatment of children with KD. Material(s) and Method(s): We worked with the Swiss Paediatric Surveil-lance Unit (SPSU) to take a census of the children hospitalised with the diagnosis of KD in Switzerland from March 2013 to February 2017, in a prospective manner. We defined complete KD by the AHA criteria: the presence of >=5 days of fever and >=4 of the 5 principal clinical features (cutaneous rash, cervical lymphadenopathy >1,5 cm diameter, conjunc-tivitis, changes of lips or oral/pharyngeal erythema and extremity changes). The cases with less than 4 clinical signs were considered in-complete. We included all children under 17 years of age. Result(s): We included 175 patients, 105 (60%) were boys, with a median age of 38,2 months (standard deviation (SD): 31,0). The most frequent clinical sign was a rash (85,4%). The diagnosis was made 7,3 days (SD 4,1) after the first symptom was identified. The complete form of the dis-ease was reported in 107 children (61,1%) and an abnormal echocardi-ography was found in 91 patients (52,3%). Most of the patients had the recommended treatment of intravenous immunoglobulin (IVIG) (174; 99,4%) and aspirin (172; 98,3%). A second dose of IVIG because of per-sisting fever was given in 39 cases (23,8%). Second line treatment with corticosteroids or infliximab was necessary in 29 children (16,6%) and 1 patient (0,6%) received rituximab as 3rd line treatment. One (0,6%) child died of KD. The global incidence of KD in children under 16 years of age in Switzerland 3,05/100'000/year. For the children less than 5 years old, the inci-dence is 6,8/100'000/year.

Conclusion(s): The incidence of the disease in our cohort is in the range of other European countries (5-10/100'000/year in children less than 5 years old). The complete form of the disease was reported in 61,1% of the patients. More than half had an abnormal echocardiography during the acute phase. In most cases, IVIG and aspirin are appropriately be-fore day 10 of fever.

Eymery, M., et al. (2019). "Viral respiratory tract infections in young children with cystic fibrosis: A prospective full-year seasonal study." Virology Journal **16 (1) (no pagination)**(111).
Background: Viral respiratory tract infections are common during early childhood. How they impact cystic fibrosis lung disease history in young children is poorly known. The principal aim of our study was to determinate respiratory tract infections frequency in this cystic fibrosis young population. Secondary outcomes were nature of viral agents recovered and impact of such infections. Method(s): We conducted a prospective cohort study of 25 children affected by cystic fibrosis and aged less than 2 years. Nasal samplings were taken systematically monthly or bimonthly with additional samples taken during respiratory tract infections episodes. Ten pathogens were tested by a combination of five duplex RT-PCRs or PCRs: influenza A and B, respiratory syncytial virus (RSV), metapneumovirus (MPV), rhinovirus/enterovirus (RV/EV)), coronavirus (HKU1, NL63, 229E and OC43), parainfluenza virus (1-4), adenovirus and bocavirus (Respiratory Multi-Well System MWS r-gene, BioMerieux, Marcy l'Etoile, France). Cycle thresholds (CTs) were reported for all positive samples and considered positive for values below 40. Quantitative variables were compared using a nonparametric statistical test (Wilcoxon signed rank for paired comparisons). Pearson's correlation coefficient (r) was used to assess relationships between two variables. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) or GraphPad Prism V6.00 (GraphPad Software, La Jolla, CA, USA). The significance level was set at 0.05. Result(s): The mean age at inclusion was 9.6 +/- 6.7 months. The patients had 3.4 +/- 1.7 respiratory tract infections episodes per child per year. Forty-four respiratory tract infections (69%) were associated with virus: rhinovirus and enterovirus (RV/EV) were implied in 61% of them and respiratory syncytial virus (RSV) in 14%. Only one patient required hospitalization for lower respiratory tract infections. 86% of the patients were treated by antibiotics for a mean of 13.8 +/- 6.2 days. RSV infections (n = 6) were usually of mild severity. Conclusion(s): Respiratory tract infections in young children with cystic fibrosis were of mild severity, rarely requiring hospitalization. Unsurprisingly, RV/EV were the most frequent agents. RSV-related morbidity seems low in this population. This raises the question of the usefulness of RSV preventive medication in this young population.

Fares, M., et al. (2019). "Pharmacologic stress cardiovascular magnetic resonance in the pediatric population: A review of the literature, proposed protocol, and two examples in patients with Kawasaki disease." Congenital Heart Disease **14**(6): 1166-1175.
Pharmacologic stress cardiovascular magnetic resonance (PSCMR) is a well-established and reliable diagnostic tool for evaluation of coronary artery disease in the adult population. Stress imaging overall and PSCMR in particular is less utilized in the pediatric population with limited reported data. In this review, we highlight the potential use of PSCMR in specific pediatric cohorts with congenital and acquired heart disease, and we review the reported experience. A suggested protocol is presented in addition to two case examples of patients with Kawasaki disease where PSCMR aided decision making.

Fernandez-Cooke, E., et al. (2019). "Epidemiological and clinical features of Kawasaki disease in Spain over 5 years and risk factors for aneurysm development. (2011- 2016): KAWA-RACE study group." PLoS ONE **14 (5) (no pagination)**(e0215665).
Background Kawasaki disease (KD) is an acute self-limited systemic vasculitis of unknown etiology affecting mainly children less than 5 years of age. Risk factors for cardiac involvement and resistance to treatment are insufficiently studied in non-Japanese children. Objective This study aimed to investigate the epidemiology, clinical features and risk factors for resistance to treatment and coronary artery lesions (CAL) in KD in Spain. Methods Retrospective study (May

2011-June 2016) of all patients less than 16 years of age diagnosed with KD included in KAWA-RACE network (84 Spanish hospitals). Results A total of 625 cases were analyzed, 63% were males, 79% under 5 year-olds and 16.8% younger than 12 months. On echocardiographic examination CAL were the most frequent findings (23%) being ectasia the most common (12%). Coronary aneurysms werediagnosed in 9.6%, reaching 20% in infants under 12 months ($p<0.001$). A total of 97% of the patients received intravenous immunoglobulin (IVIG) with a median number of days from fever onset to IVIG administration of 7.2. A second dose was given to 15.7% and steroids to 14.5% patients. Only 1.4% patients received infliximab. No deaths were reported. A multivariate analysis identified anemia, hypoalbuminemia, hyponatremia, higher creatinine and procalcitonin as independent risk factors for treatment failure and length under 103 cm, hemoglobin < 10.2 mg/dL, platelets > 900,000 cells/mm3, maximum temperature < 39.5degreeC, total duration of fever > 10 days and fever before treatment >= 8 days as independent risk factors for developing coronary aneurysms. Conclusions In our population, children under 12 months develop coronary aneurysms more frequently and children with KD with anemia and leukocytosis have high risk of cardiac involvement. Adding steroids early should be considered in those patients, especially if the treatment is not started before 8 days of fever. A score applicable to non-Japanese children able to predict the risk of aneurysm development and IVIG resistance is necessary.

Ferrandiz-Espadin, R. and M. Ferrandiz-Zavaler (2019). "Childhood- Versus Adult-Onset Primary Vasculitides: Are They Part of the Same Clinical Spectrum?" Current Rheumatology Reports **21 (10) (no pagination)**(51).

Purpose of the Review: Most of the primary vasculitis in children and adults has different clinical manifestations for the same disease, which suggests that they might not be part of the same clinical spectrum and requires a different approach in order to reduce the morbidity and mortality of these patients. In this work, we review the most recent literature and the most important studies that describe and compare adult and children primary vasculitides pathogenesis, clinical presentation, and treatment approach. Accordingly, we discuss recent research involving clinical trials, comparison studies, and pathogeny for these vasculitides. Recent Findings: Clinical manifestations in the different primary vasculitis change in predominance from adults to children. There is a female sex predominance for the ANCA vasculitides in children compared with adults, but the same treatment works in most cases for both groups. Summary: Identifying the diverse clinical spectrum in both adults and children primary vasculitides will reduce the need to extrapolate the diagnostic criteria from one group to another and individualize it, which will allow the clinician to establish a better approach.

Ferreira, H. L. D. S., et al. (2019). "High incidence of rhinovirus infection in children with community-acquired pneumonia from a city in the Brazilian pre-Amazon region." Journal of Medical Virology **91**(10): 1751-1758.

Community-acquired pneumonia (CAP) is the leading cause of child death worldwide. Viruses are the most common pathogens associated with CAP in children, but their incidence varies greatly. This study investigated the presence of respiratory syncytial virus (RSV), adenovirus, human rhinovirus (HRV), human metapneumovirus (HMPV), human coronavirus (HCoV-OC43 and HCoV-NL63), and influenza A virus (FluA) in children with CAP and the contributing risk factors. Here, children with acute respiratory infections were screened by pediatrics; and a total of 150 radiographically-confirmed CAP patients (aged 3 months to 10 years) from two clinical centers in Sao Luis, Brazil were recruited. Patient's clinical and epidemiological data were recorded. Nasopharyngeal swab and tracheal aspirate samples were collected to extract viral nucleic acid. RSV, adenovirus, rhinovirus, FluA, HMPV, HCoV-OC43, and HCoV-NL63 were detected by

real-time polymerase chain reaction. The severe CAP was associated with ages between 3 and 12 months. Viruses were detected in 43% of CAP patients. Rhinovirus infections were the most frequently identified (68%). RSV, adenovirus, FluA, and coinfections were identified in 14%, 14%, 5%, and 15% of children with viral infection, respectively. Rhinovirus was associated with nonsevere CAP (P =.014); RSV, FluA, and coinfections were associated with severe CAP (P <.05). New strategies for prevention and treatment of viral respiratory infections, mainly rhinovirus and RSV infections, are necessary. Copyright © 2019 Wiley Periodicals, Inc.

Ferstenfeld, I., et al. (2019). "An uncommon complication of a common disease: Pneumatosis intestinalis in an infant with Kawasaki disease." Israel Medical Association Journal **21**(11): 763-765.

Foeldvari, I. (2019). "Rheumatological Differential-diagnostic Investigation in Childhood Uveitis." Aktuelle Rheumatologie **44**(3): 199-204.
Approximately 10% of uveitis cases start developing in childhood with an incidence of 6.9 in 100,000 individuals under 14 years of age and 26.6 in 100,000 individuals aged 15 to 24. Uveitis may be subdivided into infectious and non-infectious uveitis. The classification provided by the SUN working group is based on the anatomic location and the development over time. The most common non-infectious cause of uveitis in children is juvenile idiopathic arthritis, followed by Behcet's disease and sarcoidosis. Autoinflammatory diseases may also be associated with uveitis. Anterior uveitis predominantly occurs in cases of juvenile idiopathic arthritis, localised scleroderma and Kawasaki's syndrome. Intermediate uveitis is notably associated with sarcoidosis, Blau's syndrome, tubulointerstitial nephritis and uveitis (TINU syndrome), and cystic fibrosis. Posterior involvement is characteristic of Behcet's disease, but may also occur in patients with cryopirin-associated periodic fever syndrome or Cogan's syndrome. Early diagnosis is important for initiating an effective treatment in due time and preventing loss of eyesight. © Georg Thieme Verlag KG Stuttgart.

Fu, L. Y., et al. (2019). "The IL-1B Gene Polymorphisms rs16944 and rs1143627 Contribute to an Increased Risk of Coronary Artery Lesions in Southern Chinese Children with Kawasaki Disease." Journal of Immunology Research **2019**.
Background. Kawasaki disease (KD) is a systemic form of self-limited vasculitis in children less than five years old, and the main complication is coronary artery injury. However, the etiology of KD remains unclear. The IL-1B polymorphisms rs16944 GG and rs1143627 AA and their diplotype GA/GA have been associated with significantly increased risk of intravenous immunoglobulin (IVIG) resistance in a Taiwanese population, but the relationship between rs16944 A/G and rs1143627 G/A and coronary artery lesions (CALs) in patients with KD has not been investigated. The present study is aimed at investigating whether the rs16944 A/G and rs1143627 G/A polymorphisms in IL-1B were associated with KD susceptibility and CALs in a southern Chinese population. Methods and Results. We recruited 719 patients with KD and 1401 healthy children. Multiplex PCR was used to assess the genotypes of single nucleotide polymorphisms (SNPs), including two SNPs of IL-1B, rs16944 A/G and rs1143627 G/A. According to the results, no significant association was observed between the IL-1B (rs16944 and rs1143627) polymorphisms and KD risk in the patients compared with the healthy controls in our southern Chinese population. However, in further stratified analysis, we found that children younger than 12 months with the rs16944 GG and rs1143627 AA genotypes of IL-1B had a higher risk of CALs than those with the AA/AG genotypes of rs16944 and GG/AG genotypes of rs1143627 (OR=2.28, 95% CI=1.32-3.95, P=0.0032, adjusted OR=2.33, 95% CI=1.34-4.04, P=0.0027). Conclusions. Our results indicated that there was no association between the rs16944 A/G and rs1143627 G/A gene polymorphisms and KD susceptibility. However, the rs16944 GG and rs1143627 AA genotypes of IL-1B may significantly impact the risk of CAL formation in children younger than 12 months, which may contribute to the pathogenesis of KD. These findings need further validation in multicenter studies with larger sample sizes. © 2019 Lan Yan Fu et al.

Fujiwara, T., et al. (2019). "Association of early social environment with the onset of pediatric Kawasaki disease." Annals of Epidemiology **29**: 74-80.
Purpose: The purpose of this study was to investigate the association of early social environment with Kawasaki disease (KD). Method(s): We analyzed the data of children aged up to 10 years derived from the 21st Century Longitudinal Survey in Newborns (n = 41,872) in Japan. Parental education, total household income, and family size were obtained via a questionnaire at 0.5 years after birth. Physician's diagnosis of KD during the past year was surveyed via a questionnaire for caregiver with children aged up to 10 years. We used Cox proportional hazards modeling to examine the risk factors for KD onset. Result(s): Children born in households with an annual income of JPY 10 million or more were 1.76 times more likely to have KD onset compared with children born in households with an income of less than JPY 4 million (hazard ratio: 1.76, 95% confidence interval [CI]: 1.15-2.69). Children born in households with three or less persons were 1.62 times more likely to have KD onset compared with those born in households with six or more persons (95% CI: 1.10-2.40). The children who were born in urban municipalities also showed higher risk of KD onset compared with those born in rural municipalities (hazard ratio: 1.55, 95% CI: 1.06-2.26). Conclusion(s): Higher household income, smaller family size, and urbanization at birth were associated with increased KD incidence. This study, however, did not find a significant association between lack of exposure to infection in early life and onset of KD. Copyright © 2018 Elsevier Inc.

Fuller, M. G. (2019). "Kawasaki Disease in Infancy." Advanced Emergency Nursing Journal **41**(3): 222-228.
Kawasaki disease (KD) is an acute vasculitis that primarily affects young children and, if untreated, is associated with development of coronary artery aneurysms in approximately 25% of those affected. Infants, especially those younger than 6 months, often have atypical (incomplete) presentations of KD and are most at risk for development of aneurysms. Identification of KD requires a careful and thorough history and physical examination because multiple other conditions cause similar findings. Providers in acute care settings need to have a high degree of suspicion for KD so that those affected may receive appropriate and timely treatment.

Gal, M., et al. (2019). "Priority Needs for Conducting Pandemic-relevant Clinical Research with Children in Europe: A Consensus Study with Pediatric Clinician-researchers." Pediatric Infectious Disease Journal **38**(5): E82-E86.
Background: Infectious disease (ID) pandemics pose a considerable global threat and can disproportionately affect vulnerable populations including children. Pediatric clinical research in pandemics is essential to improve children's healthcare and minimize risks of harm by interventions that lack an adequate evidence base for this population. The unique features of ID pandemics require consideration of special processes to facilitate clinical research. We aimed to obtain consensus on pediatric clinician-researchers' perceptions of the priorities to feasibly conduct clinical pediatric pandemic research in Europe. Method(s): Mixed method study in 2 stages, recruiting pediatric clinician-researchers with experience of conducting pediatric ID research in clinical settings in Europe. Stage 1 was an expert stakeholder workshop and interviews. Discussions focused on participant's experience of conducting pediatric ID research and processes to facilitate pandemic research. Information informed stage 2, an online consensus survey to identify pediatric inician-researchers priorities to enable ID pandemic research. Result(s): Twenty-three pediatric clinician-researchers attended the workshop and 39 completed the survey. Priorities were primarily focused on structural and operational requirements of research design and regulation: (1) clarity within the European Clinical Trials Directive for pediatric pandemic research; (2) simplified regulatory processes for research involving clinical samples and data; and (3) improved relationships between regulatory bodies and researchers. Conclusion(s): Results suggest that changes need to be made to the current regulatory environment to facilitate and improve pediatric research in the pandemic context. These findings can provide expert evidence to research policy decision-makers and regulators

and to develop a strategy to lobby for change. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Galanti, M., et al. (2019). "Longitudinal active sampling for respiratory viral infections across age groups." Influenza and other Respiratory Viruses **13**(3): 226-232.
Background: Respiratory viral infections are a major cause of morbidity and mortality worldwide. However, their characterization is incomplete because prevalence estimates are based on syndromic surveillance data. Here, we address this shortcoming through the analysis of infection rates among individuals tested regularly for respiratory viral infections, irrespective of their symptoms. Method(s): We carried out longitudinal sampling and analysis among 214 individuals enrolled at multiple New York City locations from fall 2016 to spring 2018. We combined personal information with weekly nasal swab collection to investigate the prevalence of 18 respiratory viruses among different age groups and to assess risk factors associated with infection susceptibility. Result(s): 17.5% of samples were positive for respiratory viruses. Some viruses circulated predominantly during winter, whereas others were found year round. Rhinovirus and coronavirus were most frequently detected. Children registered the highest positivity rates, and adults with daily contacts with children experienced significantly more infections than their counterparts without children. Conclusion(s): Respiratory viral infections are widespread among the general population with the majority of individuals presenting multiple infections per year. The observations identify children as the principal source of respiratory infections. These findings motivate further active surveillance and analysis of differences in pathogenicity among respiratory viruses. Copyright © 2018 The Authors. Influenza and Other Respiratory Viruses Published by John Wiley & Sons Ltd.

Gaur, B., et al. (2019). "Use of TaqMan Array card for the detection of respiratory viral pathogens in children under 5 years old hospitalised with acute medical illness in Ballabgarh, Haryana, India." Indian Journal of Medical Microbiology **37**(1): 105-108.
Historical specimens collected from hospitalized children were tested for the following 13 viruses: influenza A and B; respiratory syncytial virus (RSV); parainfluenza viruses 1-3; human metapneumovirus; rhinovirus; coronaviruses 229E, OC43, NL63 and HKU1 and Adenovirus using monoplex real-time reverse transcriptase polymerase chain reaction (rRT-PCR). They were retested using TaqMan Array Card (TAC), a micro-fluidic system, capable of simultaneous multi-pathogen testing, to evaluate its sensitivity and specificity against monoplex rRT-PCR. TAC showed high sensitivity (71%-100%) and specificity (98%-100%) for these viruses in comparison to monoplex rRT-PCR. Multi-specimen detection with high sensitivity and specificity makes TAC a potentially useful tool for both surveillance and outbreak investigations. Copyright © 2019 Indian Society of Anaesthetists. All rights reserved.

Ghimire, L. V., et al. (2019). "An update on the epidemiology, length of stay, and cost of Kawasaki disease hospitalisation in the United States." Cardiology in the Young **29**(6): 828-832.
Background: Kawasaki disease is an acute vasculitis of childhood and is the leading cause of acquired heart disease in the developed countries. Method(s): Data from hospital discharge records were obtained from the National Kids Inpatient Database for years 2009 and 2012. Hospitalisations by months, hospital regions, timing of admission, insurance types, and ethnicity were analysed. Length of stay and total charges were also analysed. Result(s): There were 10,486 cases of Kawasaki disease from 12,678,005 children hospitalisation. Kawasaki disease was more common between 0 and 5 years old, in male, and in Asian. The January-March quarter had the highest rate compared to the lowest in the July-September quarter (OR=1.62, $p < 0.001$). Admissions on the weekend had longer length of stay [4.1 days (95 % CI: 3.97-4.31)] as compared to admissions on a weekday [3.72 days (95 % CI: 3.64-3.80), $p < 0.001$]. Blacks had the longest length of stay and whites had the shortest [4.33 days (95 % CI: 4.12-4.54 days) versus 3.60 days (95 % CI: 3.48-3.72 days), $p < 0.001$]. Coronary artery aneurysm was identified in 2.7 % of all patients with Kawasaki disease. Children with coronary artery aneurysm

were hospitalised longer and had higher hospital charge. Age, admission during weekend, and the presence of coronary artery aneurysm had significant effect on the length of stay. Conclusion(s): This report provides the most updated epidemiological information on Kawasaki disease hospitalisation. Age, admissions during weekend, and the presence of coronary artery aneurysm are significant contributors to the length of stay.

Gonzalez Mata, A. J., et al. (2019). "Kawasaki disease: Unusual presentation with only fever. Barquisimeto, Venezuela. Brief report. [Spanish]." Enfermedades Infecciosas y Microbiologia **39**(3): 83-85.
Kawasaki disease (kd) was first described in Japan by doctor T. Kawasaki in 1967, since then classic clinical manifestations that define it, remain in force. Patients, methods and results: prospective cohort analysis of 12 cases of children that were assessed between January 2016 and April 2019 at the Agustin Zubillaga Hospital in Barquisimeto, Venezuela, with fever and elevation of the values of acute phase reactants. Median age 18 months; seven of the female sex. None had the criteria for Kawasaki disease complete. As part of their diagnostic approach, echocardiography was performed where there was evidence of coronary alterations. The information is presented with descriptive statistic. It is proposed that in every child under six months of age with seven days or more feverish without other obvious clinical criteria, with positive acute phase reactants, echocardiogram should be performed, evaluate if it is applicable to all infants regardless of age in months. In Venezuela there has been a significant change in the epidemiology of kd, being currently more suspected and perhaps that influences the greater frequency of cases detected.

Grande Gutierrez, N., et al. (2019). "Hemodynamic variables in aneurysms are associated with thrombotic risk in children with Kawasaki disease." International Journal of Cardiology **281**: 15-21.
Background: Thrombosis is a major adverse outcome associated with coronary artery aneurysms (CAAs) resulting from Kawasaki disease (KD). Clinical guidelines recommend initiation of anticoagulation therapy with maximum CAA diameter (D max) ≥8 mm or Z-score ≥ 10. Here, we investigate the role of aneurysm hemodynamics as a superior method for thrombotic risk stratification in KD patients. Methods and results: We retrospectively studied ten KD patients with CAAs, including five patients who developed thrombosis. We constructed patient-specific anatomic models from cardiac magnetic resonance images and performed computational hemodynamic simulations using SimVascular. Our simulations incorporated pulsatile flow, deformable arterial walls and boundary conditions automatically tuned to match patient-specific arterial pressure and cardiac output. From simulation results, we derived local hemodynamic variables including time-averaged wall shear stress (TAWSS), low wall shear stress exposure, and oscillatory shear index (OSI). Local TAWSS was significantly lower in CAAs that developed thrombosis (1.2 ± 0.94 vs. 7.28 ± 9.77 dynes/cm 2 , p = 0.006) and the fraction of CAA surface area exposed to low wall shear stress was larger (0.69 ± 0.17 vs. 0.25 ± 0.26%, p = 0.005). Similarly, longer residence times were obtained in branches where thrombosis was confirmed (9.07 ± 6.26 vs. 2.05 ± 2.91 cycles, p = 0.004). No significant differences were found for OSI or anatomical measurements such us D max and Z-score. Assessment of thrombotic risk according to hemodynamic variables had higher sensitivity and specificity compared to standard clinical metrics (D max , Z-score). Conclusions: Hemodynamic variables can be obtained non-invasively via simulation and may provide improved thrombotic risk stratification compared to current diameter-based metrics, facilitating long-term clinical management of KD patients with persistent CAAs.

Gu, H. B., et al. (2019). "Median effective dose of intranasal dexmedetomidine for transthoracic echocardiography in children with kawasaki disease who have a history of repeated sedation." Medical Science Monitor **25**: 381-388.

The aim of this study was to investigate the median effective dose (ED50) of intranasal dexmedetomidine for echocardiography in children with Kawasaki disease who had a history of repeated sedation. There were 73 pediatric Kawasaki disease patients aged 1 to 36 months enrolled in this study who had American Society of Anesthesiologists (ASA) I–II, were scheduled to undergo echocardiography under sedation. They were assigned to 2 groups (group A: age 1–18 months, and group B: age 19–36 months). Intranasal dexmedetomidine was administered before echocardiography. The dose of intranasal dexmedetomidine was determined with the up-down sequential allocation, and the initial dose was 2 μg/kg with an increment/decrement of 0.2 μg/kg. The ED50 of intranasal dexmedetomidine for sedation was determined with the up-and-down method of Dixon and Massey and probit regression. The time to effective sedation, time to regaining consciousness, vital signs, oxygen saturation, echocardiographic examination time, clinical side-effects, and characteristics of regaining consciousness were recorded and compared. The ED50 of intranasal dexmedetomidine for sedation was 2.184 μg/kg (95% CI, 1.587–2.785) in group A and 2.313 μg/kg (95% CI, 1.799–3.426) in group B. There were no significant differences in the time to sedation and time to regaining consciousness between groups. Additionally, change in hemodynamic and hypoxemia were not noted in both groups. The ED50 of intranasal dexmedetomidine was determined in children with Kawasaki disease who had a history of repeated sedation to be appropriate for repeated-routine sedation of echocardiographic examination in pediatric patients. The ED50 of intranasal dexmedetomidine for echocardiography in this circumstance is similar to that in children receiving initial sedation. © Med Sci Monit, 2019;.

Han, S. B., et al. (2019). "Respiratory viral infections in children and adolescents with hematological malignancies." Mediterranean Journal of Hematology and Infectious Diseases **11 (1) (no pagination)**(e2019006).
Background: Despite the introduction of a polymerase chain reaction (PCR) test for the diagnosis of respiratory viral infection (RVI), guidance on the application of this test and the management of RVI in immunocompromised children is lacking. This study evaluated the clinical characteristics of RVI and established strategies for the PCR test in children and adolescents with hematological malignancies. Method(s): This study included children and adolescents with underlying hematological malignancies and respiratory symptoms, in whom a multiplex PCR test was performed. Patients in whom RVI was identified and not identified were categorized into Groups I and II, respectively. Group I was sub-divided into patients with upper and lower respiratory infections. The medical records of the enrolled patients were retrospectively reviewed. Result(s): A total of 93 respiratory illnesses were included. Group I included 46 (49.5%) cases of RVI, including 31 (67.4%) upper and 15 (32.6%) lower respiratory infections. Rhinovirus (37.0%) was the most common viral pathogen. Significantly more patients in Group I had community-acquired respiratory illnesses (p=0.003) and complained of rhinorrhea (p<0.001) and sputum (p=0.008) than those in Group II. In Group I, significantly more patients with lower respiratory infections had uncontrolled underlying malignancies (p=0.038) and received re-induction or palliative chemotherapy (p=0.006) than those with upper respiratory infections. Conclusion(s): A multiplex PCR test should be considered for RVI diagnosis in immunocompromised children and adolescents with respiratory symptoms, especially in those with rhinorrhea or sputum prominent over a cough. The early application of the PCR test in patients with uncontrolled underlying malignancies may improve outcomes. Copyright © Universita Cattolica del Sacro Cuore. All rights reserved.

Han, S. P., et al. (2019). "Masked pemphigus among pediatric patients with Castleman's disease." International Journal of Rheumatic Diseases **22**(1): 121-131.
Aim: Paraneoplastic pemphigus (PNP) is a mucocutaneous autoimmune disorder accompanied with a neoplasm. Castleman's disease (CD), although rare, is the most common cause of PNP in children. It can be life-threatening when pulmonary involvement occurs. Our study aimed to describe the features of PNP resulting from CD and to find clues for the early diagnosis in

pediatric patients. Method(s): We report the case of a 13-year-old girl who initially presented with oral ulcers and lichen planus, with progression to respiratory failure. A literature review of PNP and CD in children between 1997 and 2016 was performed. The clinical manifestations, pathological findings, treatment, and outcome were analyzed. Result(s): Thirty-two children were included in our study: 16 boys and 16 girls. Intractable mucocutaneous lesions developed early before CD was diagnosed. The clinical manifestations comprised oral ulcers (100%), polymorphous skin rash (86.7%) and genital (62.5%) erosion. Histopathological findings revealed lymphoplasmacytic cells infiltration (92%), vacuolar interface change (72%), acantholysis (68%), and keratinocytes necrosis (36%). Thirty patients underwent tumor resection. These patients mainly had unicentric CD, with the hyaline-vascular variant dominant. Twenty-six patients (81.2%) exhibited pulmonary involvement. The mortality rate was 70.0%. Among them, 90.5% exhibited pulmonary involvement, and 81.0% died of respiratory failure. Conclusion(s): Intractable mucocutaneous lesions with a concurrent tumor in children strongly indicate PNP resulting from CD. Because stomatitis or skin erosion may be the first presentation, mucocutaneous tissue biopsy and early detection of the underlying tumor are important. Earlier diagnosis is mandatory for the effective treatment of PNP and pulmonary involvement.

Hasegawa, K., et al. (2019). "Respiratory Virus Epidemiology among US Infants with Severe Bronchiolitis: Analysis of 2 Multicenter, Multiyear Cohort Studies." Pediatric Infectious Disease Journal **38**(8): E180-E183.
In 2 multicenter cohort studies of 2912 infants hospitalized for bronchiolitis during 2007-2014, the 5 most common pathogens were RSV (76.5%), rhinovirus (23.8%), coronavirus (6.9%), adenovirus (6.4%) and human metapneumovirus (6.0%). Hospitalization months significantly differed for these common pathogens (P <= 0.01), except for coronavirus (P = 0.30). There was a significant heterogeneity in temporal patterns by region in RSV-A and -B (both P < 0.001).

Hatem, A., et al. (2019). "Clinical characteristics and outcomes of patients with severe acute respiratory infections (SARI): Results from the Egyptian surveillance study 2010-2014." Multidisciplinary Respiratory Medicine **14 (1) (no pagination)**(11).
Background: Respiratory viral and atypical bacterial infections data in Egyptian patients are sparse. This study describes the clinical features and outcomes of patients with severe acute respiratory infections (SARI) in hospitalized patients in Egypt. Method(s): SARI surveillance was implemented at Cairo University Hospital (CUH) during the period 2010-2014. All hospitalized patients meeting the WHO case definition for SARI were enrolled. Nasopharyngeal/oropharyngeal (NP/OP) swabs were collected and samples were tested using RT-PCR for influenza A, B, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza virus (PIV 1,2,3,4), adenovirus, bocavirus, coronavirus, enterovirus, rhinovirus, and atypical bacteria. Data were analyzed to calculate positivity rates for viral pathogens and determine which pathogens related to severe outcomes or resulted in death. Result(s): Overall, 1,075/3,207 (33.5%) cases had a viral etiology, with a mean age of 5.74 (+/-13.87) years. The highest rates were reported for RSV (485 cases, 45.2%), PIV (125, 11.6%), and adenovirus (105, 9.8%). Children had a higher viral rate (981, 91.2%) compared to 94 (8.8%) cases in adults. Patients with identified viruses had significantly lower rates for ICU admission, hospital stay, mechanical ventilation, and overall mortality than those without identified viruses. No infections were independently associated with severe outcomes. Conclusion(s): Viral pathogens were encountered in one-third of hospitalized adult and pediatric Egyptian patients with SARI, while atypical bacteria had a minor role. Highest rates of viral infections were reported for RSV, PIV, and adenovirus. Viral infections had neither negative impacts on clinical features nor outcomes of patients with SARI in our locality.

Hatem, A. M., et al. (2019). "Viral and atypical bacterial etiologies of severe acute respiratory infection (SARI) in Egyptian patients: Epidemiological patterns and results from the sentinel surveillance study 2010-2014." Egyptian Journal of Chest Diseases and Tuberculosis **68**(1): 88-95.
Background Respiratory viral and atypical bacterial infections data in Egyptian patients are sparse. This study described the epidemiological pattern of viral and atypical bacteria as causes for severe acute respiratory infections (SARI) in hospitalized patients in Egypt. Patients and methods SARI surveillance was carried out at a Teaching University Hospital during the period 2010-2014. All hospitalized adults and pediatric patients meeting the WHO case definition criteria for SARI were enrolled. Nasopharyngeal/oropharyngeal swabs were collected and samples were tested using reverse transcription-PCR for influenza A, B, respiratory syncytial virus, human metapneumovirus, parainfluenza viruses 1, 2, 3, 4, adenovirus, human bocavirus, coronavirus, enterovirus, rhinovirus, and atypical bacteria (Mycoplasma spp., Chlamydia spp., and Legionella spp.). Results Overall, 1075/3207 (33.5%) cases had a viral etiology, and included 912 (84.4%) women and 163 (15.6%) men, with a mean age of 5.74+/-13.87 years. The highest rates were reported for respiratory syncytial virus (485 cases, 45.2%), parainfluenza virus (125, 11.6%), and adenovirus (105, 9.8%). Single viral etiology was reported in 901 (83.3%), while 174 (16.7%) cases had multiple etiologies. Children had a higher rate (981, 91.2%) compared with 94 (8.8%) cases in adults. Only three and one cases were positive for Mycoplasma spp. and Chlamydia spp. infections, respectively. Neither coronavirus nor Legionella spp. were detected. Conclusion Viral infections were encountered in one-third of hospitalized Egyptian adult and pediatric patients with SARI. Atypical bacteria had a minor role in SARI in our locality. Ongoing surveillance programs will better describe the epidemiology of SARI and will provide specific data to enable decision makers to take appropriate prevention measures. Copyright © 2019 The Egyptian Journal of Chest Diseases and Tuberculosis.

Heimdal, I., et al. (2019). "Human coronavirus in hospitalized children with respiratory tract infections: A 9-year population-based study from Norway." Journal of Infectious Diseases **219**(8): 1198-1206.
Background. Te burden of human coronavirus (HCoV)-associated respiratory tract infections (RTIs) in hospitalized children is poorly defned. We studied the occurrence and hospitalization rates of HCoV over 9 years. Methods. Children from Sor-Trondelag County, Norway, hospitalized with RTIs and asymptomatic controls, were prospectively enrolled from 2006 to 2015. Nasopharyngeal aspirates were analyzed with semiquantitative polymerase chain reaction (PCR) tests for HCoV subtypes OC43, 229E, NL63, and HKU1, and 13 other respiratory pathogens. Results. HCoV was present in 9.1% (313/3458) of all RTI episodes: 46.6% OC43, 32.3% NL63, 16.0% HKU1, and 5.8% 229E. Hospitalization rates for HCoV-positive children with lower RTIs were 1.5 and 2.8 per 1000 <5 and <1 years of age, respectively. Te detection rate among controls was 10.2% (38/373). Codetections occurred in 68.1% of the patients and 68.4% of the controls. In a logistic regression analysis, high HCoV genomic loads (cycle threshold <28 in PCR analysis) were associated with RTIs (odds ratio = 3.12, P =.016) adjusted for relevant factors. Conclusions. HCoVs occurred in 1 of 10 hospitalized children with RTIs and asymptomatic controls. A high HCoV genomic load was associated with RTI. HCoVs are associated with a substantial burden of RTIs in need of hospitalization. Copyright © 2018 The Author(s).

Hoshino, S., et al. (2019). "Biomarkers of inflammation and fibrosis in the young adults with history of Kawasaki disease." Circulation. Conference: American Heart Association Scientific Sessions, AHA **140**(Supplement 1).
Introduction: Molecular profiling using shotgun proteomics, transcriptomics, and glycomics methods revealed active inflammation in adult patients with a history of Kawasaki disease (KD) and giant coronary aneurysms (GA). These patients showed increased levels of calprotectin, a marker of inflammation secreted by neutrophils and monocytes. Histology from autopsies of young adults with GA from KD showed myocardial bridging fibrosis and fibrosis in the coronary arterial wall. We postulated that the subset of adult KD patients with GA have persistent inflammation that leads to fibrosis long after KD onset. Method(s): We measured calprotectin,

galectin-3 (Gal-3), soluble ST2 (ST2), growth differentiation factor (GDF)-15 and procollagen type I C-terminal propeptide (PIPC) by ELISA. Median biomarker levels and IQR for patient groups and matched controls were compared by Mann Whitney U test. Result(s): We studied 93 adult KD subjects (ages 4.7-60.8 years, 0.9-55.0 years after KD onset; normal coronary artery: n=45, small aneurysm (CAA): n=18, and GA: n=30) and 88 age-matched adult healthy controls (HC, age 17.5-41.5 years). In adult KD subjects with GA, calprotectin, Gal-3, GDF-15 and PIPC were significantly higher compared to adult HC. Conclusion(s): Elevated levels of calprotectin, Gal-3, GDF-15 and PIPC in adult KD subjects with GA suggest both inflammation and fibrosis in the arterial wall and/or myocardium. These results require validation by either histology (autopsy) or imaging, but suggest that anti-inflammatory therapy could benefit this patient population. Longitudinal follow-up will clarify the clinical significance of these changes.

Huang, Y. H., et al. (2019). "Increased incidence of Kawasaki disease in Taiwan in recent years: A 15 years nationwide population-based cohort study." Frontiers in Pediatrics **7**(MAR).
Background: Kawasaki disease (KD) is diagnosed in children suffering from fever for more than five days and five clinical characteristic symptoms. The aim of this article was to research the clinical characteristics among KD children in Taiwan in recent years through a population-based cohort study. Materials and Methods: We carried out a nationwide retrospective cohort study by analyzing the data of KD patients (ICD-9-CM code 4461) from Taiwan's National Health Insurance Research Database (NHIRD) during the period of 1996-2011. Results: Among all the insured children in the NHIRD, insurance claims data were reported for 13,260 patients diagnosed with KD, with 8394 (63.30%) subjects being administered IVIG for treatment. Of the patients diagnosed with KD, 94% were under the age of 5 years old, and the majority of cases occurred in May. Furthermore, the incidence of KD more than doubled (28.58-60.08 per 100,000) during this period in Taiwan. Conclusion: We developed a five-based mnemonic device for parents and first-line clinicians to easily use in order to diagnose KD. We also observed an increased incidence of KD in Taiwan during the study period. In addition, we develop a five-based mnemonic device for parents and first-line clinicians in clinical diagnosis of KD can easily remember: Fever > 5 days, 5 clinical criteria, predominantly in children < 5 years of age, and peak seasonal clustering in the 5th month, May (April-June) in Taiwan. © 2019 Huang, Lin, Ho, Yan, Lo and Kuo.

Huang, Y. H., et al. (2019). "Increase expression of CD177 in Kawasaki disease." Pediatric Rheumatology **17 (1) (no pagination)**(13).
Background: Kawasaki disease (KD) is the most common acute coronary vasculitis disease to occur in children. Its incidence has been attributed to the combined effects of infection, genetics, and immunity. Although the etiopathogenesis of KD remains unknown, we have performed a survey of global genetic DNA methylation status and transcripts expression in KD patients in order to determine their contribution to the pathogenesis of KD. Method(s): We recruited 148 participants for this case-control study. The chip studies consisted of 18 KD patients that were analyzed both before undergoing intravenous immunoglobulin (IVIG) treatment and at least 3 weeks afterward, as well as 36 non-KD control subjects, using Illumina HumanMethylation450 BeadChip and Affymetrix GeneChip Human Transcriptome Array 2.0. We then carried out real-time quantitative PCR on a separate cohort of 94 subjects for validation. Result(s): According to our microarray study, CD177, a neutrophil surface molecule, appeared to be significantly upregulated in KD patients when compared to controls with epigenetic hypomethylation. After patients received IVIG treatment, CD177 mRNA levels decreased significantly. PCR validation indicated that the CD177 expression is consistent with the Transcriptome Array 2.0 results. Furthermore, the area under the curve values of CD177 between KD patients and controls is 0.937. We also observed significantly higher CD177 levels in typical KD than in incomplete presentation or KD with IVIG resistance. Conclusion(s): In this study, we have demonstrated the epigenetic hypomethylation and increased expression of CD177 during the acute stage of KD. Furthermore, a higher expression of CD177 in KD patients with typical presentation was

associated with IVIG resistance. Copyright © 2019 The Author(s).

Isidori, C., et al. (2019). "A case of incomplete and atypical kawasaki disease presenting with retropharyngeal involvement." International Journal of Environmental Research and Public Health **16**(18).
Kawasaki disease (KD) is a childhood acute febrile vasculitis of unknown aetiology. The diagnosis is based on clinical criteria, including unilateral cervical lymphadenopathy, which is the only presenting symptom associated with fever in 12% of cases. A prompt di_erential diagnosis distinguishing KD from infective lymphadenitis is therefore necessary to avoid incorrect and delayed diagnosis and the risk of cardiovascular sequelae. Case presentation: We describe the case of a 4 years old boy presenting with febrile right cervical lymphadenopathy, in which the unresponsiveness to broad-spectrum antibiotics, the following onset of other characteristic clinical features and the evidence on the magnetic resonance imaging (MRI) of retropharyngeal inflammation led to the diagnosis of incomplete and atypical KD. On day 8 of hospitalisation (i.e., 13 days after the onset of symptoms), one dose of intravenous immunoglobulins (IVIG; 2 g/kg) was administered with rapid defervescence, and acetylsalicylic acid (4 mg/kg/day) was started and continued at home for a total of 8 weeks. Laboratory examinations revealed a reduction in the white blood cell count and the levels of inflammatory markers, thrombocytosis, and persistently negative echocardiography. Clinically, we observed a gradual reduction of the right-side neck swelling. Fifteen days after discharge, the MRI of the neck showed a regression of the laterocervical lymphadenopathy and a resolution of the infiltration of the parapharyngeal and retropharyngeal spaces. Conclusion: Head and neck manifestations can be early presentations of KD, which is frequently misdiagnosed as suppurative lymphadenitis or retropharyngeal infection. A growing awareness of the several possible presentations of KD is therefore necessary. Computed tomography (CT) or MRI can be utilised to facilitate the diagnosis. © 2019 by the authors. Licensee MDPI, Basel, Switzerland.

Javedani, P. P. and M. Zukowski (2019). "Cerebrovascular Accident in a Pediatric Patient Presenting With Influenza." Journal of Emergency Medicine **57**(1): e17-e19.
Background: Acute ischemic stroke (AIS) in pediatric populations accounts for more than half of pediatric strokes and is associated with significant morbidity and mortality. Pediatric AIS can present with nonspecific symptoms or symptoms that mimic alternate pathology. Case Report: A 4-month-old female presented to the emergency department for fever, decreased oral intake, and "limp" appearance after antibiotic administration. She was febrile, tachypneic, and hypoxic. Her skin was mottled with 3-s capillary refill, her anterior fontanelle was tense, and she had mute Babinski reflex bilaterally but was moving all extremities. The patient was hyponatremic, thrombocytopenic, and tested positive for influenza A. A computed tomography scan of the brain revealed an acute infarction involving the right frontal, parietal, temporal, and occipital lobes in addition to hyperdensities concerning for thrombosed cortical veins. The patient was transferred for specialty evaluation and was discharged 2 weeks later on levetiracetam. Why Should an Emergency Physician be Aware of This?: Pediatric AIS can present with nonspecific symptoms that mimic alternate pathology. A high level of suspicion is needed so as not to miss the diagnosis of pediatric AIS in the emergency department. A thorough neurologic assessment is warranted, and subtle abnormalities should be investigated further. Copyright © 2019 Elsevier Inc.

Jin, P., et al. (2019). "Kawasaki Disease Complicated With Macrophage Activation Syndrome: Case Reports and Literature Review." Frontiers in Pediatrics **7 (no pagination)**(423).
Macrophage activation syndrome (MAS) is a rare and severe complication of Kawasaki disease (KD). The clinical feature, early diagnosis and treatment options, and prognosis need to be further determined in patients with KD complicated with MAS. In this report, we retrospectively analyzed three KD patients complicated with MAS who were treated in pediatric intensive care units (PICU) and reviewed the relevant literatures. We find that being male, being age over 2

years old, incomplete KD, intravenous immunoglobulin (IVIG) non-responder, or persistent fever greater than 10 days are all highly associated with occurrence of MAS. Additional work-ups should be performed promptly in patient with above predisposing factors to rule out complication of MAS. Patients with KD complicated with MAS are at a higher risk of having coronary artery involvement or aneurysm formation, which can be reversed with timely treatment. Early identification and prompt treatment are key points for improving the prognosis of KD patients complicated with MAS. © Copyright © 2019 Jin, Luo, Liu, Xu and Liu.

Jindal, A. K., et al. (2019). "Kawasaki disease: characteristics, diagnosis, and unusual presentations." Expert Review of Clinical Immunology **15**(10): 1089-1104.
Introduction: Kawasaki disease (KD) is one of the commonest pediatric vasculitides and is associated with a significant risk of development of coronary artery abnormalities if left untreated. Areas covered: In this review, we have highlighted the incomplete and unusual presentations of KD and also emphasize the controversies pertaining to 2D echocardiography in KD. A PubMed search was performed regarding diagnosis and unusual presentations of KD. Expert opinion: Diagnosis of KD is essentially clinical and based on recognition of typical clinical features that may appear sequentially and all signs and symptoms may not be present at one point of time. There is no confirmatory laboratory test for diagnosis of this condition. Further complicating the picture is the fact that incomplete and atypical forms KD may be seen in up to 50% patients. Although 2D echocardiography continues to be the preferred imaging modality for cardiac assessment in patients with KD, it has its limitations. Copyright © 2019, © 2019 Informa UK Limited, trading as Taylor & Francis Group.

Kaman, A., et al. (2019). "Dynamic thiol/disulphide homeostasis and pathogenesis of Kawasaki disease." Pediatrics International **61**(9): 913-918.
Background: Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of unknown etiology. In the present study, we investigated whether there is a relationship between KD and dynamic thiol/disulphide homeostasis. Methods: This case–control study involved KD patients and healthy controls. Plasma total, native and disulphide thiol and the disulphide/native, disulphide/total and native thiol/total thiol ratios of all patients and the control group were analyzed simultaneously. Results: A total of 20 patients with KD (male/female, 12/8) and 25 age- and gender-matched healthy controls (male/female, 12/13) were evaluated. Native, total thiol and native thiol/total thiol ratio were significantly lower in KD patients than in the control group ($P < 0.001$). In contrast, disulphide thiol, disulphide/native thiol and disulphide/total thiol ratios were significantly higher in KD patients than control subjects ($P < 0.001$). In KD patients with coronary artery lesion (CAL), the native thiol and total thiol were significantly lower than in KD patients without CAL. In KD patients with CAL, the ratios of disulphide/total thiol and disulphide/native thiol were significantly higher than in those without CAL ($P = 0.02$ and $P = 0.02$, respectively), whereas the ratio of native/total thiol was significantly lower ($P = 0.02$). Conclusion: The KD patients had lower plasma thiol (native and total) and higher disulphide thiol than controls, indicating that dynamic thiol/disulphide homeostasis might be an important indicator of inflammation in KD. Alteration and shifting of thiol/disulphide homeostasis to the oxidized side are correlated with the pathogenesis of KD and CAL. © 2019 Japan Pediatric Society

Kanner, E. V., et al. (2019). "Clinical and laboratory characteristics of acute infections with combined lesions to the respiratory and gastrointestinal tracts in children. [Russian]." Infektsionnye Bolezni **17**(4): 5-12.
Objective. To assess clinical and laboratory characteristics of acute respiratory and gastrointestinal infections in children, as well as infections simultaneously affecting both respiratory and gastrointestinal tracts. Materials and methods. We analyzed medical records of 4,842 children aged between 3 months and 14 years admitted to infectious disease hospitals in Moscow. We evaluated the course of some most common infections with combined lesions to the

respiratory and gastrointestinal tracts (rotavirus, norovirus, coronavirus, bocavirus, adenovirus, and influenza) and mixed infections. Results. Rotavirus was the most common causative agent in patients with combined lesions to the respiratory and gastrointestinal tracts (CLRGT) (both in case of monoinfections and mixed infections). Of 542 children with rotavirus infection and CLRGT, 210 patients (38.7%) had monoinfections, whereas 332 patients (61.3%) had mixed infections. Almost half of the children with norovirus infection (n = 194; 49.6%) presented with CLRGT. Among 267 patients (8%) infected with bocavirus, 74 participants (27.7%) had CLRGT, while 179 children (67.0%) had manifestations of acute respiratory infections; 5.2% of children with symptoms of acute intestinal infections alone were found to have bocavirus, primarily in combination with other infectious agents. Adenovirus infection type 40 and 41 was mainly characterized by gastrointestinal symptoms. Gastrointestinal lesions alone were observed in 42 out of 76 patients diagnosed with adenovirus infection (55.26%); the remaining 34 patients (44.74%) presented with CLRGT. Influenza, adenovirus infection type 40 and 41, and rotavirus infection were associated with the most severe symptoms. Coronavirus infection and parainfluenza were more likely to manifest with laryngitis; bocavirus infection manifested itself with purulent inflammatory lesions of the respiratory tract and diarrhea; influenza was characterized by tracheitis and persistent hyperthermia. Conclusion. Some infections manifesting with CLRGT have specific symptoms and types of lesions, which allows the identification of disease etiology and prediction of its course and outcomes. Copyright © 2019, Dynasty Publishing House. All rights reserved.

Kantarcı, M., et al. (2019). "Vascular imaging findings with high-pitch low-dose dual-source CT in atypical kawasaki disease." Diagnostic and Interventional Radiology **25**(1): 50-54.
PURPOSE Determining the presence of aneurysms, thrombosis, and stenosis is very important for the diagnosis of atypical Kawasaki disease (AKD) and in the follow-up of AKD patients with aneurysms. We aimed to demonstrate high-pitch low-dose dual-source computed tomography (CT) angiography findings in pediatric patients with AKD. METHODS Over a 5-year period, high-pitch low-dose CT angiography was performed to determine vascular aneurysms or occlusions in 17 patients who had suspected AKD. The patients ranged from 2 months of age to 11.3 years, with a mean age of 3 years. The American Heart Association's criteria were used to diagnose AKD. RESULTS We did not detect any vascular problems in 6 of the patients, and they were not included in our study. Arterial aneurysms were present in 11 patients (aged 2 months to 11.3 years; mean age, 4.2 years; 7 males). In one patient, there was also a thrombus at an arterial aneurysm. Coronary artery aneurysms were detected in 7 patients and systemic artery aneurysms were detected in 7 patients. Three patients had both systemic and coronary aneurysms. CONCLUSION Our results suggest that high-pitch low-dose dual-source CT can detect all types of aneurysms, stenosis and occlusions of vessels in patients with AKD who were not previously diagnosed. This useful, easy, robust and fast technique may be preferred to diagnose AKD. © Turkish Society of Radiology 2019.

Kelly, A., et al. (2019). "Fifteen-minute consultation: Kawasaki disease: How to distinguish from other febrile illnesses: Tricks and tips." Archives of Disease in Childhood: Education and Practice Edition **(no pagination)**(316834).
Kawasaki disease (KD) is challenging to diagnose because there is no specific laboratory test and the presentation is often similar to common childhood infections. We highlight some of those KD diagnostic challenges. KD, a self-limiting vasculitis, can cause coronary artery aneurysms. The aim is to optimise management during the acute febrile illness to try and prevent these because a giant coronary artery aneurysm is devastating enough without thinking that it might have been prevented. The conundrum for acute paediatricians is which clinical features best distinguish the febrile child with possible KD, needing intravenous immunoglobulin, from the many other children with febrile illnesses. Copyright © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Kido, S., et al. (2019). "Seasonality of i.v. immunoglobulin responsiveness in Kawasaki disease." Pediatrics International **61**(6): 539-543.
Background: Evidence suggests that seasonal variation in the onset of Kawasaki disease (KD) exists worldwide. Whether a seasonal component to successful i.v. immunoglobulin (IVIG) therapy exists in KD-positive children, however, is unknown. We addressed this question by focusing on patients with primary onset KD who were non-responsive to IVIG treatment, in the large nationwide Japanese KD survey datasets from 2009 to 2016. Method(s): In these datasets, the IVIG therapy non-responders were defined as patients whose fever persisted >=24 h or recurred <=24 h after the end of the initial IVIG treatment (dosage, 2,000 mg/kg). Those who successfully responded to this treatment were defined as IVIG responders. The consecutive monthly trend of the proportion of IVIG non-responders was analyzed throughout the study period to investigate seasonal periodicity on Fourier analysis, and the monthly distributions of non-responders and responders were compared. Result(s): From a total of 113 691 KD-positive patients, 15.7% were IVIG non-responders, and 61% were male. The proportion of non-responders increased across each calendar year with fluctuation, and Fourier analysis indicated seasonal periodicity. The seasonality effect differed between responders and non-responders, with the proportion of responders tending to increase in autumn through winter, while the non-responders showed a decreasing trend in autumn. The seasonality effect tended to differ by sex. Conclusion(s): The results indicate that the currently unknown etiological agents of KD might differ between IVIG responders and non-responders. In addition, immune reactivity against such agents possibly differs by sex in the IVIG non-responders. Copyright © 2019 Japan Pediatric Society

Kim, D. U., et al. (2019). "Eating related epilepsy in a 5-month-old baby." Epilepsia **60 (Supplement 2)**: 238.
Purpose: Eating epilepsy is one of the rare forms of reflex epilepsy worldwide. There are only few cases reported in children. We report a 5-month-olds patient with eating epilepsy. Method(s): Medical records were reviewed. Blood chemistry, metabolic screening, video electroencephalography (vEEG) and brain magnetic resonance image (MRI) were analyzed. Result(s): The patient was a 5-month-old girl, previously in good health. She suddenly started seizure without fever. At admission, she had no respiratory or gastrointestinal symptoms, or other generalized illness. She had no history of familial seizures. Vaccination was not related. After admission, multiple brief seizures less than 1 minute (frequency: 3-4 clusters/day, 3-4 times/cluster) were noted with motion arrest, staring, brief tonic arms, desaturation and subtle clonic movements. After use of intravenous (IV) lorazepam, levetiracetam, and IV fos-phenytoin half loading, her seizures seemed to be controlled until HD #4. As her condition was getting better, we started bottle feeding and seizures were recurred and more aggravated (HD#5). By careful observation, her seizures were stereotypically induced by sucking pacifier or swallowing the milk. Video EEG monitoring revealed that sucking events repeatedly provoked the ictal discharges from the left temporal electrodes and propagated to left hemisphere and bilateralization. After IV phenobarbital loading, her seizure was dramatically controlled and she gradually recovered to normal condition. There was no structural lesion on brain MRI, however, perfusion was decreased in left temporo-parietal region after seizure. Blood chemistry, metabolic tests were all normal. Corona virus by respiratory sample and stool rota virus were identified, however, the relations with seizures were not sure. Conclusion(s): Eating epilepsy is rare in children and temporoparietal network may be responsible for eating epilepsy by sucking movement. Phenobarbital was effective for seizure control.

Kong, W. X., et al. (2019). "Biomarkers of intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease." World Journal of Pediatrics **15**(2): 168-175.
Background: Currently, there are no reliable indicators for predicting intravenous immunoglobulin resistance and coronary artery lesions in the early stage of Kawasaki disease. Methods: A total of 300 patients with Kawasaki disease were studied retrospectively. Laboratory data were compared

between the intravenous immunoglobulin resistant (29 patients) and responsive groups, and between the groups with coronary artery lesions (48 patients) and without coronary artery lesions. Results: The intravenous immunoglobulin resistant group had significantly higher D-dimer, globulin, interleukin-6 and serum ferritin levels in comparison to the intravenous immunoglobulin responder group. D-dimer level had a sensitivity of 87.0% and a specificity of 56.3% for predicting intravenous immunoglobulin resistance at a cutoff point of 1.09 mg/L. Globulin had a sensitivity of 62.1% and a specificity of 82.3% for predicting intravenous immunoglobulin resistance at a cutoff point of 34.7 g/L. Serum ferritin level had a sensitivity of 42.9% and a specificity of 88.8% for predicting intravenous immunoglobulin resistance at a cutoff point of 269.7 ng/mL. The patients with coronary artery lesions had higher D-dimer and tumor necrosis factor-α level. D-dimer level had a sensitivity of 50% and a specificity of 78.6% for predicting coronary artery lesions at a cutoff point of 1.84 mg/L. Based on analysis by multivariate logistic regression, serum ferritin and globulin were independent risks for intravenous immunoglobulin resistance, D-dimer was independent risk for coronary artery lesions. Conclusions: Elevated serum ferritin, globulin and D-dimer levels are significantly associated with intravenous immunoglobulin resistance in Kawasaki disease. Moreover, serum D-dimer is significantly increased in Kawasaki disease with coronary artery lesions.

Kuo, H. C., et al. (2019). "Global investigation of immune repertoire suggests Kawasaki disease has infectious cause." Circulation Journal **83**(10): 2070-2078.
Background: Kawasaki disease (KD) severely threatens young children's health worldwide. The pathogenic mechanism of KD has not yet been solved, so there is still debate over whether KD is an infectious disease or an autoimmune disease. Methods and Results: To solve this problem, an immune repertoire analysis of KD was conducted. We collected blood cell RNA samples and prepared them into amplicons with iRepertoire kits. The amplicons were sequenced and analyzed with the iRepertoire pipeline. We first identified KD-specific VJ and VDJ forms that had the potential to serve as biomarkers of KD. In addition, the KD-specific VDJ forms were contributed mostly by immunoglobulin G. The D50 value analysis showed that B-cell diversity in KD is decreased, suggesting unique immunoglobulins are produced in KD. Moreover, V, D and J segment usage in IgA, IgG and IgM was consistent with previous KD studies. Further comparison showed no difference in CDR3 peptide length between KD and fever controls (subjects with fever but not diagnosed as KD), indicting KD had B-cell selection phenomenon that has a non-autoimmune pattern. The comparison of amino acid usage of the CDR3 region demonstrated a preference for hydrophilic amino acids in KD. Conclusions: The results of D50 value, VDJ usage and CDR3 peptide length analyses suggested the characteristics of infectious disease for KD.

Kwon, Y. C., et al. (2019). "Identification of the TIFAB Gene as a Susceptibility Locus for Coronary Artery Aneurysm in Patients with Kawasaki Disease." Pediatric Cardiology **40**(3): 483-488.
Kawasaki disease (KD) is a self-limiting systemic vasculitis of unknown etiology. KD is often complicated by coronary artery aneurysms (CAAs), which develop in about 20-25% of untreated children and 3-5% of children treated with intravenous immunoglobulin therapy. To identify the risk loci for CAA susceptibility in patients with KD, we performed a genome-wide association study (GWAS) using our previous Illumina HumanOmni1-Quad BeadChip data (296 KD patients) and a new replication study in an independent sample set (713 KD patients) by grouping KD patients without CAA (control) versus KD patients with extremely large aneurysms (diameter >= 5 mm) (case). Among 44 candidate single -nucleotide polymorphisms (SNPs) selected from the initial GWAS data (33 cases vs. 215 controls), a SNP (rs899162) located 7 kb upstream of the TIFAB gene on chromosome five was replicated in an independent sample (12 cases vs. 532 controls). In the combined analysis (45 cases vs. 747 controls), the SNP (rs899162) showed a highly significant association with CAA formation (diameter >= 5 mm) in patients with KD (odds ratio = 3.20, 95% confidence interval = 2.02-5.05, P<inf>combined</inf> = 1.95 x

10⁻⁷). These results indicate that the TIFAB gene may act as a CAA susceptibility locus in patients with KD. Copyright © 2018, Springer Science+Business Media, LLC, part of Springer Nature.

Lanata, M. M., et al. (2019). "A Case of Fever, Rash, and a Painful Limb in an Infant." Clinical Pediatrics **58**(6): 711-714.

Laukka, D., et al. (2019). "Unlikely association between Kawasaki disease and intracranial aneurysms: A prospective cohort study." Journal of Neurosurgery: Pediatrics **23**(5): 593-596.
OBJECTIVE Kawasaki disease (KD) is a vasculitis that can cause aneurysm formation in coronary arteries and, more rarely, in peripheral arteries. A possible connection between KD and intracranial aneurysms is unclear. The purpose of this study was to determine if KD is associated with intracranial aneurysms. METHODS In this prospective cohort study, all patients hospitalized and diagnosed with KD in the authors' hospital district area in the period from 1978 to 1995 were identified. Patients with a current age >= 25 years and a history of KD in childhood were included in the study, which was conducted between 2016 and 2017. Magnetic resonance angiography (MRA) of the brain was performed in all patients. RESULTS Forty patients (25 males), whose mean age was 33.5 +/- 3.9 years (mean +/- standard deviation), were eligible for study inclusion. The mean age at KD diagnosis was 3.9 +/- 3.1 years, and the mean follow-up was 29.5 +/- 4.3 years. Six patients (15%) had coronary arterial lesions during the acute illness of KD. None of the patients (0%) had intracranial aneurysms on brain MRA, which is significantly under the prevalence of 10% (95% CI 0%-8.8%, p = 0.03) that is the recommended limit for intracranial aneurysm screening. CONCLUSIONS The study results suggest that KD is not associated with an increased prevalence of intracranial aneurysms and that screening for intracranial aneurysms is not warranted in patients with a history of KD. Copyright ©AANS 2019, except where prohibited by US copyright law

Levin, R., et al. (2019). "Acute myocardial infarction in an adolescent with kawasaki disease." Revista Argentina de Cardiologia **87**(2): 149.

L'Huillier, A. G., et al. (2019). "Identification of Viral Signatures Using High-Throughput Sequencing on Blood of Patients With Kawasaki Disease." Frontiers in Pediatrics **7 (no pagination)**(524).
Aims: Kawasaki disease is an acute pediatric vasculitis whose etiology remains unknown but epidemiology and clinical presentation suggest a viral etiology. We performed unbiased high-throughput-sequencing on blood of patients with Kawasaki Disease (KD). Material(s) and Method(s): High-throughput-sequencing was performed directly on blood of children with typical KD. Sequences were aligned against a database of clinically relevant viruses. Result(s): Four patients were acutely infected in the blood, with respectively, poliovirus (vaccine strain), measles (vaccine strain), rhinovirus and bocavirus. Patients with poliovirus and measles had received oral polio and measles vaccines, respectively, twelve and 2 weeks prior. Conclusion(s): Viral signatures were identified in more than half of the patients, including some corresponding to their vaccinal history. This could suggest a temporal association with KD. © Copyright © 2019 L'Huillier, Brito, Wagner, Cordey, Zdobnov, Posfay-Barbe and Kaiser.

Li, W., et al. (2019). "Clinical features and mid-term follow-up in infants younger than 3 months with Kawasaki disease in a Chinese population." Journal of Paediatrics and Child Health **55**(5): 523-527.
Aim: To explore the clinical features and mid-term follow-up of Kawasaki disease (KD) in infants younger than 3 months of age in a Chinese population. Methods: We performed a retrospective analysis of clinical signs, laboratory data, echocardiography results and outcomes for patients with KD diagnosed at our hospital from January 2009 to December 2013. A total of 1150 children were diagnosed with KD, and 200 KD patients were enrolled in this study. Group 1 included 40 children younger than 3 months of age. We randomly selected a control group as Group 2

included 160 children older than 3 months of age who fulfilled diagnostic criteria for KD and maintained follow-up for more than 1 year. Results: There was a significant difference in clinical manifestations between the two groups, except respiratory infection. Group 1 was more likely to have incomplete presentation (P < 0.001). There were no significant differences in laboratory data except for white blood cell counts between the two groups. Coronary artery abnormalities were significantly different between the two groups (P < 0.001). At a mean follow-up of 18 months (range 12–48 months), all patients with coronary artery abnormalities, except for giant coronary aneurysms, returned to normal in terms of diameter as assessed by echocardiography. Conclusions: Infants younger than 3 months of age with KD often present with incomplete criteria, and diagnosis may be delayed. In addition, there may be a higher risk of developing coronary artery abnormalities. All patients except those with giant coronary aneurysms recovered well without complications at mid-term follow-up. © 2018 Paediatrics and Child Health Division (The Royal Australasian College of Physicians)

Li, Y., et al. (2019). "A case of Kawasaki disease presenting with parotitis: A case report and literature review." Medicine **98**(22): e15817.
RATIONALE: Kawasaki disease affects multiple organ systems. Its typical symptoms include fever, rash, oropharyngeal mucosal erythema, bilateral non-exudative conjunctivitis, cervical lymphadenopathy, extremity changes, and membranous desquamation of the fingers and toes. In severe cases, cardiovascular, respiratory, musculoskeletal, gastrointestinal, neurological, and genitourinary complications may occur. In the early stage, Kawasaki disease is often manifested by uncommon symptoms, such as pyuria, meningitis, shock, and retropharyngeal or parapharyngeal abscess, which may delay diagnosis and treatment. We have reported a case of Kawasaki disease presenting with mumps and reviewed the clinical features of 14 other similar cases, in order to facilitate the early diagnosis and treatment of this unusual presentation of Kawasaki disease. PATIENT CONCERNS: A 10-year-old boy presented with persistent fever and parotitis and was diagnosed with suppurative parotitis. After antibiotic therapy, the parotid swelling reduced, but the fever persisted and other typical symptoms of Kawasaki disease appeared, including bilateral conjunctival hyperaemia, cervical lymphadenopathy, oropharyngeal mucosal erythema, membranous desquamation of the fingers, and left coronary artery widening. DIAGNOSES: The patient was diagnosed with Kawasaki disease 12 days after the onset of fever. INTERVENTIONS: The patient was administered gamma-globulin 1.0 g/kg.d for 2 consecutive days and oral aspirin 5 mg/kg.d. OUTCOME(S): The left coronary artery returned to a width of 3.8 mm after 1 month and of 3.1 mm after 3 months. The dose of aspirin was reduced to 3 mg/kg.d after 2 months and to 1.5 mg/kg.d after 3 months. LESSONS: Physicians should be aware that Kawasaki disease may develop after parotitis.

Lindquist, M. E. and M. D. Hicar (2019). "B cells and antibodies in kawasaki disease." International Journal of Molecular Sciences **20 (8) (no pagination)**(1834).
The etiology of Kawasaki disease (KD), the leading cause of acquired heart disease in children, is currently unknown. Epidemiology supports a relationship of KD to an infectious disease. Several pathological mechanisms are being considered, including a superantigen response, direct invasion by an infectious etiology or an autoimmune phenomenon. Treating affected patients with intravenous immunoglobulin is effective at reducing the rates of coronary aneurysms. However, the role of B cells and antibodies in KD pathogenesis remains unclear. Murine models are not clear on the role for B cells and antibodies in pathogenesis. Studies on rare aneurysm specimens reveal plasma cell infiltrates. Antibodies generated from these aneurysmal plasma cell infiltrates showed cross-reaction to intracellular inclusions in the bronchial epithelium of a number of pathologic specimens from children with KD. These antibodies have not defined an etiology. Notably, a number of autoantibody responses have been reported in children with KD. Recent studies show acute B cell responses are similar in children with KD compared to children with infections, lending further support of an infectious disease cause of KD. Here, we will review and discuss the inconsistencies in the literature in relation to B cell responses, specific antibodies,

and a potential role for humoral immunity in KD pathogenesis or diagnosis. Copyright © 2019 by the authors. Licensee MDPI, Basel, Switzerland.

Luo, L., et al. (2019). "Serum Levels of Syndecan-1 in Patients With Kawasaki Disease." The Pediatric infectious disease journal **38**(1): 89-94.
BACKGROUND: Kawasaki disease (KD) is an acute systemic vasculitis with coronary artery lesions (CALs) being the major concern. Syndecan-1 (SDC-1) is a major core protein expressed on the glycocalyx of endothelial cells. Shed SDC-1 in serum is regarded as a biomarker for endothelial activation or damage. METHOD(S): In this study, we aimed to determine the serum levels of SDC-1 and evaluate the relationship between serum levels of SDC-1 and the CALs in the acute phase of KD. Serum SDC-1 levels were measured in 119 children with KD and in 43 healthy children as normal controls and in 40 children with febrile disease. All KD patients were administrated a single dose of intravenous immunoglobulin and aspirin per os within 10 days of KD onset. RESULT(S): Serum levels of SDC-1, in addition to albumin and hemoglobin, were significantly increased in patients with KD than in healthy controls and febrile controls. Furthermore, the serum levels of SDC-1, albumin and hemoglobin were significantly elevated in KD patients with CALs than those without CALs. Additionally, serum levels of SDC-1 were significantly correlated with levels of hemoglobin and serum albumin in patients with KD. After intravenous immunoglobulin therapy, serum levels of interleukin-6, soluble cell adhesion molecules-1 and resistin were reduced while serum levels of SDC-1 were significantly increased in KD patients. CONCLUSION(S): SDC-1 serum levels may mirror vascular endothelial damage and inflammation in KD. This might be utilized as a potential novel target for coronary artery protection in KD patients.

Makino, N., et al. (2019). "Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016." Pediatrics International **61**(4): 397-403.
Background: Approximately 50 years have passed since Kawasaki disease (KD) was first reported. The KD nationwide survey began in 1970. Although >360 000 cases have already been reported in Japan, the cause is still unknown. In Japan, the number of patients and incidence rate of KD has continued to increase. It is necessary to examine the trend of the occurrence in the surveillance of KD. Method(s): The nationwide survey of patient incidence in 2015 and 2016 was conducted in 2017, as the 24th nationwide survey of KD. A questionnaire was sent to pediatric departments in hospitals with >100 beds and specialized pediatric hospitals, and was responded to by the attending pediatricians. Result(s): The total number of patients in 2 years was 31 595, and the sex ratio (male/female) was 1.34. The incidence rate (/100 000 children aged 0-4 years/year) was 330.2 (371.2 in boys, 287.3 in girls) in 2015, and 309.0 (343.2 in boys, 273.2 in girls) in 2016. The number of patients by month peaked in January. The age-specific incidence rate according to sex was highest in children between 9 and 11 months of age, after which the incidence rate gradually decreased with advancing age. Conclusion(s): We summarize the most recent nationwide survey of KD and consider the change in the epidemiologic picture. Copyright © 2019 Japan Pediatric Society

Makino, N., et al. (2019). "Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016." Pediatrics International **61**(4): 397-403.
Background: Approximately 50 years have passed since Kawasaki disease (KD) was first reported. The KD nationwide survey began in 1970. Although >360 000 cases have already been reported in Japan, the cause is still unknown. In Japan, the number of patients and incidence rate of KD has continued to increase. It is necessary to examine the trend of the occurrence in the surveillance of KD. Methods: The nationwide survey of patient incidence in 2015 and 2016 was conducted in 2017, as the 24th nationwide survey of KD. A questionnaire was sent to pediatric departments in hospitals with >100 beds and specialized pediatric hospitals, and was responded to by the attending pediatricians. Results: The total number of patients in 2 years was 31 595, and the sex ratio (male/female) was 1.34. The incidence rate (/100 000 children aged

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Mărginean, C. O., et al. (2019). "The peculiarities of Kawasaki disease at the extremes of age: Two case reports." Medicine **98**(42): e17595.
RATIONALE: Extremes of age is an important risk factor for the development of coronary arteries aneurysms (CAAs) associated to Kawasaki disease (KD) along with male gender, prolonged fever and a delay in diagnosis or treatment. PATIENT CONCERNS: We report two cases of KD in the extremes of age, a 5-month-old male infant and a 9-year-old child in order to underline the features of this disorder outside the typical age range of 1 to 4years. The 5-month-old male was admitted in our clinic for generalized polymorphous exanthema and fever for approximately 7days. The laboratory test pointed out leukocytosis and increased inflammatory biomarkers. The 9-year-old male child was admitted in our clinic for fever and submandibular adenopathy. The onset was approximately 5days before the admission with a sudden development of unilateral, painless, submandibular lymphadenopathy for which the ENT specialist recommended antibiotics and nonsteroid anti-inflammatory drugs. In the 2nd day of admission, he presented severe desquamation of hands and soles. DIAGNOSIS: Both cases were diagnosed with KD. The echocardiography showed no cardiac impairment in the infant, while in the older patient it revealed mild dilation of the left coronary artery. INTERVENTIONS: Both patients received intravenously immunoglobulin and pulsed methylprednisolone. OUTCOMES: The evolution was favorable in both cases, but in the infant, the C-reactive protein levels persisted mildly elevated for approximately 2months after the diagnosis. LESSONS: The peculiarities of KD in the extremes of age are related to a higher frequency of incomplete features and an increased incidence of coronary artery lesions resulting in a delay of the diagnosis, and subsequent poorer outcomes.

Matsumoto, K., et al. (2019). "Coronary vessel wall visualization via three-dimensional turbo spin-echo black blood imaging in Kawasaki disease." Magnetic Resonance Imaging **62**: 159-166.
Purpose: To evaluate the feasibility of coronary vessel wall visualization using three-dimensional turbo spin-echo black blood imaging (3D-TSE) in children with Kawasaki disease. Materials and methods: Nine patients (6 girls and 3 boys; mean age ± standard deviation, 5.6 ± 3.3 years; range, 1.4–10.3 years) were included. Coronary magnetic resonance angiography (MRA) with an axial slice orientation and 3D-TSE with axial and sagittal slice orientations (3D-TSE-axi and 3D-TSE-sag) were acquired for the whole heart. Coronary vessel walls were evaluated separately in aneurysm and normal-proximal regions. The internal diameter and wall thickness of the reformatted cross-sectional images were measured in both the regions. Reproducibility between MRA and 3D-TSE was evaluated via interclass correlation coefficients (ICCs) and Bland-Altman plots. Results: In total, 164 points (aneurysmal regions, 73; normal-proximal regions, 64; normal-distal regions, 27) were evaluated. The ICC for 3D-TSE-axi was higher than that for 3D-TSE-sag (aneurysmal regions, ICC = 0.88 and 0.81; normal-proximal regions, ICC = 0.90 and 0.32, respectively). Bland-Altman plots of the internal diameter via MRA and 3D-TSE-axi showed a wide 95% limit of agreement (−0.13 to 2.89 mm) and significant fixed and proportional biases ($P < 0.001$ and $P = 0.002$) in the aneurysmal regions. However, the 95% limit of agreement was narrow (−0.14 to 0.57 mm) in the normal-proximal regions. If 1 mm was set as the cut-off for a thickened wall, wall thickness via 3D-TSE-axi was found to be abnormal across many points (84.0% of aneurysmal regions; 18.4% of normal-proximal regions). Conclusions: 3D-TSE imaging of the normal-proximal regions of the coronary vessel in individuals with Kawasaki disease was found to be feasible. However, in aneurysmal regions, larger aneurysmal diameters led to an increased bias between MRA and 3D-TSE.

Matsuno, A. K., et al. (2019). "Human coronavirus alone or in co-infection with rhinovirus C is a risk factor for severe respiratory disease and admission to the pediatric intensive care unit: A one-year study in Southeast Brazil." PLoS ONE **14 (6) (no pagination)**(e0217744).
Objective We aimed to assess the profile of respiratory viruses in young children hospitalized for acute lower respiratory tract infection (ALRI) and its association with disease severity, defined as need for pediatric intensive care unit (PICU) admission. Design Prospective observational cohort study. Setting A tertiary-care university hospital in Brazil. Patients Children younger than three years attending the pediatric emergency room with ALRI who were admitted to the hospital. Interventions None. Measurements and main results Nasopharyngeal aspirates were collected from patients from June 1st, 2008 to May 31st, 2009within the first 48 hours of hospitalization. Nasopharyngeal aspirates were tested for 17humanrespiratory viruses by molecular and immunofluorescence based assays. Simple and multiple log-binomial regression models were constructed to assess associations of virus type with a need for PICU admission. Age, prematurity, the presence of an underlying disease and congenital heart disease were covariates. Nasopharyngeal aspirates were positive for at least one virus in 236 patients. Rhinoviruses were detected in 85.6% of samples, with a preponderance of rhinovirus C (RV-C) (61.9%). Respiratory syncytial virus was detected in 59.8% and human coronavirus (HCoV) in 11% of the samples. Co-detections of two to five viruses were found in 78% of the patients. The detection of HCoV alone (adjusted relative risk (RR) 2.18; 95% CI 1.15-4.15) or in co-infection with RV-C (adjusted RR 2.37; 95% CI 1.23-4.58) was independently associated with PICU admission. Conclusions The detection of HCoV alone or in co-infection with RV-C was independently associated with PICU admission in young children hospitalized for ALRI. Copyright © 2019 Matsuno et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

McCarthy, S., et al. (2019). "Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness." Clinical Infectious Diseases **69**(11): 1903-1911.
Background: Effective therapeutics for respiratory viruses are needed. Early data suggest that nitazoxanide (NTZ) may be beneficial for treating acute respiratory viral illness. Method(s): From March 2014 through March 2017, a double-blind, placebo-controlled trial was conducted in 260 participants >=1 year old hospitalized with influenza-like illness at 6 hospitals in Mexico. Participants were randomized 1:1 to NTZ (age >=12 years, 600 mg twice daily; age 4-11 years and 1-3 years, 200 or 100 mg twice daily, respectively) or placebo for 5 days in addition to standard of care. The primary endpoint was time from first dose to hospital discharge. Influenza reverse-transcription polymerase chain reaction and Respifinder 22 multiplex test were used for virus detection. Result(s): Of 260 participants enrolled, 257 were randomized and took at least 1 dose of study treatment (intention-to-treat population): 130 in the NTZ group and 127 in the placebo group. The Kaplan-Meier estimate of the median duration of hospitalization was 6.5 (interquartile range [IQR], 4.0-9.0) days in the NTZ group vs 7.0 (IQR, 4.0-9.0) days in the placebo group (P =. 56). Duration of hospitalization between the 2 treatments was similar in children (P =. 29) and adults (P =. 62), influenza A and B (P =. 32), and other respiratory viruses. Seven (5.4%) and 6 (4.7%) participants in the NTZ and placebo groups, respectively, reported serious adverse events. Conclusion(s): Treatment with NTZ did not reduce the duration of hospital stay in severe influenza-like illness. Further analyses based on age and evaluations by virus did not reveal any subgroups that appeared to benefit from NTZ. Clinical Trials Registration: NCT02057757. Copyright © 2019 Published by Oxford University Press for the Infectious Diseases Society of America 2019.

Menikou, S., et al. (2019). "Kawasaki Disease: The Role of Immune Complexes Revisited." Frontiers in Immunology **10**: 1156.
Kawasaki disease (KD) is an inflammatory disease in children associated with vasculitis affecting predominantly the coronary arteries and is now the most common cause of acquired heart

disease in children in developed countries. The etiology of KD is unknown but epidemiological studies implicate an infectious agent or toxin, which causes disease in genetically predisposed individuals. The presence of immune complexes (ICs) in the serum of children with KD was established in numerous studies during the 1970s and 80s. More recent genetic studies have identified variation in Fcgamma receptors and genes controlling immunoglobulin production associated with KD. In this review we link the genetic findings and IC studies and suggest a key role for their interaction in pathophysiology of the disease.

Na, J. H., et al. (2019). "Utilization of Coronary Artery to Aorta for the Early Detection of Kawasaki Disease." Pediatric Cardiology **40**(3): 461-467.
Timely diagnosis of coronary involvement is paramount in Kawasaki disease (KD) as it can be associated with long-term morbidity. However, echocardiographic measurements of coronary artery dilation in KD are inconsistent and not proficient for all abnormal arteries. The purpose of this study was to investigate more valuable indices and determine their sensitivity and specificity for early diagnosis of coronary involvement in KD. We performed this retrospective study in 218 children. All patients underwent laboratory and echocardiographic evaluations upon admission. We measured the size of the left main coronary artery (LMA), left anterior descending coronary artery (LAD), right coronary artery (RCA), and aorta (Ao), and calculated the LMA/Ao, LAD/Ao, and RCA/Ao ratios. We also calculated the cut-off values of each index using receiver operating characteristic curves. LMA, LAD, and RCA measurements did not correlate with white blood cell count, platelet count, erythrocyte sedimentation rate, C-reactive protein level, or brain natriuretic peptide level. The LMA measurement was associated with hemoglobin, hematocrit, and iron saturation. LAD/Ao was correlated with white blood cell and platelet counts ($P < 0.05$), whereas RCA/Ao was correlated with ferritin level ($P < 0.05$). The cut-off value of LMA/Ao was 0.2, with a sensitivity of 85% and specificity of 70%. Individual coronary artery/Ao ratios might provide helpful insight for detection of coronary abnormality in KD in the acute phase. Further investigation is essential to clarify prompt early diagnosis of coronary involvement in KD.

Nanda, S., et al. (2019). "Recurrent fevers and a diffuse, evanescent papular rash." Pediatric Dermatology **36**(4): 535-537.

Nandi, A., et al. (2019). "A comparison of serum IL6 and CRP levels with respect to coronary changes and treatment response in Kawasaki disease patients: a prospective study." Rheumatology International **39**(10): 1797-1801.
To evaluate serum levels of IL6 in patients with Kawasaki disease and compare it with CRP, and to assess the role of these biomarkers in predicting coronary changes and resistance to the first-line therapy of this disease in a subset of Indian population. A single centre prospective observational study was conducted amongst all Kawasaki disease patients for a period of 18 months from January 2017 at Institute of Child Health, Kolkata. Serum IL6 and CRP were compared at diagnosis and after 48 h of administering IVIG in patients who developed coronary changes with those who did not and also among the responders and non-responders to IVIG, the first-line therapy given to these patients. Out of total 72 patients of KD [mean age of presentation: 24 months, M:F = 1.22:1], 30% (n = 22) had coronary artery involvement (CALs), and 15% (n = 11) were IVIG non-responders. Mean IL6 prior to IVIG in those with CALs was 143.60 pg/ml, which was about three times higher than in those without CALs (mean = 52.90 pg/ml), the difference being significant ($p < 0.01$). Mean CRP values also were significantly raised in patients with CALs ($p < 0.01$) whereas post-IVIG levels of mean serum IL6 was found to be 108.15 pg/ml in non-responders which was about 17 times raised than that in the responders (mean IL6 = 6.22),the difference again was statistically significant ($p < 0.001$).Also, ROC analysis revealed a sensitivity and specificity of 81.0% and 82.0%, respectively, for IL6; 72% and 74%, respectively, for CRP for predicting CALs. This study also shows a sensitivity of 72% and specificity of 68% for IL6 in predicting IVIG resistance whereas that of CRP being 90%

sensitive and 36% specific. These results suggest that higher levels of IL-6 and CRP at diagnosis are associated with occurrence of CALs and IVIG resistance in KD patients. Using the cutoff for IL6 and CRP from our study, chances of developing CALs and IVIG resistance can be predicted, which might prevent the development of future complications like aneurysms in such patients. Copyright © 2019, Springer-Verlag GmbH Germany, part of Springer Nature.

Nguyen, T., et al. (2019). "Kawasaki Disease in a 3-Month-Old Infant: How to Remain Vigilant?" Pediatric Emergency Care **35**(12): 884-885.
Background Kawasaki disease is an acute vasculitis occurring between 6 months and 5 years old. Patients younger than 6 months have mostly incomplete form. This clinical symptoms lead to confusion and delayed diagnosis. Case Report We developed the diagnostic difficulties with a 3-month-old infant. At the beginning, his incomplete presentation misled pediatricians. Conclusions We highlight the possibilities of Kawasaki disease in infants younger than 6 months. Indeed, every diagnostic delay increases cardiovascular risk. Nonetheless, in our case, treatment was prescribed in the first 5 days, and the patient developed aneurysms. Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Ogimi, C., et al. (2019). "Characteristics and outcomes of coronavirus infection in children: The role of viral factors and an immunocompromised state." Journal of the Pediatric Infectious Diseases Society **8**(1): 21-28.
Background. Immunocompromised children might be predisposed to serious infections from human coronaviruses (HCoVs), including strains OC43, NL63, HKU1, and 229E; however, the virologic and clinical features of HCoV infection in immunocompromised children have not been compared to those in nonimmunocompromised children. Methods. We retrospectively analyzed a cohort of children who presented to Seattle Children's Hospital and in whom HCoV was detected by a multiplex respiratory polymerase chain reaction assay of a nasal sample between October 2012 and March 2016. Lower respiratory tract disease (LRTD) was defined as possible or definite infiltrate seen in chest imaging, need for oxygen, or abnormal lung examination in conjunction with a physician diagnosis of LRTD. We used logistic regression modeling to evaluate risk factors for LRTD and LRTD that necessitated oxygen use (severe LRTD), including an immunocompromised state, in children with HCoV infection. Results. The median ages of 85 immunocompromised and 1152 nonimmunocompromised children with HCoV infection were 6.3 and 1.6 years, respectively. The prevalence of LRTD and of severe LRTD did not differ greatly between the immunocompromised and nonimmunocompromised patients (22% vs 26% [LRTD] and 15% vs 11% [severe LRTD], respectively); however, in a multivariable model, an immunocompromised state was associated with an increased likelihood of severe LRTD (adjusted odds ratio, 2.5 [95% confidence interval, 1.2-4.9]; P = .01). Younger age, having an underlying pulmonary disorder, and the presence of respiratory syncytial virus were also associated with LRTD or severe LRTD in multivariable models. The risks of LRTD or severe LRTD did not differ among the children with different HCoV strains. Conclusions. The presence of a copathogen and host factors, including an immunocompromised state, were associated with increased risk for severe LRTD. Recognizing risk factors for severe respiratory illness might assist in risk stratification. Copyright © The Author(s) 2018. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved.

Ohashi, R., et al. (2019). "M1 macrophage is the predominant phenotype in coronary artery lesions following Kawasaki disease." Vascular Medicine (United Kingdom) **24**(6): 484-492.
Kawasaki disease (KD) is a systemic inflammatory process that affects the medium-sized arteries, causing various cardiovascular complications. However, it is not clear if the vascular sequelae following KD can predispose to the development of atherosclerosis later in life. Our aim was to examine the macrophage phenotypes in the coronary arteries forming giant aneurysms after KD to gain insight into the pathogenesis of vascular lesions in KD. We examined histological sections of the coronary arteries from five patients with KD who underwent coronary bypass grafting

procedure as treatment for giant aneurysms and subsequent stenosis. Immunohistochemical expression of M1- and M2-macrophage markers was assessed to determine the macrophage phenotype of KD to compare with that of atherosclerosis in eight adult patients. All the KD specimens showed a mild to moderate degree of intimal thickening consisting of mature fibrous tissue and distortion of elastic fibers, mimicking the histological features of atherosclerosis. The total number of CD68 positive macrophages was higher in atherosclerosis than in KD specimens. Among the CD68 positive macrophages, the proportion of M1 phenotype, detected by CD86 or SOCS3, was higher in KD than in atherosclerosis. In contrast, the proportion of M2 phenotype, detected by CD163 or MRC1, was higher in patients with atherosclerosis. Despite similar histological features, KD and atherosclerosis appear to have a different immunological etiology for progression of the chronic vascular lesions. A further study enrolling a larger number of cases is required to delineate underlying mechanisms of vascular complications in KD. Copyright © The Author(s) 2019.

Okada, S., et al. (2019). "Erythema nodosum masking Kawasaki disease with an initial manifestation of skin lesions." Yonsei Medical Journal **60**(3): 312-314.
We report the first case demonstrating an association between Kawasaki disease (KD) and erythema nodosum (EN). A 3-year-old girl presented with EN as an initial manifestation of KD. At the initial visit, she showed high fever of 40°C, injection of the orophar-ynx, cervical lymphadenopathy, and red-purple cutaneous nodules, particularly on the lower limbs. She complained of severe pain in the neck and cutaneous lesions. Initially, the development of EN was attributed to Salmonella spp infection, which was detected in stool culture. However, the patient did not respond to high-dose ampicillin/sulbactam to which the Salmonella spp is sensitive. Echocardiography performed as screening for fever of unknown origin revealed medium-sized aneurysms of the left anterior descending artery. EN masked the diagnosis of KD, and the patient developed a coronary artery lesion. KD should be considered in the differential diagnosis of refractory EN in pediatric patients. © Yonsei University College of Medicine 2019.

Padilla, L. A., et al. (2019). "Racial difference in clinical and epidemiological characteristics of kawasaki disease in southeast us." Circulation. Conference: American Heart Association Scientific Sessions, AHA **140**(Supplement 1).
Introduction: Kawasaki Disease (KD) displays substantial variation in prevalence and response to intravenous gamma globulin (IVIG) by race and ethnicity. However, studies including and making conclusions about African Americans (AA) were hampered by low subject numbers. Hypothesis: Our main objective was to more clearly identify racial discrepancies in treatment response and examine underlying causes. Method(s): EMR (2000-2015) ICD codes served to identify KD children admitted to a single tertiary Southeast U.S. center. Subjects diagnosed and treated according to AHA criteria were included. Those, receiving IVIG off site and then transferred > 36 hours after completing IVIG infusion, were excluded. Demographic, laboratory, clinical and echocardiographic data were compared between AA and Whites using x, Fisher's exact and t-test. Result(s): A total 369 subjects (192;52% Whites and 177;48% AA) were included. AA C-Reactive protein levels at admission and discharge were almost double than Whites (Admission: 14.4+/-10.2 vs 8.6+/-7.7, p <0.0001; Discharge: 8.4+/-8.2 vs 4.7+/-5, p 0.0419). No significant differences occurred in time from fever onset to IVIG, admission time to treatment, or in percent coronary artery (CA) with z > 2.5 on initial ECHO. Although, no difference in IVIG refractory rate or persistently dilated coronaries at second hospital ECHO occurred, AA received proportionally more ancillary drugs (i.e. Remicade, Heparin, Plavix) (9.6% v 2.6%, p 0.0037), and had longer hospital stay (5+/-3.9 days vs 3.4+/-2.2, p 0.0018). After one-year in those with follow-up ECHO, proportionally more AA (14.5%) showed persistent CA abnormalities than Whites (6.3%, p 0.0308). At two-years CA abnormalities persisted in AA when compared to Whites (21.2% vs 6.9%, p 0.0126). Conclusion(s): This KD study includes the largest AA cohort reported to date, and indicates that the disparity in treatment response likely relates to factors other than time to KD recognition and treatment. Rather, AA display more severe inflammation at KD onset resulting

in more ancillary treatment and longer hospitalization. Although no differences occurred in IVIG resistance and CA abnormalities during hospitalization, AA KD patients showed greater persistence of CA abnormalities.

Pascall, B., et al. (2019). "Immunoglobulin for Kawasaki disease: A 3-year retrospective audit." BMJ Paediatrics Open **3**(1).
Aim To evaluate whether intravenous immunoglobulin (IVIG) use in children with suspected Kawasaki disease (KD) was given according to local trust and the newly revised American Heart Association (AHA) guidelines. Methods In our tertiary hospital, any child with suspected KD given IVIG, over the past 3 years, was identified. Their electronic notes were then reviewed. Results Ten patients were identified. Nine patients had a fever lasting 5 days or more. Four patients had either 5/5 or 4/5 of the diagnostic criteria for KD and were diagnosed with complete KD. The remaining six patients were suspected to have incomplete KD. 7/10 patients received IVIG within 10 days of onset of illness. Patients suspected to have incomplete KD experienced a mean delay in administration of IVIG of 5.3 days compared with those with complete KD. In four patients, an alternative diagnosis was established. Three patients had coronary artery abnormalities on first echocardiogram. From these patients, only one had a follow-up echocardiogram recorded in their notes. No patient had more than one follow-up echocardiogram (at both 2 and 6 weeks). Conclusion Identifying patients with incomplete KD is more difficult than identifying those with complete KD and any delay in giving IVIG could be due to this reason. This audit suggests that increasing awareness of incomplete KD and a clear guideline will aid prompter diagnosis and administration of IVIG. This audit also suggests that all patients with KD should receive more than one follow-up echocardiogram. © 2019 Author(s).

Peng, Y., et al. (2019). "Prevalence and characteristics of arthritis in Kawasaki disease: a Chinese cohort study." Clinical and Experimental Medicine **19**(2): 167-172.
Arthritis is a major complication of Kawasaki disease (KD). The aims of this study were to define the frequency and the clinical characteristics of arthritis in KD in China and to analyze the relation between arthritis and coronary outcome in KD. We included 1420 KD patients followed at Jiangxi Children's Hospital from January 2014 to December 2017. Demographic, clinical and laboratory features of KD were analyzed. Among the 1420 patients enrolled, 151 had arthritis. The median age of KD patients with arthritis was 29 months and older than those without arthritis (20 months). Of the 151 patients developed arthritis, 101 patients (66.9%) had oligoarticular involvement and 50 patients (33.1%) had polyarticular involvement. Early-onset and late-onset arthritis were, respectively, observed in 123 (81.45%) and 28 (18.54%) patients. The KD patients with arthritis had significantly increased levels of inflammatory markers, and we observed a higher incidence rate of coronary artery aneurysms among those with arthritis (7.28%) compared to those without arthritis (2.75%) ($p = 0.003$), but the prevalence of coronary artery lesions (CALs) was similar in the two groups. The arthritis in KD was self-limited, left no sequelae and did not require additional medications. KD patients with arthritis were more likely to get coronary artery aneurysms than the patients without arthritis, so examination of joints in KD was necessary. Copyright © 2019, Springer Nature Switzerland AG.

Petrarca, L., et al. (2019). "Human bocavirus in children hospitalized for acute respiratory tract infection in Rome." World Journal of Pediatrics.
Background: The role of human bocavirus (HBoV) as a respiratory pathogen has not been fulfilled yet. We aimed to describe clinical and serological characteristics of children with HBoV hospitalized for acute respiratory tract infection and to evaluate whether differences occur between HBoV alone and in co-infection. Method(s): We retrospectively reviewed data from 60 children (median age of 6.2 months, range 0.6-70.9) hospitalized for acute respiratory symptoms, with HBoV detected from a respiratory sample, using a reverse transcriptase-PCR for 14 respiratory viruses (including respiratory syncytial virus (RSV), influenza virus A and B, human coronavirus OC43, 229E, NL-63 and HUK1, adenovirus, rhinovirus, parainfluenza virus1-3, and

human metapneumovirus). Result(s): HBoV was detected alone in 29 (48.3%) patients, while in co-infection with other viruses in 31 patients (51.7%), with a peak between December and January. Among the 60 patients, 34 were bronchiolitis, 19 wheezing, 3 pneumonia, 2 upper respiratory tract infection, and 2 whooping cough. Seven children (11.6%) required admission to the paediatric intensive care unit (PICU) for respiratory failure. No differences was observed in age, family history for atopy and/or asthma, clinical presentations, chest X-ray, or laboratory findings in children with HBoV alone vs. multiple viral detection. RSV was the most frequently co-detected virus (61.3%). When compared with HBoV detection alone, the co-detection of RSV and HBoV was associated with male sex (P = 0.013), younger age (P = 0.01), and lower blood neutrophil count (P = 0.032). Conclusion(s): HBoV can be detected alone and in co-infection respiratory samples of children with an acute respiratory tract infection. A cause-effect relationship between HBoV and respiratory infection is not clear, so further studies are needed to clarify this point. Copyright © 2019, Children's Hospital, Zhejiang University School of Medicine.

Pi, L., et al. (2019). "A PEAR1 polymorphism (rs12041331) is associated with risk of coronary artery aneurysm in Kawasaki disease." Annals of Human Genetics **83**(1): 54-62.
Kawasaki disease (KD) is an acute systemic vasculitis that is most seriously complicated by coronary artery aneurysm (CAA). The polymorphisms of platelet endothelial aggregation receptor 1 (PEAR1), notably rs12041331 and rs12566888, were found to be closely related to cardiac disease. However, little is known regarding the connection between PEAR1 and KD. In this study, we genotyped PEAR1 rs12566888 and rs12041331 in 637 healthy infants and 694 KD patients (74 with CAA). Subsequently, odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the strength of their relationships. No significant differences in the frequency of rs12566888 or rs12041331 in PEAR1 were observed between KD and healthy controls. However, regardless of the statistical combination of rs12566888 genotype, the rs12041331 recessive inheritance model was associated with an increased risk of CAA after Bonferroni correction (for rs12041331, AA vs. GG/GA: adjusted OR = 2.37, 95% CI = 1.41-4.01, P = 0.009; combination of two recessive genotypes vs. combination of 0-1 recessive genotypes: adjusted OR = 2.39, 95% CI = 1.42-4.04, P = 0.009). This study suggests for the first time that PEAR1 polymorphisms did not indicate susceptibility for KD occurrence but the rs12041331 polymorphism was associated with increased risk of CAA formation in KD, and the functions of the gene warrant further research. Copyright © 2018 John Wiley & Sons Ltd/University College London

Pilania, R. K., et al. (2019). "An Update on Treatment of Kawasaki Disease." Current Treatment Options in Rheumatology **5**(1): 36-55.
Purpose of review: The primary aim of therapy of Kawasaki disease (KD) is to halt inflammation and prevent development of coronary artery aneurysms (CAAs). In this review, we provide an update on recent advances and current recommendations on management of KD. Recent findings: High-dose aspirin has not been found to have significant effect on development of CAAs in KD. Role of corticosteroids has been suggested in patients with high-risk disease and a recent Cochrane review has recommended addition of oral corticosteroids to all children with KD. Intensified initial therapy in the form of IVIg plus infliximab may be considered for patients with KD and CAAs. Recent literature has also suggested the role of infliximab, ant-IL-1 antagonist (anakinra), and cyclosporine in IVIg-resistant KD. Patients with giant CAAs or multiple complex medium-sized aneurysms in a single coronary artery need anticoagulation and aspirin. Summary: Intravenous immunoglobulin (2 g/kg) is the standard of care in all patients with KD. However, a proportion of patients may need additional therapy with corticosteroids or infliximab. Infliximab is also the drug of choice for IVIg-resistant KD. Copyright © 2019, Springer Nature Switzerland AG.

Pilania, R. K. and S. Singh (2019). "Rheumatology Panel in Pediatric Practice." Indian Pediatrics **56**(5): 407-414.
Common rheumatological disorders encountered in pediatric practice are juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, Kawasaki disease, Henoch-Schonlein purpura,

systemic lupus erythematosus, chronic uveitis and juvenile dermatomyositis. Diagnosis of these disorders requires a critical appraisal of the clinical history, physical examination and relevant investigations. Laboratory tests are helpful for screening purposes as also for confirmation of diagnosis and monitoring of disease activity. These tests should, however, only be ordered after due deliberation and in the context of clinical findings in a given patient. © 2019, Indian Academy of Pediatrics.

Portman, M. A., et al. (2019). "Etanercept with IVIG for acute Kawasaki disease: A randomized controlled trial." Pediatrics **143**(6).
OBJECTIVES: Patients with Kawasaki disease can develop life-altering coronary arterial abnormalities, particularly in those resistant to intravenous immunoglobulin (IVIg) therapy. We tested the tumor necrosis factor a receptor antagonist etanercept for reducing both IVIg resistance and coronary artery (CA) disease progression. METHODS: In a double-blind multicenter trial, patients with Kawasaki disease received either etanercept (0.8 mg/kg; n = 100) or placebo (n = 101) subcutaneously starting immediately after IVIg infusion. IVIg resistance was the primary outcome with prespecified subgroup analyses according to age, sex, and race. Secondary outcomes included echocardiographic CA measures within subgroups defined by coronary dilation (z score .2.5) at baseline. We used generalized estimating equations to analyze z score change and a prespecified algorithm for change in absolute diameters. RESULTS: IVIg resistance occurred in 22% (placebo) and 13% (etanercept) of patients (P = .10). Etanercept reduced IVIg resistance in patients .1 year of age (P = .03). In the entire population, 46 (23%) had a coronary z score .2.5 at baseline. Etanercept reduced coronary z score change in those with and without baseline dilation (P = .04 and P = .001); no improvement occurred in the analogous placebo groups. Etanercept (n = 22) reduced dilation progression compared with placebo (n = 24) by algorithm in those with baseline dilation (P = .03). No difference in the safety profile occurred between etanercept and placebo. CONCLUSIONS: Etanercept showed no significant benefit in IVIg resistance in the entire population. However, preplanned analyses showed benefit in patients .1 year. Importantly, etanercept appeared to ameliorate CA dilation, particularly in patients with baseline abnormalities. Copyright © 2019 by the American Academy of Pediatrics

Qiang, R., et al. (2019). "The differential equation model of pathogenesis of Kawasaki disease with theoretical analysis." Mathematical Biosciences and Engineering **16**(5): 3488-3511.
Fever is a extremely common symptom in infants and young children. Due to the low resistance of infants and young, long-term fever may cause damage to the child's body. Clinically, some children with long-term fever was eventually diagnosed with Kawasaki disease (KD). KD, an autoimmune disease, is a systemic vasculitis mainly affecting children younger than 5 years old. Due to the delayed therapy and diagnosis, coronary artery abnormalities (CAAs) develop in children with KD, and leads to a high risk of acquired heart disease. Later, patients may have myocardial infarction or even die a sudden death. Unfortunately, at present, the pathogenesis of KD remains unknown and KD lacks of specific and sensitive biomarkers, thus bringing difficulties to diagnosis and therapy. Therefore it is a highly focused topic to research on the mechanism of KD. Some scholars believe that KD is caused by the cross reaction of external infection and organ tissue composition, hereby triggering disorder of the immune system and producing a variety of cytokines. On the basis of considering the cytokines such as vascular endothelial cells, inflammatory factors, adhesion factors and chemokines, endothelial cell growth factors, put forward a kind of dynamic model of pathogenesis of KD by the theory of ordinary differential equation. It is found that the dynamic model can show complex dynamic behavior, such as the forward and backward bifurcation of the equilibria. This article reveals the possible complexity of KD infection, and provides a theoretical references for the research of pathogenic mechanism and clinical treatment of KD. © 2019 the Author(s).

Qiu, H., et al. (2019). "Association between left ventricular ejection fraction and Kawasaki disease shock

syndrome." Cardiology in the Young **29**(2): 178-184.
Objective: This study was performed to explore the clinical features of Kawasaki disease shock syndrome and analyse the association between the left ventricular ejection fraction and Kawasaki disease shock syndrome. Methods: We retrospectively reviewed the medical records of all consecutive inpatients with Kawasaki disease at Wenzhou Medical University Second Affiliated Hospital and Yuying Children's Hospital in Wenzhou, China from January 2009 to December 2016. We compared the clinical characteristics, laboratory data, and left ventricular ejection fraction between patients with and without Kawasaki disease shock syndrome and analysed the effect of the left ventricular ejection fraction on Kawasaki disease shock syndrome under different clinical conditions of Kawasaki disease. Results: In total, 1147 patients were diagnosed with Kawasaki disease. Of these 1147 patients, 17 were diagnosed with Kawasaki disease shock syndrome; 68 patients admitted to the hospital at the same time, ±2 weeks, with Kawasaki disease but without Kawasaki disease shock syndrome served as the control group. Compared with the control group, the Kawasaki disease shock syndrome group had a significantly higher incidence of coronary artery lesions, cardiac troponin I concentration, N-terminal prohormone of brain natriuretic peptide concentration, neutrophil count and ratio, alanine aminotransferase concentration, aspartate aminotransferase concentration, and C-reactive protein concentration and a significantly lower platelet count, serum albumin concentration, and left ventricular ejection fraction. A low left ventricular ejection fraction was associated with Kawasaki disease shock syndrome under different conditions of Kawasaki disease. Conclusion: Among patients with Kawasaki disease, cardiac injury is more likely in those with Kawasaki disease shock syndrome than without, and a low left ventricular ejection fraction may be associated with the development of Kawasaki disease shock syndrome. © 2018 Cambridge University Press.

Rabarison, J. H., et al. (2019). "Burden and epidemiology of influenza- and respiratory syncytial virus-associated severe acute respiratory illness hospitalization in Madagascar, 2011-2016." Influenza and other Respiratory Viruses **13**(2): 138-147.
Background: Influenza and respiratory syncytial virus (RSV) infections are responsible for substantial global morbidity and mortality in young children and elderly individuals. Estimates of the burden of influenza- and RSV-associated hospitalization are limited in Africa. Method(s): We conducted hospital-based surveillance for laboratory-confirmed influenza- and RSV-associated severe acute respiratory illness (SARI) among patients of any age at one hospital and a retrospective review of SARI hospitalizations in five hospitals situated in Antananarivo during 2011-2016. We estimated age-specific rates (per 100 000 population) of influenza- and RSV-associated SARI hospitalizations for the Antananarivo region and then extrapolated these rates to the national level. Result(s): Overall, the mean annual national number of influenza-associated SARI hospitalizations for all age groups was 6609 (95% CI: 5381-7835-rate: 30.0; 95% CI: 24.4-35.6), 4468 (95% CI: 3796-5102-rate: 127.6; 95% CI: 108.4-145.7), 2141 (95% CI: 1585-2734-rate: 11.6; 95% CI: 8.6-14.8), and 339 (95% CI: 224-459-rate: 50.0; 95% CI: 36.3-74.4) among individuals aged <5, >=5, and >=65 years, respectively. For these same age groups, the mean annual number of RSV-associated SARI hospitalizations was 11 768 (95% CI: 10 553-12 997-rate: 53.4; 95% CI: 47.9-59.0), 11 299 (95% CI: 10 350-12 214-rate: 322.7; 95% CI: 295.6-348.8), 469 (95% CI: 203-783-rate: 2.5;95% CI: 1.1-4.2), and 36 (95% CI: 0-84-rate: 5.8; 0.0-13.5), respectively. Conclusion(s): The burden of influenza- and RSV-associated SARI hospitalization was high among children aged <5 years. These first estimates for Madagascar will enable government to make informed evidence-based decisions when allocating scarce resources and planning intervention strategies to limit the impact and spread of these viruses. Copyright © 2018 The Authors. Influenza and Other Respiratory Viruses Published by John Wiley & Sons Ltd.

Rabinowitz, E. J., et al. (2019). "Examining the Utility of Coronary Artery Lack of Tapering and Perivascular Brightness in Incomplete Kawasaki Disease." Pediatric Cardiology **40**(1): 147-153.
Background: In 2017, the AHA published revised guidelines for the diagnosis of Kawasaki disease

(KD). In the absence of compelling data supporting or refuting the utility of lack of tapering (LT) and perivascular brightness (PB), expert panel consensus removed LT and PB from consideration. We hypothesize that LT and PB are unreliable, subjective findings, non-specific to KD, which can be seen in systemic febrile illnesses without KD and in normal controls. Methods: We performed a single-center retrospective study from 1/2008 to 12/2016. De-identified coronary artery (CA) echocardiographic clips from patients 0–10 years old were interpreted blindly by six pediatric cardiologists. Subjects were grouped as follows: (1) healthy: afebrile with benign murmur, (2) KD: IVIG treatment, 4–5 clinical criteria at presentation, (3) incomplete KD (iKD): IVIG, 1–3 clinical criteria, (4) Febrile: ≥3 days of fever, no IVIG, KD not suspected. The presence or absence of LT and PB was recorded. Inter-rater and intra-rater reliabilities were analyzed using intra-class correlation coefficient, Fleiss' Kappa and Cohen's Kappa coefficients. Results: We interpreted 117 echocardiograms from healthy (27), KD (30), iKD (32), and febrile (28) subjects. Analysis showed moderate agreement in CA z score measurements. LT and PB were observed by most readers in control groups. LT exhibited fair inter-reader agreement (reliability coefficient 0.36) and PB slight inter-reader agreement (reliability coefficient 0.13). Intra-rater reliability was inconsistent for both parameters. Conclusions: LT and PB are subjective, poorly reproducible features that can be seen in febrile patients without KD and in healthy children. © 2018, Springer Science+Business Media, LLC, part of Springer Nature.

Rahman, M. Z., et al. (2019). "Respiratory and febrile illnesses in children due to human parainfluenza virus type 4 (HPIV4) and human coronavirus (HCOV) OC43 in Dhaka, Bangladesh." American Journal of Tropical Medicine and Hygiene **101 (5 Supplement)**: 260.
Human parainfluenza virus (HPIV) and human coronavirus (HCoV) are globally recognized viral pathogens causing more than 15% of the overall respiratory tract infections. In Bangladesh, respiratory viral studies were mostly linked to the epidemiological and clinical impact of Influenza, RSV, HPIV-1, 2, 3, hMPV and adenovirus. However, information regarding HPIV4 or HCoV infections, its specific clinical syndromes, age distribution, seasonal patterns and the extent of genetic variation among the strains are limited. A total of 200 samples (20%) were randomly selected out of 1022 archived nasopharyngeal wash (NPW) specimens that were tested negative for a panel of viruses (Influenza, RSV, HPIV-1, 2, 3, hMPV, adenovirus). These specimens were collected under an urban rural surveillance for pneumonia, diarrhea and febrile illness among children under five years old in between 2014 and 2015. In order to detect novel paramyxoviruses, semi-nested RT-PCR was performed to amplify large polymerase (L) gene fragment and for detection of HCoV, samples were also subjected to RdRp (RNA Dependant RNA Polymease) gene nested RT-PCR followed by Sanger sequencing. Upon PCR based direct nucleotide sequencing, 10 samples were positive for either HPIV4 (n=4) or HCoV (n=6). The HPIV4 strains were phylogenetically belonged to HPIV4a (n=3) and HPIV4b (n=1) having sequence similarity of >98% with the other globally circulating strains. The sequence analysis of the RdRp gene fragment revealed that all the 6 samples that were positive for HCoV belonged to HCoV-OC43 with the sequences similarity of >99%. This study results may help to identify the contribution of HPIV4 and HCoV, causing respiratory and febrile illness in children and their circulating pattern among Bangladeshi children.

Rajak, K., et al. (2019). "Prevalence of kawasaki disease in a tertiary care hospital: A descriptive cross-sectional study." Journal of the Nepal Medical Association **57**(220): 416-419.
Introduction: Kawasaki disease is an acute vasculitis of unknown etiology. The epidemiological data available for Nepal remains insufficient. In Nepal, Kawasaki disease has only been reported in cases of brief reports, leaving the true disease burden unknown. Many cases go undiagnosed and untreated due to a lack of knowledge regarding this entity. The objective of this study was to find the prevalence of Kawasaki disease in a tertiary care hospital. Methods: This descriptive cross-sectional study was carried out in a tertiary care hospital of Nepal from 2013 to 2018 after taking ethical approval from the Institutional Review Committee. The sample size was calculated and the consecutive sampling method was done. Data collection and entry was done in Microsoft

Excel, point estimate at 99% Confidence Interval was calculated along with frequency and proportion for binary data. Results: The overall prevalence of Kawasaki disease was found to be 0.10% at 95% Confidence Interval (0.07-0.13%) among 11,416 patients under the age of 5 years admitted in pediatrics ward. There were 4 (33.33%) cases of complete Kawasaki and 8 (66.67%) cases of incomplete Kawasaki. There were 9 (75%) males and 3 (25%) females and the male to female ratio was 3:1. There was a male preponderance. The age at diagnosis ranged between 4 and 60 months. The median age at diagnosis was 10.5 months. The most common presentation was fever, conjunctivitis, rash, and oral changes. Conclusions: Prevalence of Kawasaki disease was found to be lesser compared to other studies done in other countries. Knowledge of Kawasaki disease among Nepalese pediatricians should be enhanced to guarantee the appropriate diagnosis and treatment of this disease. © The Author(s) 2018.

Ramphul, K., et al. (2019). "Kawasaki disease among children in the United States." Reumatologia **57**(4): 253-254.
Kawasaki disease (KD) is a medium-sized-vessel vasculitis that affects mostly children. The 2016 Healthcare Cost and Utilization Project Kid's Inpatient Database (HCUP KID) was used in weighted form to investigate differences in gender, month of year, race, region, total charges, and household income in the United States. 5503 weighted cases were found. It was more common in males (3345, 60.8%) than females (2158, 39.2%) ($p < 0.01$). Most admitted KD patients were white (1913, 38.1%). A higher prevalence of Kawasaki disease was seen among patients of Asian or Pacific Islander background (0.2%). The southern regions of the United States reported the highest rate of admission with 2036 patients (37%). The median age on admission was 2 years (interquartile range [IQR] of 1-5, $p < 0.01$) and the median charge was $32,170 (IQR: $20,825-$50,502.05) ($p < 0.01$). Most admissions of Kawasaki disease were recorded in winter with a peak in March (623, 11.3%) ($p < 0.01$).

Rhim, J. W., et al. (2019). "A presumed etiology of Kawasaki disease based on epidemiological comparison with infectious or immune-mediated diseases." Frontiers in Pediatrics **7**(MAY).
Background: Kawasaki disease (KD) may be associated with infection of unknown pathogen(s). For predicting of the etiology of KD, we evaluated epidemiological characteristics in KD, common infectious diseases and immune-mediated diseases in childhood. Methods: We respectively, reviewed the data of patients with KD, influenza, aseptic meningitis, exanthem subitum (ES), Mycoplasma pneumoniae (MP) pneumonia, acute pyelonephritis (APN), Henoch-Schönlein purpura (HSP), acute poststreptococcal glomerulonephritis (APSGN), and childhood asthma. We compared and interpreted epidemiological data across the groups. Results: In age distribution, KD, APN, and ES showed a similar pattern in that majority of patients were infants or young children, and other diseases showed a relatively even age-distribution which had a peak age, mainly 5-6 years, with bell-shape patterns. In annual-case pattern, there were epidemic years in aseptic meningitis and MP pneumonia, and the fluctuated annual cases were seen in other diseases. The trends of decreasing cases were seen in APSGN, HSP, and childhood asthma in recent years. In seasonal frequency, influenza or aseptic meningitis occurred in mainly winter or summer season, respectively. HSP and APSGN cases had less in summer, and KD, APN, and ES showed relatively even occurrence throughout a year without significant seasonal variations. Conclusions: Our results suggest that KD agents may be associated with normal flora that are influenced by environmental changes, since pathogens of APN and ES could be regarded as normal flora that originate from the host itself or ubiquitously existing human reservoirs.

Rivas-Larrauri, F., et al. (2019). "Kawasaki disease and immunodeficiencies in children: case reports and literature review." Rheumatology International **39**(10): 1829-1838.
Kawasaki disease (KD) has features that appear supporting an infectious cause with a secondary deranged inflammatory/autoimmune response. The association of KD in adults with human immunodeficiency virus infection and the presence of KD in patients with immunodeficiency disorders support the infectious theory. We present four KD patients associated with immunodeficiencies: one with X-linked agammaglobulinemia, one with HIV infection, and two with leukemia; one of these patients also had Down syndrome. We did a literature search to find out all reported cases of immunodeficiency with KD in children. In immunodeficiency disorders, the inability of the immune system to eradicate the pathogens coupled to an exaggerated inflammatory response, especially in chronic granulomatous disease, may lead to the development of KD. The study of patients with immunodeficiencies complicated with KD may shed light into the etiopathogenesis of the disease. Copyright © 2019, Springer-Verlag GmbH Germany, part of Springer Nature.

Rodríguez-González, M., et al. (2019). "Usefulness of age-adjusted n-terminal prohormone of brain natriuretic peptide level as a diagnostic marker for incomplete kawasaki disease in children." Emergencias **31**(2): 111-114.
Objectives. The main objective was to assess the diagnostic usefulness of age-adjusted level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as a diagnostic marker in children suspected of having incomplete Kawasaki disease (IKD). The secondary aim was to compare the diagnostic yield of NT-proBNP level with the yield of other markers currently recommended by the American Heart Association (AHA). Methods. Descriptive cross-sectional study of a case series of patients under the age of 14 years admitted with clinical suspicion of IKD between 2013 and 2017. We analyzed NT-proBNP level adjusted for age. Demographic, clinical, echocardiographic, analytic, and microbiologic findings were gathered from computerized charts. Two independent evaluators made the diagnosis of IKD according to AHA criteria. Results. We included 70 cases, and 19 (27%) were diagnosed with IKD. Patients with IKD had higher NT-proBNP levels than patients with other febrile diseases, and the proportion of cases of elevated age-adjusted NT-proBNP level was also higher in the IKD group (84% vs 4%; P<.001). The diagnostic yield of age-adjusted NT-proBNP for IKD was good (area under the receiver operating characteristic curve, 0.90; 95% CI, 0.80–0.99) and significantly higher than the yields for C-reactive protein, erythrocyte sedimentation rate, albumin, and sterile pyuria (P<.001, all comparisons). Conclusions. NT-proBNP level may prove to be a valid diagnostic marker for IKD, possibly offering a higher diagnostic yield than the analyses currently recommended for children suspected of having IKD. © 2019, Saned. All rights reserved.

Rodriguez-Gonzalez, M., et al. (2019). "N-terminal probrain natriuretic peptide as biomarker for diagnosis of Kawasaki disease." Biomarkers in Medicine **13**(4): 307-323.
Kawasaki disease (KD) is a systemic childhood vasculitis with peculiar tropism for the heart. Coronary artery aneurysms are the primary cause of morbidity and mortality in these patients. The timely administration of gammaglobulin decreases the risk for development of coronary artery aneurysms, highlighting the importance of early KD recognition. However, the most significant dilemma in the management of KD is the diagnosis itself. In this article, we review the recent literature focusing on the diagnostic utility of N-terminal probrain natriuretic peptide as a biomarker for diagnosis of KD. The main conclusion is that N-terminal probrain natriuretic peptide is an useful biomarker for KD diagnostic that represents a valuable addition to the current diagnostic workup of patients with suspected KD, increasing the diagnostic accuracy.

Rouault, M., et al. (2019). "Otorhinolaryngological manifestations and delayed diagnosis in Kawasaki disease." International Journal of Pediatric Otorhinolaryngology **121**: 137-142.
Objectives: Kawasaki disease (KD) is a febrile multisystemic vasculitis of unknown etiology whose

coronary prognosis is improved by early diagnosis and management. The objective of this study was to describe ENT manifestations encountered and to look for a delayed diagnosis associated with these manifestations. Methods: A retrospective descriptive single-center study was conducted in Lyon between January 2009 and December 2017. All children treated for Kawasaki disease were included in the study. Clinical, biological and cardiac ultrasound data were collected. According to the diagnosis made at the first medical visit, children were classified into two groups: diagnosis of ENT spectrum or non-ENT diagnosis. The diagnostic times were compared by a Student test. Results: 142 patients were included: 64 in the ENT diagnostic group, 78 in the non-ENT diagnostic group. When the initial diagnosis was of ENT spectrum, the diagnostic time of KD was significantly longer: 8.51 days vs 5.77 days - ($p < 0.01$). The total duration of fever was also longer - 10.92 vs 8.32 days – ($p = 0.013$) - and the frequency of antibiotics intake more important - 92.2% vs 46.2% - ($p < 0.01$). Four children underwent surgery in the ENT diagnostic group: two retro-pharyngeal abscesses, one paracentesis and one cervicectomy. Conclusions: ENT manifestations are frequently at the forefront of KD and constitute a misleading clinical picture responsible for delayed diagnosis and potentially inappropriate medico-surgical management. It is necessary to provide more education to practitioners for earlier recognition of Kawasaki disease. © 2019 Elsevier B.V.

Rowley, A., et al. (2019). "A hepacivirus-like protein is targeted by the antibody response to kawasaki disease (KD)." Open Forum Infectious Diseases **6 (Supplement 2)**: S48.
Background. Clinical and epidemiologic data support a viral cause of KD, but the etiology has eluded 50 years of study. We previously identified virus-like intracytoplasmic inclusion bodies (ICI) in ciliated bronchial epithelium of KD children but not infant controls, but the antigens within the ICI were unknown. At 1-2 weeks following infection, 75% of peripheral blood plasmablasts (PB) specifically target the infectious agent. We cloned the PB response to KD to identify KD-specific antibodies and their target antigens. Methods. We isolated single PB from children with KD 1-3 weeks after fever onset by flow cytometry, and amplified immunoglobulin VDJ and VJ genes from each PB by RT-PCR. We sequenced the products and made monoclonal antibodies (Mab) from clonally expanded PB in individual patients. Mab were tested for binding to KD tissues and to a viral peptide array containing 29,939 peptides from known B cell epitopes of animal viruses (www.iedb.org). Results. We sequenced 1156 PB from 11 KD patients, and identified 44 clonally expanded sets of PB. We prepared 61 Mab from clonally expanded and highly mutated IgA PB, and found that 33/61 bind to KD ICI, 10 strongly and 23 weakly. Of 10 Mab that strongly bind, 2 were VH3-33 (single patient), 2 VH3-23 (single patient), 1 VH3- 15, 1 VH3-74, 3 VH1-46 (2 patients), and 1 VH4-59. These Mab CDR3s varied from 11 to 20 aacids, with 4-28 aacid mutations. Mab KD4-2H4 recognized multiple similar peptides from nonstructural protein 4A of hepacivirus C; pt KD4 sera was negative for hepatitis C by fourth-generation ELISA. Amino acid substitution analysis yielded an optimized peptide, and 6 KD Mab recognized this peptide by ELISA. These 6 Mab derived from 3 KD patients, all of whom had coronary aneurysms, and were VH3-74 (n = 1), VH3-33 (n = 2, single patient), VH1-45 (n = 1), and VH3-72 (n = 2, single patient). Strong binding of KD Mab KD4-2H4 and KD6-2B2 to ICI was totally blocked by pre-incubation with optimized peptide. KD but not control sera react with optimized peptide expressed as a glutathione S-transferase fusion protein by western blot. Conclusion. Children with KD make antibodies to a hepacivirus-like protein, and KD ICI contain this protein. These results strongly suggest that a previously unidentified hepacivirus with a respiratory portal of entry is etiologically related to KD.

Rugwizangoga, B., et al. (2019). "IFNL4 Genotypes Predict Clearance of RNA Viruses in Rwandan Children With Upper Respiratory Tract Infections." Frontiers in Cellular and Infection Microbiology **9 (no pagination)**(340).
Polymorphisms in the interferon lambda gene locus (IFNL) such as the IFNL4 genetic variants rs12979860 and rs368234815 are predictive of resolution of hepatitis C virus infection, but information about the impact of these variants in other infections is scarce. This study aimed at

determining the potential impact of IFNL4 variation for the clearance of respiratory tract pathogens in Rwandan children (<=5 years old, n = 480) seeking medical care for acute respiratory infections. Nasopharyngeal swabs were retrieved from all children at the first hospital referral and from 161 children at follow-up visits 2 weeks later. The swabs were analyzed for pathogens by real-time PCR and for host cell IFNL4 genotype at rs12979860 and rs368234815. Approximately 1/3 of the children were homozygous for the rs12979860 T allele and the rs368234815 DELTAG allele, which are overrepresented in subjects of African descent. These IFNL4 variants were significantly associated with reduced clearance of RNA viruses. Our results suggest that IFNL4 genotypes that are common among subjects of African descent may determine inefficacious clearance of RNA viruses from the respiratory tract. © Copyright © 2019 Rugwizangoga, Andersson, Kabayiza, Nilsson, Armannsdottir, Aurelius, Nilsson, Hellstrand, Lindh and Martner.

Santy, C., et al. (2019). "Coronary artery aneurysm risk factors for Kawasaki disease patients in North of France." Archives of Cardiovascular Diseases Supplements **11 (4)**: e382.
Objectives: Kawasaki Disease (KD) is a child vasculitis. The prognosis is associated with a higher risk of coronary artery aneurysm (CAA). Currently the main goal of treatment consists of preventing CAA. At first the treatment consists on immunoglobulin (IVIG). The last American 2016 guidelines recommends echographical coronary diameter express as z-score. The epidemiology of KD is not well known in France. The aim of this study was to describe the population of the children in a region of North of France and to look for risk factors of CAA. Method(s): We included patients with KD who were admitted in hospital centers of the region from 2006 to 2016. We reviewed retrospectively the medical, biological and echographical records and their monitoring data. We compared patients in group with and without CAA at 4 weeks from the diagnosis. Result(s): We included 240 children from 6 hospital centers. The median age was 28 months (14-50), 20% were less than 1 year old. The male-to-female ratio was 1.8. Diagnosis was done after 7 days of fever at mean. We found 87 children with initial z-score >= 2DS and 28 with CAA. Patients were treated with IVIG and 35 get more than one cure, 95% get aspirin for anti-inflammatory then 87% as antiplatelet therapy. Five received corticosteroids, 1 an anti-TNFalpha and 1 an anti-IL1. Risk scores of CAA from Kobayashi, Egami and Sano present low sensitivity and low specificity. Several risk factors were associated with CAA: age < 6 months (OR = 4, P = 0.05), IVIG resistance (OR = 3.6, P = 0.007), z-score >= 2DS at diagnosis (OR = 6.7, P = 0.09 10⁻⁴) and platelet count (Pq) >= 444 G/L (P = 0.04). Only the initial z-score >= 2 DS (P = 0.02) and Pq >= 444 G/l (P = 0.04) were significant in multivariate analysis. Conclusion(s): The Japanese risk scores were not significant in the French population, as previously shown in North American or English populations. The initial z-score >= 2 DS is a good risk factor of CAA so is the Pq >= 444 G/l after the day 7th of fever in our population. Copyright © 2019

Seetharam, S. and A. Glass (2019). "Respiratory infections and their effect on the paediatric lung microbiome." Current Allergy and Clinical Immunology **32**(2): 82-86.
Respiratory tract infections, especially viral infections in children are a major cause of morbidity and mortality in many developing countries. The effect of infection and its potential sequelae are a consequence of the interaction of the lung microbiome, the pathogen and the immune system. The epidemiology of viral infections and Bordetella pertussis observed over a two-year period in a private-sector laboratory is presented. We then describe the paediatric respiratory microbiome on a basic level and briefly describe the effect of some of these pathogens on the developing paediatric microbiota. Copyright © 2019, Allergy Society of South Africa. All right reserved.

Serhiyenka, K. (2019). "The role of PCR in diagnostics of acute respiratory viral infections in children." European Respiratory Journal. Conference: 29th International Congress of the European Respiratory Society, ERS. Spain. **54**(Supplement 63).
Acute respiratory virus infections (ARVI) are most frequent pathology in the structure of

morbidity and mortality among infectious diseases worldwide. Material(s) and Method(s): Materials for laboratory study served as nasopharyngeal swabs in the first 2 days of illness onset in patients under the age of 18 years. Swabs were detected for the presence of genetic material of influenza viruses A and B, parainfluenza, respiratory syncytial virus (RSV), adenovirus, rhinovirus, metapneumovirus, bokavirus and coronavirus by PCR detection in real time were delivered at the laboratory of influenza and influenzalike illness. Results and Discussion: Among 607 surveyed patients the frequency of detection of RNA/DNA respiratory viruses in different years ranged from 55% to 72% (average 65%), which confirms the viral etiology of ORI in most cases. The analysis of the results showed that 88% of cases respiratory viruses identified monoinfection and in 12% of cases observed simultaneous infection with two or more agents. In the structure of the pathogens of ARVI as the main etiological agents of ARVI were prevalent parainfluenza (24%), rhinoviruses (16%) and RSV (16%). The frequency of detection of influenza A viruses and bocaviruses amounted to 11% and 4% respectively. Metapneumo-, adeno-, and influenza B viruses were identified with the same frequency (5%), coronavirus was isolated in 2% of cases. The analysis of the study by PCR nasopharyngeal smears taken from patients with symptoms of ARVI leads to the following CONCLUSION(S): O in most cases (65%) acute respiratory infections are viral O application of PCR method to detect a wide range of respiratory viruses and co-infection several viruses.

Shah, H., et al. (2019). "Trends of Coronary Artery Disease in Kawasaki Disease in Patients Younger Than 18 Years Old from the Nationwide Inpatient Sample: 2005-2014." Journal of the American College of Cardiology **73 (9 Supplement 1)**: 1778.
Background: Kawasaki disease (KD) is the one of the most common vasculitis of childhood and is the leading cause of Coronary Artery Disease (CAD) in the younger population. Our aim is to study the trends of CAD in pediatric KD patients. Method(s): We studied Nationwide Inpatient Sample (NIS) database from year 2005 to 2014 using ICD 9 diagnosis codes and those with the diagnosis of KD Disease were included. Trends of CAD in KD Patients were identified using Cochran-armitage trend test. Descriptive statistics and outcome measurements were calculated using univariate analysis. Result(s): Out of total 50263 hospitalizations of patients with KD from 2005-2014, 1920 (3.82%) hospitalizations were due to CAD related to KD: 1674 (87.2%) had predominantly coronary artery aneurysms and 246 (12.8) had coronary artery dissection. Temporal trend of CAD remained stable over the study period. Male gender (4.3% vs. 3.1%; $p < 0.001$), patients with age>10 Years (13% vs 3.3%; $p < 0.001$) and Hispanics (4.6 % vs 3.3%; $p = 0.01$) were more likely to develop CAD. Patient who developed CAD, 0.14% and 0.06% developed cardiogenic shock and cardiac arrest respectively and 0.03% underwent PCI, 0.11% received CABG and 0.05% died during the hospitalization. Conclusion(s): Our study delineates epidemiology of KD at national level after introduction of intravenous immunoglobulin infusion. Long-term complications of KD such as Giant coronary aneurysms, coronary stenosis and occlusion complicated by myocardial infarction, ischemic heart disease or arrhythmic death still affects significant proportion of subjects with KD. This study shows that there is increased preponderance of coronary artery disease in younger patients with KD. Standard follow up protocols and imaging procedures must be established for these vulnerable children to improve outcomes.

Sharma, K., et al. (2019). "Guillain-Barre syndrome with unilateral peripheral facial and bulbar palsy in a child: A case report." SAGE Open Medical Case Reports **7**(no pagination).
Guillain-Barre syndrome is characterized by progressive motor weakness, sensory changes, dysautonomia, and areflexia. Cranial nerve palsies are frequent in Guillain-Barre syndrome. Among cranial nerve palsies in Guillain-Barre syndrome, facial nerve palsy is the most common affecting around half of the cases. Facial palsy in Guillain-Barre syndrome is usually bilateral. We describe a pediatric Guillain-Barre syndrome variant presenting with unilateral peripheral facial palsy and dysphagia. A 5-year-old boy had progressive lower extremity weakness and pain 3 days prior to onset of unilateral peripheral facial palsy. On presentation, diagnosis of

Guillain-Barre syndrome was supported by areflexia and albuminocytologic dissociation. His condition deteriorated with a decline in his respiratory effort and inability to handle secretions. He was given non-invasive ventilation to prevent worsening of his acute respiratory failure. Brain and spine magnetic resonance imaging scans showed enhancement of the left bulbar nerve complex and anterior and posterior cervical nerve roots with gadolinium. Treatment with intravenous immunoglobulin led to an uneventful clinical course with partial recovery within 2 weeks. In summary, Guillain-Barre syndrome should be considered as a possible cause of unilateral peripheral facial palsy. Guillain-Barre syndrome patients with facial nerve and bulbar palsy require close monitoring as they are at risk of developing acute respiratory failure. Early intervention with intravenous immunoglobulin may benefit these patients. Magnetic resonance imaging findings may lend support to early intervention. Copyright © The Author(s) 2019.

Sharma, S. D., et al. (2019). "Recurrence of coronary artery lesions after complete regression in a peculiar case of Kawasaki disease." Cardiology in the Young **29**(5): 714-716.
Kawasaki disease is a leading cause of acquired heart disease in children with serious repercussions of coronary artery lesions. Recurrences of the disease are relatively rare in clinical practice. We present a case of recurrent Kawasaki disease, wherein the coronary artery lesions which were documented during the initial illness demonstrated complete regression over the following months, but reappeared with recurrence of the disease. © Cambridge University Press 2019.

Song, M. S. (2019). "Predictors and management of intravenous immunoglobulin-resistant Kawasaki disease." Korean Journal of Pediatrics **62**(4): 119-123.
Kawasaki disease (KD) is a systemic vasculitis that mainly affects younger children. Intravenous immunoglobulin (IVIG) resistant cases are at increasing risk for coronary artery complications. The strategy on prediction of potential nonresponders and treatment of IVIG-resistant patients is now controversial. In this review the definition and predictors of IVIG-resistant KD and current evidence to guide management are discussed. Copyright © 2019 by The Korean Pediatric Society.

Soudani, N., et al. (2019). "Prevalence and characteristics of acute respiratory virus infections in pediatric cancer patients." Journal of Medical Virology **91**(7): 1191-1201.
Background: Patients with pediatric cancer have a higher risk of morbidity and mortality because of respiratory viral infections than other patient populations. Objective(s): To investigate the causative viruses of respiratory infections and their burden among patients with pediatric cancer in Lebanon. Study design: Nasopharyngeal swabs along with clinical and demographic data were collected from patients with pediatric cancer presenting febrile episodes with upper respiratory tract symptoms. Total nucleic acid was extracted from specimens followed by the real-time PCR analysis targeting 14 respiratory viruses to estimate the frequency of infections. Result(s): We obtained 89 nasopharyngeal swabs from patients with pediatric cancer (mean age, 5.8 +/- 4.2 years). Real-time PCR confirmed viral infection in 77 swabs (86.5%). Among these, 151 respiratory viruses were detected. Several viruses cocirculated within the same period; respiratory syncytial virus (RSV) being the most common (45.45%), followed by parainfluenza virus (PIV; 26%), influenza type B (26%), human metapneumovirus (24.6%), and human coronavirus (HCoV; 24.6%). Coinfections were detected in 55% of the subjects, and most of them involved RSV with one or more other viruses. A strong correlation was found between PIV, Flu (influenza of any type), RSV, and HCoV with the incidence of coinfections. RSV was associated with lower respiratory tract infections, nasal congestion, bronchitis, and bacteremia. HCoV was associated with bronchiolitis; rhinovirus was associated with hospital admission. Conclusion(s): Patients with pediatric cancer have a high burden of respiratory viral infections and a high incidence of coinfections. Molecular diagnostics can improve management of febrile episodes and reduce antibiotic use. Copyright © 2019 Wiley Periodicals, Inc.

Sugahara-Tobinai, A., et al. (2019). "Augmented ILT3/LILRB4 Expression of Peripheral Blood Antibody Secreting Cells in the Acute Phase of Kawasaki Disease." Pediatric Infectious Disease Journal **38**(4): 431-438.
Background: Kawasaki disease (KD) is an acute, systemic vasculitis syndrome that occurs in children. The clinical symptoms and epidemiologic features of KD strongly suggest that KD is triggered by unidentified infectious agents in genetically predisposed patients. In addition, a number of studies have described the role of B cells in the development of KD. To obtain a mechanistic insight into the humoral immune response of B-lineage cells in KD patients, we examined peripheral blood antibody secreting cells (ASCs) and inhibitory immunoreceptors, immunoglobulin-like transcript (ILT)/leukocyte immunoglobulin-like receptor (LILR), on each B cell subpopulation. Method(s): Eighteen Japanese KD patients and thirteen healthy control subjects were recruited for this study. Their peripheral blood mononuclear cells were examined by flow cytometry for the number of CD19⁺ B cells, the size of each B cell subset and the expression of the inhibitory isoforms of ILT/LILR on the B cell subset. Result(s): The frequency of CD19⁺CD27^{high} ASCs was significantly increased in the acute phase of KD and reduced after high-dose intravenous immunoglobulin (IVIG) treatment. Interestingly, while ILT2/LILRB1 expression was ubiquitously observed on every B cell/ASCs subset and the level was not significantly different after IVIG, ILT3/LILRB4 (B4) was uniquely expressed on only ASCs, and its expression was significantly decreased after IVIG. Conclusion(s): In the acute phase of KD, the frequency of ASCs is high with augmented B4 expression, whereas it is lower with decreased B4 expression after IVIG. Further studies of B4 expression on ASCs in autoimmune and infectious diseases will be needed to confirm the significance of our findings. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Tanoshima, R., et al. (2019). "Effectiveness of antiplatelet therapy for Kawasaki disease: a systematic review." European Journal of Pediatrics.
Kawasaki disease is an acute systemic vasculitis in children. Antiplatelet medicines are commonly used for Kawasaki disease to attenuate vasculitis and prevent thromboembolism; however, the mechanisms have not been elucidated. The objective of this study is to assess the effectiveness of antiplatelet medications for Kawasaki disease. We used Medline, Embase, Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi (Ichushi) from January 1947 to August 2018. Studies describing the platelet functions of antiplatelet drugs for Kawasaki disease were included. Twenty studies met the inclusion criteria. There were no randomized controlled trials. Seven studies compared platelet aggregation ability before and after treatment. Eight studies compared platelet aggregation with that in Kawasaki disease patients without treatment. Four studies compared aggregation among different types of antiplatelet drugs or at different doses. Antiplatelet medications administered in the studies included aspirin, flurbiprofen, dipyridamole, and choline salicylate. Methods for the measurement of platelet aggregation ability varied among studies. The groups with antiplatelet treatment tended to have a decreased platelet aggregation function. The statistical analyses were impossible due to insufficient quantitative data and heterogeneity among the studies. Conclusion(s): The present systematic review revealed that there was insufficient evidence for the effectiveness of antiplatelet therapy for Kawasaki disease.What is Known:* Antiplatelet therapy is widely used for Kawasaki disease to mitigate cardiac complications.* The mechanisms of antiplatelet therapy for Kawasaki disease are not clarified.What is New:* This systematic review showed that the groups with antiplatelet treatment tended to have a decreased platelet aggregation function.* There is insufficient evidence for the effectiveness of antiplatelet therapy for Kawasaki disease. Copyright © 2019, Springer-Verlag GmbH Germany, part of Springer Nature.

Thiha, K., et al. (2019). "Investigation of novel variations of ORAI1 gene and their association with Kawasaki disease." Journal of Human Genetics **64**(6): 511-519.
ORAI1 encodes a calcium channel essential in the store-operated calcium entry mechanism. A previous genetic association study identified a rare in-frame insertion variant of ORAI1 conferring

Kawasaki disease (KD). To deepen our understanding of the involvement of rare variants of ORAI1 in KD pathogenesis, we investigated 3812 patients with KD and 2644 healthy individuals for variations in the protein-coding region of ORAI1. By re-sequencing the study participants' DNA, 27 variants with minor allele frequencies (MAFs) < 0.01 that had not been examined in the previous study were identified. Although no significant association with KD was observed either in single-variant analyses or in a collapsing method analysis of the 27 variants, stratification by MAFs, variant types, and predicted deleteriousness revealed that six rare, deleterious, missense variants (MAF < 0.001, CADD C-score >= 20) were exclusively present in KD patients, including three refractory cases (OR = , P = 0.046). The six missense variants include p.Gly98Asp, which has been demonstrated to result in gain of function leading to constitutive Ca²⁺ entry. Conversely, five types of frameshift variants, all identified near the N terminus and assumed to disrupt ORAI1 function, showed an opposite trend of association (OR = 0.35, P = 0.24). These findings support our hypothesis that genetic variations causing the upregulation of the Ca²⁺/NFAT pathway confer susceptibility to KD. Our findings also provide insights into the usefulness of stratifying the variants based on their MAFs and on the direction of the effects on protein function when conducting association studies using the gene-based collapsing method. Copyright © 2019, The Author(s), under exclusive licence to The Japan Society of Human Genetics.

Tinoco, Y. O., et al. (2019). "Etiology of acute respiratory infections in children under five years old. results from an active community surveillance and passive hospital surveillance in Lima, Peru." American Journal of Tropical Medicine and Hygiene **101 (5 Supplement)**: 576.
Acute respiratory infections (ARI) constitutes a major cause of morbidity and mortality in children. Different pathogens were described to cause ARI however their contribution and role as etiological agents are not well understood. We aimed to describe the etiology of ARI among children < 5 years in two settings: (1) Severe acute respiratory illness (SARI) in a hospital setting and (2) influenza-like illness (ILI) from a community active surveillance, both in a similar geographic area and time period. To perform the testing we used Taqman Array Cards, which detect 30 respiratory pathogens. From February 2014-March 2015, we sampled 258 nasopharyngeal & oropharyngeal (OP) swabs from SARI children. SARI was defined as fever >=38 C with cough & disease onset in last 10 days prior to hospitalization. Simultaneously, we collected 150 OP swabs from children with ILI in community cohort; ILI was defined as sudden onset of fever >=38 C, with cough and /or rhinorrhea and/ or nasal congestion. Of the SARI-patients, 95% (244) had at least one agent detected. Respiratory Syncytial Virus was the most common (33%, 13) followed by Streptococcus pneumonia ([STPN], 15%, 6) and Human metapneumovirus (13%, 5). Among ILI patients, 91% (136) had at least one agent detected. Among those with a detected, pathogen, 31% (12) were Moraxella catarrhalis (MOCA) and 13% (5) for each Influenza A & B, Haemophilus influenza (Hib) and STPN. Identification of only one pathogen was not common among SARI patients (16%, 39) or ILI patients (29%, 39); however, there were statistically significantly more single detections among ILI patients compared with SARI patients (p= 0.003). Hib, MOCA and STPN were the most common co-detections (46%-62%) found among ILI and SARI children. Importantly, we found that Legionella species, Human coronavirus NL63 and 229E, Bordetella pertussis, Pseudomonas aeruginosa, Influenza C, Group A streptococcus and Pneumocystis jiroveci were present only in SARI hospitalized children. Our results demonstrate that more than 90% of pathogens could be identified in OP swabs and pathogens detected were different between community and hospitalized settings.

Tobolowsky, F. A., et al. (2019). "Association of body mass index with rates of hospitalization in patients with respiratory viral infections?Puerto Rico, 2012-2018." Open Forum Infectious Diseases **6 (Supplement 2)**: S986-S987.
Background: Obesity is a serious public health problem in Puerto Rico, where 31% of the population is obese. Multiple studies have suggested that adults with influenza who are underweight, overweight, or obese have increased risk of hospitalization compared with those of

normal weight. We sought to determine whether risk of hospitalization among patients infected with influenza or other respiratory viruses differs by BMI among patients in Puerto Rico. Method(s): We analyzed data from patients enrolled in the Sentinel Enhanced Dengue Surveillance System (SEDSS), a prospective study of patients with acute febrile illness (AFI), from May 2012 to September 2018. We evaluated those older than 24 months, who had height, weight, and clinical disposition recorded, and tested positive by RT-PCR for infection with influenza A (n = 1253), influenza B (n = 844), adenovirus (n = 435), respiratory syncytial virus (n = 289), parainfluenza virus (n = 361), metapneumovirus (n = 247), or coronavirus (n = 15). BMI categories were determined using standard cutoffs in adults and BMI-for-age percentiles for children and adolescents. Risk of hospitalization by BMI category was calculated using multivariate Poisson regression. Result(s): Among the 3,388 patients included, 675 (20%) were overweight, 926 (27%) were obese, 405 (12%) were underweight, and 1382 (41%) were normal weight. Median age was 13.4 (range: 2-100 years), and 50% were male. Risk of hospitalization was not significantly different in children and adult patients infected with a respiratory virus who were overweight relative to those that had normal BMI; however, once hospitalized, obese individuals of any age had a mean length of hospital stay 1.7 days longer than normal weight persons (95% CI: 0.27-3.17 days). Among adult patients, underweight patients were nearly 3 times more likely to be hospitalized compared with normal weight patients (relative risk 2.8, 95% CI: 1.4-5.9). Underweight children were not at increased risk of hospitalization. Conclusion(s): Among patients infected with a respiratory virus, risk of hospitalization was higher among underweight adult patients, and obese patients had a longer mean length of stay once hospitalized. Body mass index should be considered when evaluating risk and managing these patients.

Tokak, S., et al. (2019). "Determination of epidemiology and seasonal distribution of viral agents detected in children with respiratory tract infection." Cocuk Enfeksiyon Dergisi **13**(4): e158-e164.
Objective: The aim of this study was to determine the viral pathogens in the respiratory tract infections of children who applied to various outpatient clinics of our hospital and to investigate their seasonal distribution. Material(s) and Method(s): Between January 2016 and January 2017, 997 children (45.1% female, 54.9% male, 0 month-17 years) who were diagnosed with upper or lower respiratory tract infection were included in the study. Twenty-one viral respiratory pathogens were analyzed by multiplex polymerase chain reaction method by using Fast Track FTD kit (Fast Track Diagnosis, Luxemburg). Result(s): One or more respiratory viruses were detected in 761 (76.3%) of 997 patients and no virus was detected in 236 (22.8%) of the patients. In our study, distrubition of respiratory tract viruses were as; Adenovirus (2.76%), Bocavirus (4.20%), Coronavirus 229E (0.92%), Coronavirus OC43 (6.96%), Enterovirus (6.04%), Metapneumovirus A (4.60%), Metapneumovirus B (4.47%), Parainfluenza 1 (0.13%), Parainfluenza 2 (1.18%), Parainfluenza 3 (8.80%), Parainfluenza 4 (1.18%), Parainfluenza 4a (0.13%), Parainfluenza 4b (0.13%), Rhinovirus (48.75%), RSVA/B (37.84%), Influenza B (3.02%) and Parechovirus (6.57%). When we observe the seasonal distribution of viral agents, RSV was the most common agent in winter and it was rhinovirus in spring, summer and autumn season. Conclusion(s): Approximately 80% of the patients included in the study had a viral agent that may be responsible for clinical symptoms. For this reason, the rapid and sensitive diagnosis of viruses causing viral respirato-ry infections will reduce the cost of treatment, reduce unnecessary use of antibiotics and prevent the development of resistance to antibiotics and will guide the clinician to prevent the infections caused by these viruses.

Tulloh, R. M. R., et al. (2019). "Kawasaki disease: A prospective population survey in the UK and Ireland from 2013 to 2015." Archives of Disease in Childhood **104**(7): 640-646.
Objective Kawasaki disease (KD) is an increasingly common vasculitis with risk of coronary artery aneurysms (CAAs). The last UK survey was in 1990, whereas current epidemiology, treatment patterns and complication rates are unknown. The aim of this study was to address this

knowledge gap. Methods A British Paediatric Surveillance Unit survey in the UK and Ireland from 1 January 2013 to 28 February 2015 ascertained demographics, ethnicity, seasonal incidence, treatment and complication rates. Results 553 cases were notified: 389 had complete KD, 46 had atypical KD and 116 had incomplete KD; 2 were diagnosed at postmortem with an incidence of 4.55/100 000 children under 5 years, with a male to female ratio of 1.5:1 and a median age of 2.7 years (2.5 months-15 years). Presentation was highest in January and in rural areas. Most were white (64%), and Chinese and Japanese Asians were over-represented as were black African or African mixed-race children. 94% received intravenous immunoglobulin (IVIG). The overall CAA rate was 19%, and all-cardiac complications affected 28%. Those with CAA received IVIG later than in those without (median 10 days vs 7 days). Those under 1 year had fewer symptoms, but the highest CAA rate (39%). Overall 8 of 512 cases (1.6%) had giant CAA, and 4 of 86 cases (5%) under 1 year of age developed giant CAA. Mortality from KD was 0.36%. Conclusions The UK and Ireland incidence of KD has increased and is more frequently seen in winter and rural areas. Delayed IVIG treatment is associated with CAA, suggesting earlier and adjunctive primary treatment might reduce complications to prevent CAA, particularly in the very young. Copyright © 2019 Author(s).

Volosovets, O., et al. (2019). "Epidemiology and clinical manifestations of acute viral respiratory infections in pediatric patients in Ukraine." Archives of Disease in Childhood **104 (Supplement 3)**: A371.

Background: Acute respiratory tract infections (ARTI) in children are the leading cause of morbidity in Ukraine. The role of respiratory viruses in the clinical manifestations of ARTI in children in Ukraine has not been sufficiently studied. The aim of study To investigate the etiology of ARTI and compare the clinical features of different virus infections in children during the period from September 2018 to January 2019. The methods Nasopharyngeal swabs, collected from ARTI children aged 2 months - 16 years, who received outpatient treatment or were hospitalized to Eurolab clinic (Kyiv, Ukraine) were examined. They were screened for 7 respiratory viruses using Multiplex PCRs - Respiratory Syncytial virus (RSV), Parainfluenza virus (PIV), Adenovirus (AdV), human Metapneumovirus (hMPV), Rhinovirus (RV), human Bocavirus (hBoV)and Coronavirus (CoV). Although rapid influenza diagnostic test was used. Result(s): Respiratory pathogens detected in 125 of the 147 (85,0%) samples. HMPV was detected in 33 children. Clinical manifestation of hMPV infection were: tracheobronchitis - 13, pneumonia - 6, obstructive bronchitis - 7, bronchiolitis - 3, rhinopharyngitis -3, laryngitis -3. Influenza A (IVA) was detected in 28 children with ARTI: tracheobronchitis - 13, pneumonia - 6, obstructive bronchitis - 2. Half of children with IVA also have symptoms of rhinopharyngitis. RV was detected in 21 children, 12 of them have symptoms of rhinopharyngitis, 3 - croup and 3 - wheezing, 2 - bronchitis and 1 - laryngitis. Clinical characteristics of others viruses are following: RSV was detected in 10 children, it caused pneumonia (3 cases), obstructive bronchitis (5 cases). HBoV was detected in 7 children and caused rhinopharyngitis, laryngitis (6 cases), tracheobronchitis (2), two child had viral exanthema. AdV was detected in 5 children and caused rhinopharyngitis with lymphadenopathy in 3 cases, pneumonia in 2 cases. PIV during season caused rhinopharyngitis, laryngitis (2 cases), croup (1 case), obstructive bronchitis (1 case). The coinfection percentage was 13, 5%. Conclusion(s): During epidemic season in Ukraine the most prevalent viruses were hMPV -33 (26,3%), IVA -28 (22,4%), RV - 21 (16,8%). Using Multiplex PCR assay can be helpful in prognosing of probable clinical course of disease, for optimization therapy.

Waghmare, A., et al. (2019). "Rhinovirus in children presenting to the emergency department: Role of viral load in disease severity and co-infections." Open Forum Infectious Diseases **6 (Supplement 2)**: S915-S916.

Background: Rhinovirus (RV) quantitation by reverse transcription-quantitative PCR is limited by variable amplification efficiency across genotypes. We used a precise viral quantitation method, reverse transcription-digital PCR (RT-dPCR), to characterize the role of viral load in clinical

outcomes and in viral co-infections in children presenting to a tertiary hospital emergency department (ED). Method(s): Children < 18 years with respiratory symptoms for <= 14 days were enrolled from December 1, 2016 to December 31, 2018. Participants had nasal and throat specimens obtained and multiplex PCR testing with a commercial assay (FilmArray; bioMerieux). RV positive samples were quantified using RT-dPCR. Samples with sufficient viral load were sequenced at a 543 bp fragment of the RV VP4/ VP2 region. RV species were assigned by comparison to RV sequences in GenBank using BLAST. Clinical data were collected into REDCap. T-tests were used to compare mean viral loads between groups. Result(s): Of 1703 children enrolled in the ED, 697 were RV/enterovirus positive by FilmArray [median age 18 months (interquartile range 9-39 months)]. Of 590 subjects with viral load available, 276 (47%) were admitted to the hospital. Among RV mono-infections (N = 434), mean viral load did not differ between subjects admitted vs. discharged from the ED (7.03 log copies/mL for both, P = 0.97). Among admitted subjects with RV mono-infection, viral load also did not differ between subjects requiring supplemental oxygen vs. not (7.01 vs. 7.10 log copies/mL, P = 0.6). Subjects with viral co-infections had lower mean RV viral loads (6.31 log copies/mL) compared with those with RV only (7.03 log copies/mL; P < 0.001) (figure). Significantly different RV viral loads were seen with co-infections with respiratory syncytial virus (RSV), metapneumovirus (MPV) and parainfluenza (PIV), but not with influenza, adenovirus or coronavirus. In 525 sequenced samples (46% RV-A, 4% RV-B, 50% RV-C), viral load did not vary between RV viral species (P = 0.09). Conclusion(s): Precise viral quantitation demonstrates children co-infected with RV and RSV, MPV or PIV have lower nasal viral loads than those with RV alone. Among RV mono-infections, RV viral load was not associated with admission or need for supplemental oxygen.

Walker, G. J., et al. (2019). "Viruses associated with acute respiratory infection in a community-based cohort of healthy NZ children." Journal of Medical Virology. **24**.
Acute respiratory infections (ARIs) are a major cause of morbidity among children. Respiratory viruses are commonly detected in both symptomatic and asymptomatic periods. The rates of infection, and community epidemiology of respiratory viruses in healthy children needs further definition to assist interpretation of molecular diagnostic assays in this population. Children otherwise healthy aged one to eight years were prospectively enrolled in the study during two consecutive winters, when ARIs peak in New Zealand. Parents completed a daily symptom diary for eight weeks, during which time they collected a nasal swab from the child for each clinical ARI episode. A further nasal swab was collected by research staff during a clinic visit at the conclusion of the study. All samples were tested for 15 respiratory viruses commonly causing ARI using molecular multiplex PCR assays. There were 575 ARIs identified from 301 children completing the study, at a rate of 1.04 per child-month. Swabs collected during an ARI were positive for a respiratory virus in 76.8% (307/400), compared to 37.3% (79/212) of swabs collected during asymptomatic periods. The most common viruses detected were human rhinovirus, coronavirus, parainfluenza viruses, influenzavirus, respiratory syncytial virus, and human metapneumovirus. All of these were significantly more likely to be detected during ARIs than asymptomatic periods. Parent-administered surveillance is a useful mechanism for understanding infectious disease in healthy children in the community. Interpretation of molecular diagnostic assays for viruses must be informed by understanding of local rates of asymptomatic infection by such viruses.

Wang, H., et al. (2019). "Evaluation of left ventricular function in immunoglobulin-resistant children with Kawasaki disease: a two-dimensional speckle tracking echocardiography study." Clinical Cardiology **42**(8): 753-759.
Background: Kawasaki disease (KD) patients who are unresponsive to intravenous immune globulin (IVIG) have a high occurrence of coronary artery lesions (CALs). The characteristics of left ventricular (LV) function alternation in IVIG-resistant patients are not well-described. Hypothesis: Two-dimensional speckle tracking echocardiography (STE) is a useful technique that can accurately detect myocardium subclinical dysfunction in resistant patients and may assist in

differentiating patients with KD at a higher risk of IVIG resistance. Methods: A consecutive sample of 50 IVIG-resistant patients (25 males, 2.2 ± 0.9 years), 50 IVIG-responsive patients (27 males, 2.2 ± 0.7 years) and 50 normal subjects (27 males, 2.1 ± 0.9 years) were analyzed using STE, and receiver operating characteristic curve (ROC) analysis was utilized to determine the threshold values of STE parameters associated with IVIG resistance. Results: Compared with normal children, IVIG-resistant patients had lower global longitudinal strain (GLS) (15.82 ± 3.32 vs 20.01 ± 2.98, P = 0.000) and lower global circumferential strain (GCS) (16.65 ± 3.12 vs 20.11 ± 2.86, P = 0.042). Both GLS and GCS in IVIG-resistant patients were significantly lower than in IVIG-responsive patients (15.82 ± 3.32 vs 19.95 ± 3.01, 16.65 ± 3.12 vs 19.01 ± 3.00, P =.000,.030, respectively). ROC analysis demonstrated that the absolute values of GLS < 16.8% and GCS < 15.9% were optimal predictors of IVIG unresponsiveness (area under the curve = 0.78, 0.75; sensitivity = 0.83, 0.79; specificity = 0.69, 0.65, respectively). Conclusion: IVIG-resistant patients presented with more severe LV systolic dysfunction compared with IVIG-responsive patients, which may be the result of myocarditis rather than CALs. STE may be a helpful diagnostic tool that provides supportive criteria to detect KD patients at a higher risk of IVIG resistance. © 2019 The Authors. Clinical Cardiology published by Wiley Periodicals, Inc.

Wang, J., et al. (2019). "Influenza A (H1N1) pdm09 virus infection in a patient with incomplete Kawasaki disease: A case report." Medicine **98**(15): e15009.
RATIONALE: Kawasaki disease (KD) is a vasculitic illness of childhood associated with coronary artery dilatation, coronary artery aneurysm, arrhythmia, sudden death, and other serious cardiovascular diseases. Up to date, the etiology of KD remains unclear; however, epidemiological characteristics indicate that it may be related to as-yet-undefined pathogen infection. PATIENT CONCERNS: A 19-month-old boy had a fever of unknown origin at 38°C for 9 days without rash, runny nose and cough. DIAGNOSIS: The boy was diagnosed with incomplete KD (IKD) coincident with influenza A (H1N1) pdm09 virus. INTERVENTIONS: He was received treatments including human immunoglobulin (2g/kg), aspirin (30~50mg/kg.d), and dipyridamole (3~5mg/kg.d). OUTCOMES: After 24hours of human immunoglobulin infusion, his body temperature returned normal. After hospitalization for 6 days, his symptoms disappeared and discharged from the hospital. LESSONS: More attention should be paid to the correlation between KD and pathogen infection, especially the new influenza virus H1N1. The potential mechanism underlying viral infection-mediated KD is worthy of further investigation, which may provide scientific evidence for the pathogenesis of KD.

Wang, L., et al. (2019). "Comparing the yield of oropharyngeal swabs and sputum for detection of 11 common pathogens in hospitalized children with lower respiratory tract infection." Virology Journal **16 (1) (no pagination)**(84).
Background: Advances in molecular laboratory techniques are changing the prospects for the diagnosis of viral infectious diseases. Multiplex polymerase chain reaction assay (multiplex-PCR) can detect dozens of pathogens simultaneously, greatly reducing turnaround time (TAT) and improving detection sensitivity. But as a double-edged sword, due to the high sensitivity of PCR, the type of respiratory specimens is critical to diagnosis. In this work, we performed a head-to-head comparison to evaluate the multiplex-PCR yields between two samples, sputum and flocked oropharyngeal swabs (OPS). Method(s): Eleven common respiratory pathogens were tested in hospitalized children< 13 years of age who met the criteria for lower respiratory tract infection by GeXP-based multiplex-PCR of paired OPS and sputum. Result(s): From January to June 2018, 440 children with paired OPS and sputum were tested. The positive rate was 84% (369/440) for OPS and 88% (386/440) for sputum (p =.007). The frequency of detection of HRV, RSV, Influenza A virus, HMPV, parainfluenza virus, adenovirus, M. pneumoniae, coronavirus, bocavirus and C. pneumoniae in sputa was higher than that of OPSs (all p <.001). Both types of specimens had similarly very good kappa values for most of pathogens, except for Mycoplasma pneumonia (kappa = 0.61) and Chlamydia pneumoniae (kappa = 0.24). Additionally, 79.3% (349/440) of cases showed consistent results between the two types of samples, and they were

significantly younger than patients with inconsistent results (p =.002). Conclusion(s): Flocked oropharyngeal swabs and sputum performed similarly for the detection of common respiratory pathogens in hospitalized children by multiplex-PCR, except for Mycoplasma pneumoniae and Chlamydia pneumoniae. Young patients are likely to have consistent results between the two specimens. Copyright © 2019 The Author(s).

Wang, Y. F., et al. (2019). "Serum exosomal microRNA let-7i-3p as candidate diagnostic biomarker for Kawasaki disease patients with coronary artery aneurysm." IUBMB Life **71**(7): 891-900.
Kawasaki disease (KD) is a systemic vasculitis syndrome that leads to coronary artery aneurysm (CAA). While echocardiography is the most important imaging modality for coronary artery assessment, a specific diagnostic biomarker complementary for CAA has not been reported. We aimed to analyze the profiles of exosomal miRNAs extracted from the serum of KD patients and controls to identify candidate biomarkers for CAA. Serum samples from 39 healthy children, 42 CAA patients, 38 coronary artery dilatation (CAD) patients and 45 virus-infected patients including 24 EBV patients and 21 ADV patients were randomly selected. Next generation sequencing was used to analyze serum exosomal miRNA to detect differentially expressed miRNAs. Biomarker candidates were validated by qRT-PCR. One hundred (and) ninety-six differentially expressed miRNAs (DEMs) were detected in CAA patients and healthy children. There were 70 DEMs and 140 DEMs in CAA patients versus CAD patients, and in CAA patients versus virus-infected patients, respectively. We selected the three most upregulated (let-7i-3p, miR-17-3p, and miR-210-5p) and the three most downregulated miRNAs (miR-6743-5p, miR-1246, and miR-6834-5p) in the DEMs, which were expressed differentially in CAA patients versus healthy children, and in CAA patients versus virus-infected patients, not in virus-infected patients versus healthy children, as biomarker candidates. Excluded DEMs of CAD and virus-infected patients, let-7i-3p was detected by sequence data analysis as a biomarker candidate for CAA patients, and then validated by qRT-PCR in a larger set of clinical samples. As a biomarker candidate, let-7i-3p provides an additional means of diagnosing CAA patients. Additionally, miRNA biomarkers complement ultrasonic imaging, allowing for greater diagnostic precision. © 2019 IUBMB Life, 2019. © 2019 International Union of Biochemistry and Molecular Biology

Wang, Z., et al. (2019). "Diagnostic significance of MIR-937 in peripheral blood mononuclear cells of Kawasaki disease." Clinical Laboratory **65**(11): 2157-2163.
Beckground: The current study aims to investigate whether miR-937 can be used as a diagnostic biomarker in peripheral blood mononuclear cells (PBMCs) for children with Kawasaki disease (KD) with or without coronary artery dilation (CAD). Methods: Gene chip technology was used to screen miRNAs differentially expressed between KD children and normal healthy children. Furthermore, real time PCR was carried out to validate the expression of miR-937 in 50 children with KD (25 cases with and 25 cases without CAD) and 25 healthy children. Meanwhile, target genes of miR-937 were analyzed using TargetScan and dual luciferase reporter assay. Results: First, 20 miRs with significantly differentially expressed mononuclear cell (PBMCs) in peripheral blood between children with KD and normal healthy children were identified by gene chip technology. Real time PCR analysis validated that the expression of miR-937 decreased most significantly among all differentially expressed miRNAs. Secondly, miR-937 was down-regulated significantly before treatment with gamma globulin (IVIG), while its expression was significantly up-regulated after IVIG treatment. In addition, the expression of miR-937 in KD children with CAD was significantly lower than that of KD children without CAD. Person's correlation assay showed that miR-937 negatively correlated with CAD. Dual luciferase reporter assay indicated that IL-1β was a target gene of miR-937. Conclusions: In summary, miR-937 in PBMCs was involved in the occurrence and development of KD, which provides new ideas for the prevention and treatment of KD coronary artery dilation.

Watanabe, M., et al. (2019). "Virtual histology intravascular ultrasound evaluation of coronary artery lesions within 1 year and more than 10 years after the onset of Kawasaki disease." Journal of Cardiology.
Background: Coronary artery evaluation by virtual histological intravascular ultrasonography (VH-IVUS) late in Kawasaki disease (KD) shows intimal thickening, calcification, fatty components, and necrosis of regressed coronary artery lesions (CALs). However, it is not clear when these VH-IVUS findings start to occur. Therefore, we evaluated coronary arteries using VH-IVUS in patients with early-stage KD and tried to determine whether these atherosclerotic findings on VH-IVUS were different from that in patients with late-stage KD. Method(s): Eighteen patients with KD aged between 1 and 32 years who had CALs and underwent cardiac catheterization between January 1, 2008 and December 31, 2014 were included. They were divided into 2 groups-those with the disease for <1 year (group A) and those with it for >10 years (group B). VH-IVUS findings were compared between the groups. The coronary arteries were divided based on coronary angiography findings into normal, regressed (dilated CALs regressed to a normal size), and aneurysmal lesions. The Wilcoxon signed-rank test was used in the statistical analysis. Result(s): In both regressed and aneurysmal lesions, marked intimal proliferation and atherosclerotic findings (fibro-fatty and necrotic core lesions) were observed. In addition, there was no difference in the area percentage of atherosclerosis between the groups. Conclusion(s): VH-IVUS revealed that atherosclerotic-like findings exist in CALs in patients with KD, even within a year of onset. The findings were almost the same in those with the disease for >10 years. Because there is no histological evidence of atherosclerosis in KD, these VH-IVUS findings may indicate complex histological findings of KD. Nevertheless, early interventions to help reduce the risk factors of atherosclerosis may be required in these patients. Copyright © 2019

Wormsbecker, A. E., et al. (2019). "Demonstration of background rates of three conditions of interest for vaccine safety surveillance." PLoS ONE **14 (1) (no pagination)**(e0210833).
Introduction Adverse events following immunization (AEFIs) are unwanted or unexpected health outcomes following vaccination, which may or may not be causally-linked to vaccines. AEFI reporting is important to post-marketing vaccine safety surveillance and has the potential to identify new or rare AEFIs, show increases in known AEFIs, and help to maintain public confidence in vaccine programs. Knowledge of the expected incidence (i.e. background rate) of a possible AEFI is essential to the investigation of vaccine safety signals. We selected three rarely reported AEFIs representing the spectrum of causal association with vaccines, from proven (immune thrombocytopenia [ITP]) to questioned (Kawasaki disease [KD]) to unsubstantiated (multiple sclerosis [MS]) and determined their background rates. Methods We extracted data on hospitalizations (CIHI Discharge Abstract Database) for ITP, KD, and MS among Ontario children for the period 2005 to 2014 from IntelliHEALTH. As ITP can be managed without hospitalization, we also extracted emergency department (ED) visits from the CIHI National Ambulatory Care Reporting System. For all conditions, we only counted the first visit and if the same child had both an ED visit and a hospitalization for ITP, only the hospitalization was included. We calculated rates by year, age group and sex using population estimates from 2005-2014, focusing on age groups within the Ontario immunization schedule around vaccine(s) of interest. Results Per 100,000 population, annual age-specific incidence of ITP in children age 1 to 7 years ranged from 8.9 to 12.2 and annual incidence of KD in children less than 5 years ranged from 19.1 to 32.1. Average annualized incidence of adolescent (11-17 years) MS across the study period was 0.8 per 100,000. Discussion Despite limitations, including lack of clinical validation, this study provides an example of how health administrative data can be used to determine background rates which may assist with interpretation of passive vaccine safety surveillance. Copyright © 2019 Wormsbecker et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Wu, J., et al. (2019). "Aberrant expression of serum circANRIL and hsa:circ_0123996 in children with Kawasaki disease." Journal of Clinical Laboratory Analysis **33**(5).
Background: Kawasaki disease is a childhood systemic vasculitis that causes coronary artery abnormalities. The etiology remains unknown and there are no specific diagnostic tests. Circular non-coding RNAs are a special class of endogenous RNAs that display some characteristics of an ideal biomarker. However, few studies have examined the expression of circRNAs in the serum of Kawasaki disease (KD) patients. The aim of this study was to identify circRNAs in the serum that can serve as potential biomarkers for KD diagnosis. Methods: The cases were children diagnosed with KD (n = 56). The controls comprised healthy children (n = 56). Blood was collected from the patients before and after intravenous immunoglobulin therapy, and from the healthy controls. Levels of circANRIL and hsa:circ_0123996 in the serum were measured by quantitative reverse transcription PCR. Then, the potential relationship between serum circRNA levels and patients' biochemical parameter levels was investigated. Receiver operating characteristic curves were constructed for evaluating the diagnostic value of these circRNAs. Results: The serum levels of circANRIL were lower in patients with KD before therapy than in the controls, but became higher in the patients after therapy than before therapy. The serum levels of hsa:circ_0123996 were higher in patients with KD before therapy than in healthy controls. Conclusion: Our study indicated that the circANRIL and hsa:circ_0123996 levels in the serum of patients with KD were significantly different from those in healthy individuals. circANRIL and hsa:circ_0123996 may become potential biomarkers for early KD diagnosis. © 2019 The Authors. Journal of Clinical Laboratory Analysis Published by Wiley Periodicals, Inc.

Wu, Y., et al. (2019). "Interleukin-6 is prone to be a candidate biomarker for predicting incomplete and IVIG nonresponsive Kawasaki disease rather than coronary artery aneurysm." Clinical and Experimental Medicine **19**(2): 173-181.
Kawasaki disease (KD) is an acute, systemic vasculitis and occurs mainly in childhood. Interleukin-6 (IL-6) is a pleiotropic cytokine synthesized predominantly by neutrophils and monocytes/macrophages and plays an important role in systemic inflammatory disease. However, a little information is currently available on the relationship of serum IL-6 with conventional inflammatory mediators, clinical classification, IVIG response and coronary artery aneurysm (CAA). 165 Chinese children with KD were enrolled and divided into six subgroups, including complete KD, incomplete KD, IVIG-responsive KD, IVIG-nonresponsive KD, coronary artery noninvolvement KD and coronary artery involvement KD. Blood samples were collected from all subjects within 24-h pre- and 48-h post-IVIG therapy, respectively. Serum IL-6 and conventional inflammatory mediators were detected. (1) Serum IL-6 markedly increased in the acute phase of KD, whereas declined to normal after IVIG therapy; it was positively correlated with C-reactive protein and erythrocyte sedimentation rate. (2) Serum IL-6 was significantly elevated in patients with incomplete KD when compared with their complete counterparts. The area under receiver operating characteristic curve (AUC) value for serum IL-6 in prediction of incomplete KD was 0.596, and the estimated sensitivity and specificity were 77.80% and 54.40% with a cutoff of IL-6 > 13.25 pg/ml, respectively. (3) Serum IL-6 was significantly elevated in patients with IVIG-nonresponsive KD when compared with their IVIG-responsive counterparts; the AUC value for serum IL-6 in prediction of IVIG-nonresponsive KD was 0.580, and the estimated sensitivity and specificity were 60.00% and 66.30% with a cutoff of IL-6 > 26.40 pg/ml, respectively. (4) No significant differences in IL-6 were found between KD patients with and without CAA. IL-6 is prone to be a candidate biomarker for predicting incomplete and IVIG nonresponsive KD rather than CAA. © 2019, Springer Nature Switzerland AG.

Xie, L. P., et al. (2019). "Epidemiologic Features of Kawasaki Disease in Shanghai From 2013 Through 2017." Journal of epidemiology. **21**.
BACKGROUND: To investigate epidemiologic features of Kawasaki disease (KD) in Shanghai from 2013 through 2017 and identify risk factors for coronary artery lesions (CAL). METHOD(S): As in our previous three surveys, a set of questionnaires and diagnostic guidelines for KD were sent to

50 hospitals providing pediatric medical care in Shanghai. Medical records of KD patients diagnosed from January 2013 through December 2017 were retrospectively analyzed. Multivariate logistic regression analysis was performed to identify risk factors for CAL. RESULT(S): A total of 4452 cases were enrolled. Male-to-female ratio was 1.7:1. The incidence of KD was 68.8 to 107.3 per 100,000 children aged <5 years from 2013 to 2017. Age at onset ranged from 15 days to 14.0 years (median: 1.8 years). KD occurred more frequently in spring and summer. Of 4325 patients (97.0%) receiving intravenous immunoglobulin (IVIG), 362 (8.4%) were resistant to initial IVIG. CAL occurred in 406 (9.1%) patients, including 118 (2.7%) with medium aneurysms and 31 (0.7%) with giant aneurysms. Recurrent cases were 60 (1.3%). No death was found in this survey. Higher platelet levels, lower albumin levels, male sex, incomplete KD, IVIG resistance, and receiving initial IVIG <=4 days or >10 days, were independently associated with CAL. CONCLUSION(S): The incidence of KD in Shanghai had substantially increased while the proportion of CAL had substantially decreased as compared with our previous surveys. Higher platelet levels, lower albumin levels, male sex, incomplete KD, IVIG resistance, and receiving initial IVIG <=4 days or >10 days, were risk factors for CAL.

Yamaji, N., et al. (2019). "Tnf-alpha blockers for the treatment of kawasaki disease in children." Cochrane Database of Systematic Reviews **2019 (8) (no pagination)**(CD012448). Background Kawasaki disease (KD) is an acute inflammatory vasculitis (inflammation of the blood vessels) that mainly affects children between six months and five years of age. The vasculitis primarily impacts medium-sized blood vessels, especially in the coronary arteries. In most children, intravenous immunoglobulin (IVIG) and aspirin therapy rapidly reduce inflammatory markers, fever, and other clinical symptoms. However, approximately 15% to 20% of children receiving the initial IVIG infusion show persistent or recurrent fever and are classified as IVIG-resistant. Tumor necrosis factor-alpha (TNF-alpha) is an inflammatory cytokine that plays an important role in host defence against infections and in immune responses. Several studies have established that blocking TNF-alpha is critical for obtaining anti-inflammatory effects in children with KD, thus, there is a need to identify benefits and risks of TNF-alpha blockers for the treatment of KD. Objectives To evaluate the efficacy and safety of using TNF-alpha blockers (i.e. infliximab and etanercept) to treat children with Kawasaki disease. Search methods The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases, the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials register to 19 September 2018. We also undertook reference checking of grey literature. Selection criteria We included randomised controlled trials (RCTs) that compared TNF-alpha blockers (i.e. infliximab and etanercept) to placebo or other drugs (including retreatment with IVIG) in children with KD, reported in abstract or full-text. Data collection and analysis Two review authors independently applied the study selection criteria, assessed risk of bias and extracted data. When necessary, we contacted study authors for additional information. We used GRADE to assess the certainty of the evidence. Main results We included five trials from 14 reports, with a total of 494 participants. All included trials were individual RCTs that examined the effect of TNF-alpha blockers for KD. Five trials (with 494 participants) reported the incidence of treatment resistance. TNF-alpha blockers reduced the incidence of treatment resistance (TNF-alpha blocker intervention group 30/237, control group 58/257; risk ratio (RR) 0.57, 95% confidence interval (CI) 0.38 to 0.86; low-certainty evidence). Four trials reported the incidence of coronary artery abnormalities (CAAs). Three trials (with 270 participants) contributed data to the meta-analysis, since we could not get the data needed for the analysis from the fourth trial. There was no clear difference between groups in the incidence of CAAs (TNF-alpha blocker intervention group 8/125, control group 9/145; RR 1.18, 95% CI 0.45 to 3.12; low-certainty evidence). Three trials with 250 participants reported the adverse effect 'infusion reactions' after treatment initiation. The TNF-alpha blocker intervention decreased infusion reactions (TNF-alpha blocker intervention group 0/126, control group 15/124; RR 0.06, 95% CI 0.01 to 0.45; low-certainty evidence). Two trials with 227 participants reported the adverse effect 'infections' after treatment initiation. There was no clear difference between

groups (TNF-alpha blocker intervention group 7/114, control group 10/113; RR 0.68, 95% CI 0.33 to 1.37; low-certainty evidence). One trial (with 31 participants) reported the adverse effect 'cutaneous reactions' (rash and contact dermatitis). There was no clear difference between the groups for incidence of rash (TNF-alpha blocker intervention group 2/16, control group 0/15; RR 4.71, 95% CI 0.24 to 90.69; very low-certainty evidence) or for incidence of contact dermatitis (TNF-alpha blocker intervention group 1/16, control group 3/15; RR 0.31, 95% CI 0.04 to 2.68; very low-certainty evidence). No trials reported other adverse effects such as injection site reactions, neutropenia, infections, demyelinating disease, heart failure, malignancy, and i duction of autoimmunity. Authors' conclusions We found a limited number of RCTs examining the effect of TNF-alpha blockers for KD. In summary, low-certainty evidence indicates that TNF-alpha blockers have beneficial effects on treatment resistance and the adverse effect 'infusion reaction' after treatment initiation for KD when compared with no treatment or additional treatment with IVIG. Further research will add to the evidence base. Due to the small number of underpowered trials contributing to the analyses, the results presented should be treated with caution. Further large high quality trials with timing and type of TNF-alpha blockers used are needed to determine the effects of TNF-alpha blockers for KD.

Yan, F., et al. (2019). "Risk factors of coronary artery abnormality in children with kawasaki disease: A systematic review and meta-analysis." Frontiers in Pediatrics **7**(SEP).
While coronary artery abnormality (CAA) has been established as the most serious complication of Kawasaki disease (KD), there have been no detailed systematic reviews of the risk factors associated with this condition. We searched six databases and performed a systematic review and meta-analysis. Study-specific odds ratios (ORs) for each factor were pooled using a random effects model. We identified four risk factors for CAA children with KD: gender (OR, 1.75; 95% confidence interval [CI], 1.59–1.92), intravenous immunoglobulin (IVIG) resistance (OR, 3.43; 95% CI, 2.07–5.67), IVIG treatment beyond 10 days of onset of symptoms (OR, 3.65; 95% CI, 2.23–5.97), and increased C-reactive protein levels (OR, 1.02; 95% CI, 1.01–1.02). More number of the five typical symptoms of KD was identified as a protective factor against CAA (OR, 0.47; 95% CI, 0.33–0.66). Pediatric patients with IVIG resistant were more likely to develop CAA within 1 month of the onset of KD than the general population, even in patients with other risk factors for CAA. Thus, there is a potential risk of CAA misdiagnosis if echocardiography is not carried out frequently. In summary, we report four risk factors for CAA and a protective factor against CAA in children with KD. We recommend that pediatricians consider these factors much more closely. With accurate prediction and early preventive treatment in high-risk patients, we can expect a reduction in CAA rates. Further research is now required to investigate the associations between CAA and other factors including the interval between KD onset and IVIG administration, platelet count, and the duration of fever. We also need to confirm whether the frequency of echocardiography within a month of KD onset should be increased in IVIG-resistant patients.

Yan, J., et al. (2019). "Diagnostic value of serum miR-1 in patients with acute Kawasaki disease." Clinical Laboratory **65**(7): 1339-1344.
Background: The current study aims to investigate the expression of miR-1 in serum of patients with Kawasaki disease (KD) and its clinical significance. Methods: The serum samples of 33 patients with KD and 15 healthy people were collected from January 2017 to June 2017 at the Affiliated Hospital of North China University of Science and Technology. The expression of serum miR-1 was detected by real-time quantitative PCR (RT-qPCR). The diagnostic value of miR-1 as a marker of KD disease was evaluated by receiver operating characteristic (ROC) curve. Results: The level of miR-1 in serum of children with acute KD was significantly higher than that of healthy children, but it decreased to normal level in convalescence. ROC curves showed that the area under the curve (AUC) of miR-1 for KD diagnosis was 0.754 (95% CI: 0.541 - 0.952). When the critical value (diagnostic threshold) was 1.08, the diagnostic sensitivity and specificity were 0.867 and 0.735, respectively. In addition, we further divided the KD patients according to clinical

characteristics. Here, we showed that the expression of miR-1 was higher in the serum of KD patients with higher platelet level. Conclusions: In summary, serum miR-1 in patients with acute KD was significantly increased, which may be one of the potential serum markers for the diagnosis of KD. © 2019 Verlag Klinisches Labor GmbH. All rights reserved.

Yang, S., et al. (2019). "Predictive tool for intravenous immunoglobulin resistance of Kawasaki disease in Beijing." Archives of Disease in Childhood **104**(3): 262-267.
Objective To construct a predictive tool for the efficacy of intravenous immunoglobulin (IVIG) therapy in children with Kawasaki disease (KD) in Beijing, China. Design This was a cohort study. Data set (including clinical profiles and laboratory findings) of children with KD diagnosed between 1 January 2010 and 31 December 2015 was used to analyse the risk factors and construct a scoring system. Data set of children with KD diagnosed between 1 January 2016 and 1 December 2016 was used to validate this model. Setting Children's Hospital Capital Institute of Pediatrics and Beijing Children's Hospital. Patients 2102 children diagnosed with KD. Interventions No. Main outcome measures Responsiveness to IVIG. Results The predictive tool included C reactive protein ≥90 mg/L (3 points), neutrophil percentage ≥70% (2.5 points), sodium ion concentration <135 mmol/L (3 points), albumin <35 g/L (2.5 points) and total bilirubin >20 μmol/L (5 points), which generated an area under the the receiver operating characteristic curve of 0.77 (95% CI 0.71 to 0.82) for the internal validation data set, and 0.69 (95% CI 0.58 to 0.81) and 0.63 (95% CI 0.53 to 0.72) for two external validation data sets, respectively. If a total of ≥6 points were considered high-risk for IVIG resistance, sensitivity and specificity were 56% and 79% in the internal verification, and the predictive ability was similar in the external validation. Conclusions The predictive tool is helpful in early screening of high-risk IVIG resistance of KD in the Beijing area. Consequently, it will guide the clinician in selecting appropriate individualised regimens for the initial treatment of this disease, which is important for the prevention of coronary complications. © Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

Yew, S. M., et al. (2019). "Molecular epidemiology of respiratory viruses among Malaysian Young children with a confirmed respiratory infection during 2014-2015." Journal of Thoracic Disease **11**(11): 4626-4633.
Background: In many developing countries, acute respiratory tract infections (ARTIs) are the main cause of morbidity and mortality among young children. This study aims to evaluate the molecular epidemiology of respiratory viruses among Malaysian children with confirmed respiratory infections between July 2014 and July 2015. Method(s): A total of 394 nasopharyngeal swabs were collected prospectively from children age 0-5 years old with ARTIs from hospitals in Kuala Lumpur. Respiratory viral panel (RVP) assay was used to identify the viral aetiology of respiratory infections. Result(s): From a total of 394 samples, the positive detection rate was 79.9% (n=315). A total of 15 types of RNA viruses and a single type of DNA virus were detected. Enterovirus/rhinovirus (n=112, 28.4%), respiratory syncytial virus (RSV) (n=85, 21.6%), adenovirus (n=64, 16.2%), human bocavirus (n=34, 8.6%), and human metapneumovirus (n=29, 7.4%) were the five predominant viruses. Enterovirus/rhinovirus and RSV constituted most of the viral respiratory infections among young children, especially among children less than 1 year old. No coronavirus was detected among children between 3 and 5 years old. Co-infection caused by 2 or 3 respiratory viruses were detected in 52 patients (13.2%). Enterovirus/rhinovirus, adenovirus, and human bocavirus demonstrated pronounced seasonality. The infection rate peaked during mid-year, while the lowest activity occurred during early of the year. Conclusion(s): The use of molecular assay as a routine diagnostic in the hospitals can improve the diagnosis and management of respiratory tract infections among children. Copyright © Journal of Thoracic Disease. All rights reserved.

Yokouchi, Y., et al. (2019). "Expression of tenascin C in cardiovascular lesions of Kawasaki disease." Cardiovascular Pathology **38**: 25-30.

Background/Objective: To examine tenascin C (TN-C) expression in coronary artery lesions (CALs) and myocardial lesions (MLs) in Kawasaki disease (KD). Methods and Results: Twenty-five KD autopsy cases (post-KD-onset range of 6 days to 17 years) were examined in this study. Time-course analysis based on the disease day was performed of the histological findings for the CALs and MLs, as well as the localization and intensity of expression of TN-C. TN-C expression was observed to coincide with the areas where inflammatory cell infiltration was present in both coronary arteries and myocardium during the acute stage of KD, and the intensity of its expression correlated with the degree of inflammation. Obvious TN-C expression persisted in the thickened intima and media of CALs even after Disease Day 27. However, in spite of the presence of inflammatory cell infiltration, TN-C expression became weaker in the adventitia and surrounding connective tissue. After 8 months or more, TN-C was not expressed in the vasculitis scars of most cases, but expression was observed around newly formed vessels in the thickened intima and around recanalized vessels after thrombotic occlusion. Conclusion(s): The findings suggest a correlation between the degree of inflammation and TN-C expression in the cardiovascular lesions of acute-stage Kawasaki disease. Copyright © 2018 Elsevier Inc.

Yokoyama, K. and A. Yoshida (2019). "Late-onset and long-term systemic dyshidrotic eczema after intravenous immunoglobulin treatment for Kawasaki disease." BMJ Case Reports **12 (3) (no pagination)**(e229596).

Yoo, G. (2019). "Laboratory markers helpful in diagnosing Kawasaki disease in febrile infant: Role of Age-adjusted Z-values of Blood Cells." Korean Circulation Journal **49**(8): 766-768.

Yorifuji, T., et al. (2019). "Early childhood exposure to maternal smoking and Kawasaki Disease: A longitudinal survey in Japan." Science of the Total Environment **655**: 141-146.
Kawasaki disease is the leading cause of acquired childhood heart disease in most developed countries, but the etiology of the disease is unknown. An aberrant immune response to some environmental triggers may play a role and involuntary exposure to tobacco smoke can alter immune functions. We thus prospectively examined the association between early childhood exposure to maternal smoking and the incidence of Kawasaki disease. We used a large, nationwide population-based longitudinal survey ongoing since 2010 and restricted participants to a total of 38,444 children for whom information on maternal smoking was available. Maternal smoking status was ascertained at 6 months of age, and responses to questions about hospital admission for Kawasaki disease between the ages of 6 and 30 months were used as outcome. We conducted binomial log-linear regression analyses adjusting for children's, parental, and residential factors with children of non-smoking mothers as our reference group. Maternal smoking increased the risk of admission, in particular for the period between 6 and 18 months of age, in a dose-dependent manner. Compared with children of non-smoking mothers, the children of mothers who smoked had a risk ratio of 1.83 (95% confidence interval: 1.06, 3.35) for hospital admissions between 6 and 30 months of age and a risk ratio of 2.69 (95% confidence interval: 1.56, 4.64) for hospital admissions between 6 and 18 months of age. Early childhood exposure to maternal smoking may increase the risk of Kawasaki disease hospitalizations in childhood. © 2018 Elsevier B.V.

Yuan, Y. and N. Lu (2019). "Facial nerve palsy presenting as rare neurological complication of Kawasaki disease: A case report." Medicine **98**(34): e16888.
RATIONALE: Facial nerve palsy (FNP) is one of the rare neurologic symptoms of Kawasaki disease (KD), associated with a higher incidence of coronary arteries lesions and may be an indicator of more severe disease. PATIENT CONCERNS: A 3-month-old male infant with persistent fever, irritability, and facial asymmetry. DIAGNOSES: KD with FNP. INTERVENTIONS: The infant received intravenous immunoglobulin (IVIG) (2 g/kg/16 hours) and aspirin (50 mg/kg/day) were started on the 8th day of illness. OUTCOMES: Fever and FNP resolved within 48 hours after IVIG treatment. The inflammatory markers all improved to normal or

near-normal levels before discharge; all infectious studies returned negative. His left facial weakness was unappreciable at day of discharge. LESSONS: FNP associated with KD is an uncommon finding but may indicate an increased risk of coronary artery involvement. KD should always be kept in mind in the differential diagnosis of a child who presents with prolonged unexplained fever, even with incomplete diagnostic features, as well as the need to be aware of unusual manifestations, such as FNP.

Zhang, B., et al. (2019). "Feverless kawasaki disease: A case report and review of the literature." International Journal of Clinical and Experimental Medicine **12**(1): 1160-1164.
Kawasaki disease is an acute systemic inflammatory disease with unknown etiology that affects blood vessels of the whole body during childhood, and is extremely rare. Herein, we report a case of 3-month-old female infant who presented with diarrhea and convulsions but without fever. Physical examination revealed an erythema at the Bacille Calmette-Guerin inoculation site on the left upper arm. Major findings from laboratory tests included increased white blood cell and platelet counts, elevated C-reactive protein concentration, increased erythrocyte sedimentation rate, and elevated B-type natriuretic peptide precursor levels. Cardiac ultrasound showed dilation of bilateral coronary arteries. The patient was diagnosed with atypical kawasaki disease and treated with gamma globulin and aspirin. After treatment, the diarrhea and convulsions were relieved, and all abnormal blood indexes returned to normal ranges. However, the patient still had coronary artery dilation during the 10-month follow-up period. In addition to presenting this rare case, we also review the literature related to feverless kawasaki disease. Copyright © 2019, E-Century Publishing Corporation. All rights reserved.

Zhang, B., et al. (2019). "Kawasaki disease manifesting as bilateral facial nerve palsy and meningitis: a case report and literature review." Journal of International Medical Research **47**(8): 4014-4018.

Zhang, D., et al. (2019). "Respiratory virus associated with surgery in children patients." Respiratory Research **20 (1) (no pagination)**(126).
Background: Viral respiratory infection (VRI) is a common contraindication to elective surgery. Asymptomatic shedding among pediatric surgery patients (PSPs) could potentially lead to progression of symptomatic diseases and cause outbreaks of respiratory diseases. The aim of this study is to investigate the incidence of infection among mild symptomatic PSP group and asymptomatic PSP group after surgical procedure. Method(s): We collected the induced sputum from enrolled 1629 children (under 18 years of age) with no respiratory symptom prior to pediatric surgery between March 2017 and February 2019. We tested 16 different respiratory virus infections in post-surgery mild symptomatic PSP group and asymptomatic PSP group using a quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) assay panel. We analyzed symptom data and quantitative viral load to investigate the association between viruses, symptoms and viral quantity in qRT-PCR-positive PSPs. Result(s): Out of 1629 children enrolled, a total of 204 respiratory viruses were present in 171 (10.50%) PSPs including 47 patients with mild symptoms and 124 with no symptoms after surgery. Commonly detected viruses were human rhino/enterovirus (HRV/EV, 42.19%), parainfluenza virus 3 (PIV3, 24.48%), coronavirus (CoV NL63, OC43, HKU1, 11.46%), and respiratory syncytial virus (RSV, 9.9%). PIV3 infection with a higher viral load was frequently found in PSPs presenting with mild symptoms, progressing to pneumonia with radiographic evidence after surgery. HRV/EV were the most commonly detected pathogens in both asymptomatic and mild symptomatic PSPs. CoV (OC43, HKU1) infections with a higher viral load were mostly observed in asymptomatic PSPs progressing to alveolar or interstitial infiltration. Conclusion(s): Our study suggested that PIV3 is a new risk factor for VRI in PSPs. Employing a more comprehensive, sensitive and quantitative method should be considered for preoperative testing of respiratory viruses in order to guide optimal surgical timing. Copyright © 2019 The Author(s).

Zhang, Q., et al. (2019). "Kawasaki disease shock syndrome: A report of two cases and literature

review." Pediatric Investigation **3**(2): 81-85.
Importance: Kawasaki disease shock syndrome (KDSS) is a rare Kawasaki disease (KD) manifestation. The pediatricians are not aware of the full range of clinical characteristics of KDSS. Objective(s): We aimed to investigate the clinical features, diagnosis and treatment of KDSS in two patients and we included a literature review. Method(s): We collected and analyzed the clinical data for two patients with KDSS. Additionally, using "Kawasaki diseases shock syndrome" as a key phrase, we searched PubMed, Biotechnology Information and Wanfang Data Knowledge Service Platform databases for any similar reports between January 2009 and March 2017. Result(s): Both of our patients diagnosed with KD developed sustained hypotension during the course of intravenous immunoglobulin treatment, as well as hypoalbuminemia, and increased C-reactive protein and brain natriuretic peptide levels during hypotension. Both patients responded well to fluid resuscitation and inotropic support. No aneurysms formed in either patient during follow-up. We reviewed two related studies in Chinese and 11 studies in English. Interpretation(s): KD may present with severe shock, and requires proper diagnosis and rapid treatment. The prognosis for most patients with KDSS is excellent. Copyright © 2019 Chinese Medical Association. Pediatric Investigation published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.

Zhang, X., et al. (2019). "Functional immunoregulation by heme oxygenase 1 in juvenile autoimmune diseases." Current Gene Therapy **19**(2): 110-116.
An autoimmune disease is an inflammatory condition in which the human body's immune system attacks normal cells, resulting in decreased and abnormal immune function, which eventually leads to tissue damage or organ dysfunction. In the field of medicine, especially in pediatrics, knowledge about autoimmune diseases is still inadequate. Some common juvenile autoimmune diseases such as Henoch-Schonlein purpura, systemic juvenile idiopathic arthritis, mucocutaneous lymph node syndrome, and autoimmune encephalitis cause considerable public concern. Recent studies revealed that heme oxygenase 1 (HO-1), an enzyme that participates in heme degradation, plays a critical role in the pathogenesis and may regulate autoimmunity. Firstly, it may promote the differentiation of T lymphocytes into CD4⁺CD25⁺ regulatory T cells and may be associated with changes in the ratios of cytokines (Th1/Th2 and Th17/Treg) as well. Secondly, HO-1 can regulate the immune system through the secretion of proteins such as transforming growth factors and interleukins. Moreover, increasing the expression of HO-1 can improve vascular function by increasing antioxidant levels. Thus, HO-1 may provide a theoretical basis and guidance for therapeutic management of juvenile autoimmune diseases. Copyright © 2019 Bentham Science Publishers.

Zhao, Q. M., et al. (2019). "Systemic artery aneurysms and kawasaki disease." Pediatrics **144**(6).
BACKGROUND: Coronary artery aneurysms (CAAs) are a well-known complication of Kawasaki disease (KD), but there are no data on incidence or outcomes of systemic artery aneurysms (SAAs) in the current era. METHODS: From April 1, 2016, to March 31, 2019, we screened for SAAs in 162 patients with KD at risk for SAAs with magnetic resonance angiography or peripheral angiography and analyzed incidence and early outcomes of SAAs. RESULTS: Twenty-three patients had SAAs, demonstrating an incidence of 14.2% (23 of 162) in patients who were screened at 1 month after onset. The proportion of patients with SAAs was estimated to be 2% (23 of 1148) of all patients with KD. The median age at onset of KD with SAAs was 5 months. All patients with SAAs had CAAs, with z scores .8. Of patients with giant CAAs, 38.6% (17 of 44) had SAAs. A total of 129 SAAs occurred in 17 different named arteries. The most common sites for SAAs were the axillary (18.6%), common iliac (12.4%), and brachial (11.6%) arteries. During a median follow-up time of 6 months, 92.9% (79 of 85) of SAAs had some degree of regression, with 80% (68 of 85) of SAAs returning to normal. The overall regression rate was higher for medium to large SAAs than for medium to giant CAAs. CONCLUSIONS: Although the incidence of SAAs may not be as dramatically reduced as we expected compared with previous data, SAAs have a high regression rate during short-term follow-up. © 2019 by the American Academy of

Pediatrics.

Zhao, Y., et al. (2019). "Comparison of viral and epidemiological profiles of hospitalized children with severe acute respiratory infection in Beijing and Shanghai, China." BMC Infectious Diseases **19 (1) (no pagination)**(729).
Background: No comparison data have been reported on viral and epidemiological profiles of hospitalized children with severe acute respiratory infection (SARI) in Beijing or Shanghai, China. Method(s): We collected 700 nasopharyngeal aspirates (NPA) from hospitalized children with SARI in Beijing (northern China) and Shanghai (southern China). Multiple respiratory viruses (including 15 common viruses) were screened by validated polymerase chain reaction (PCR) or real-time reverse transcription-PCR assays and confirmed by sequencing. Demographic data and the distribution of viral infections were also examined. Result(s): Of 700 samples, 547 (78.1%) tested positive for viral infections. The picornaviruses (PIC), which included rhinovirus (RV) and enterovirus (EV), were the most common (34.0%), followed by respiratory syncytial virus (RSV) (28.3%), human bocavirus (HBoV) (19.1%), adenovirus (ADV) (13.7%), human coronaviruses (HCoV) (10.7%), influenza A and B (8.9%), parainfluenza virus (PIV 1-3) (7.9%), and human metapneumovirus (HMPV) (5.0%). PIC (RV/EV) and RSV were the most prevalent etiological agents of SARI in both cities. The total and age-matched prevalence of RSV, HCoV, and hMPV among SARI children under 5 years old were significantly higher in Beijing than in Shanghai. Different age and seasonal distribution patterns of the viral infections were found between Beijing and Shanghai. Conclusion(s): Viral infection was tested and shown to be the most prevalent etiological agent among children with SARI in either the Beijing or the Shanghai area, while showing different patterns of viral and epidemiological profiles. Our findings provide a better understanding of the roles of geographic location and climate in respiratory viral infections in hospitalized children with SARI. Copyright © 2019 The Author(s).

Zhou, Y. L., et al. (2019). "A study of human coronavirus infections in children with community-acquired pneumonia from 2015 to 2016 in Zhejiang, China." Pediatric Pulmonology **54 (Supplement 1)**: S89-S90.
Objective: To study human coronavirus (HCOVS) infections in children with community-acquired pneumonia (CAP) in Zhejiang. Method(s): From November 2014 to November 2016, the nasopharyngeal aspirations (NPAS) or throat swabs from children diagnosed with CAP were collected from the Children's Hospital, Zhejiang University School of Medicine. Respiratory specimens were screened for 18 respiratory viruses, including HCOVS (OC43, 229E, NL63 and HKU1) by Luminex Liquid Chip Technology. In addition, the epidemiological characteristics, severe pneumonia and complications of children infected with HCOVS were analyzed. Result(s): A total of 404 cases of CAP children with NPAS or pharyngeal swabs were collected. The total virus detection rate was 52.23% (211/404), while the HCOVS detection rate was 0.5% (2/ 404). One case was HCOV-Oc43, and the other was Hcov-Hku1. Neither of the two children was infected with HCOVS alone, and enteroviruses and rhinoviruses were detected in both cases. The age of onset of HCOV-positive children in both cases was less than 1 year old, and both cases were severe pneumonia. Conclusion(s): HCOVS infections are rare in children with CAP in Zhejiang. HCOV S infections can cause severe pneumonia.

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Al-Nakib, W., et al. (2018). "Transcriptional stimulation of antiviral response components by the structural and accessory human coronavirus OC43 proteins." Open Forum Infectious Diseases **5 (Supplement 1)**: S231.
Background. In Kuwait, human coronavirus OC43 (HCoV-OC43) causes 25-30% of common cold, and 8.8% of respiratory infections in hospitalised patients. It is also associated with severe respiratory symptoms in infants, elderly, and immunocompromised patients. Our previous results

showed that the expression of antiviral genes in human embryonic kidney (HEK) 293 cells is downregulated in the presence of HCoV-OC43 proteins. To understand the role of HCoV-OC43 proteins in antagonizing antiviral responses of the host, we investigated the effect of HCoV-OC43 structural and accessory proteins on the transcriptional activation of interferon-stimulated response element (ISRE), interfer-on-beta (IFN-beta) promoter, and nuclear factor kappa B response element (NF-kappaB-RE). Methods. HCoV-OC43 ns2a, ns5a, membrane (M), and nucleocapsid (N) mRNA were amplifed and cloned into the pAcGFP1-N expression vector, followed by trans-fection in HEK-293 cells. Two days post-transfection, the cells were co-transfected with a reporter vector containing frefy luciferase under the control of ISRE, IFN-beta promoter, or NF-kappaB-RE. Renilla luciferase vector was used as an internal control for transfection efciency. Following 24 hours of incubation, the cells were treated with either IFN or tumour necrosis factor (TNF) for 6 hours. Tereafer, promoter activity was assayed using the dual-luciferase reporter assay system. Infuenza NS1 protein was used as positive control for antagonism. Results. The transcriptional activity of ISRE, IFN-beta promoter, and NF-kappaB-RE was downregulated in the presence of ns2a, ns5a, M, or N protein as there was a sharp fall in frefy luciferase levels. Overall, HCoV-OC43 proteins reduced frefy luciferase levels for ISRE and IFN-beta promoter by at least ten fold, whereas for NF-kappaB-RE the frefy luciferase levels were reduced by at least fvefold. Conclusion. HCoV-OC43 has the ability to block the activation of diferent antiviral signaling pathways.

Altammar, F. and B. Lang (2018). "Kawasaki Disease in the neonate: case report and literature review." Pediatric Rheumatology Online Journal **16**(1): 43.
BACKGROUND: Kawasaki Disease (KD), the leading cause of acquired heart disease in children in the developed world, is extremely rare in neonates. We present a case of incomplete KD in a neonate and a review of the literature on neonatal KD.
CASE PRESENTATION: A previously healthy full term 15 day old Caucasian male with an unremarkable antenatal and perinatal history, presented on Day 2 of illness with fever, rash, irritability, and poor feeding. Examination revealed fever (39.6C), tachycardia, tachypnea, extreme irritability, and a generalized maculopapular rash, but was otherwise normal. His complete blood count, CRP and ESR were normal. Empiric intravenous antibiotics and acyclovir resulted in no improvement. On day 4, he had ongoing fever and developed recurrent apnea, required supplemental oxygen, and was transferred to the pediatric intensive care unit. On day 6, he developed bilateral non-purulent conjunctivitis, palmar erythema, bilateral non-pitting edema and erythema of his feet, and arthritis. His full septic work-up and viral studies were negative. On Day 7 he was treated with intravenous immunoglobulin, and over the next 48 h his symptoms including extremity edema resolved, he no longer required supplemental oxygen, and fever did not recur. On day 9 of illness he had marked thrombocytosis. Subsequently, he developed distal extremity desquamation. Repeated echocardiograms excluded the presence of coronary artery aneurysms (CAA).
CONCLUSIONS: We believe this to be a rare case of incomplete KD in a neonate, in which timely IVIG administration led to resolution of the acute illness and may have prevented CAA. A comprehensive English-language medical literature review of KD presenting in the neonatal period revealed only fifteen case reports. Cases often presented with incomplete KD, and a number had atypical laboratory features including a normal CRP in the acute phase, similar to what was seen in our patient. This case and our literature review should increase awareness that KD can rarely occur in neonates, often presenting atypically. Recognizing KD in a neonate enables appropriate treatment that can result in resolution of symptoms and may decrease the risk of cardiac complications.

Boey, K., et al. (2018). "Seroprevalence of rodent pathogens in wild rats from St. Kitts." Journal of the American Association for Laboratory Animal Science **57 (5)**: 597.
Peridomestic and wild rats may pose an animal biosecurity risk to laboratory rodent colonies due to the possibility of pathogen spillovers. Thus, routine pathogen surveillance in the wild

population is essential to maintain a microbiologically defned rodent colony health status. A pilot surveillance study was conducted to gather information on the exposure of selected pathogens in wild rats inhabiting the Caribbean island of St. Kitts. Serum samples collected from 22 of 29 rats captured were tested for the presence of antibodies to various rodent pathogens using a rat serology panel. The rat species were identifed as Rattus norvegicus (11/29; 37.9%) and Rattus rattus (18/29; 62.1%) based on amplification and sequencing of the mitochondrial cytochrome b gene. Exposure to 11 of 19 (57.9%) pathogens tested in the panel was detected, and 21 of the 22 (95.5%) rats sampled were positive for 1 or more pathogens tested. Presence of antibodies to the following pathogens was detected: mouse adenovirus type 2 (16/22; 72.7%), Kilham's rat virus (15/22; 68.2%), cilia-associated respiratory bacillus (13/22; 59.1%), reovirus type 3 (9/22; 40.9%), rat parvovirus (4/22; 18.2%), rat minute virus (4/22; 18.2%), rat theilovirus (2/22; 9.1%), infectious diarrhea of infant rats (1/22; 4.5%), Clostridium piliforme (4/22; 18.2%), Mycoplasma pulmonis (4/22; 18.2%), and Pneumocystis carinii (1/22; 4.5%). Antibodies to Hantaan virus, lymphocytic choriomeningitis virus, Toolan's H-1 virus, mouse adenovirus type 1, pneumonia virus of mice, rat coronavirus/sialodacryoadenitis virus, Sendai virus, and Encephalitozoon cuniculi were not detected. This study provides the first evidence of exposure to various rodent pathogens in wild rats on the island of St. Kitts.

Bozio, C. H., et al. (2018). "Use of multiple imputation to estimate the proportion of respiratory virus detections among patients hospitalized with community-acquired pneumonia." Open Forum Infectious Diseases **5 (4) (no pagination)**(61).
Background: Real-time polymerase chain reaction (PCR) on respiratory specimens and serology on paired blood specimens are used to determine the etiology of respiratory illnesses for research studies. However, convalescent serology is often not collected. We used multiple imputation to assign values for missing serology results to estimate virus-specific prevalence among pediatric and adult community-acquired pneumonia hospitalizations using data from an active population-based surveillance study. Method(s): Presence of adenoviruses, human metapneumovirus, influenza viruses, parainfluenza virus types 1-3, and respiratory syncytial virus was defined by positive PCR on nasopharyngeal/oropharyngeal specimens or a 4-fold rise in paired serology. We performed multiple imputation by developing a multivariable regression model for each virus using data from patients with available serology results. We calculated absolute and relative differences in the proportion of each virus detected comparing the imputed to observed (nonimputed) results. Result(s): Among 2222 children and 2259 adults, 98.8% and 99.5% had nasopharyngeal/oropharyngeal specimens and 43.2% and 37.5% had paired serum specimens, respectively. Imputed results increased viral etiology assignments by an absolute difference of 1.6%-4.4% and 0.8%-2.8% in children and adults, respectively; relative differences were 1.1-3.0 times higher. Conclusion(s): Multiple imputation can be used when serology results are missing, to refine virus-specific prevalence estimates, and these will likely increase estimates.

Cai, K., et al. (2018). "[Research advances in the pathogenesis of familial Kawasaki disease]." Zhongguo Dangdai Erke Zazhi **20**(7): 594-597.
Kawasaki disease has become the leading cause of acquired heart disease in children in North America and Japan. The incidence rate of Kawasaki disease varies significantly across regions and races. The first-degree relatives of patients with Kawasaki disease have a significantly higher risk of this disease than the general population. This article reviews the onset of familial Kawasaki disease and possible pathogenesis.

Colomba, C., et al. (2018). "Intestinal Involvement in Kawasaki Disease." Journal of Pediatrics **202**: 186-193.
OBJECTIVES: To describe a case of Kawasaki disease with intestinal involvement and to analyze other published reports to define clinical characteristics, diagnostic issues, and therapeutic approaches of gastrointestinal involvement in Kawasaki disease.

STUDY DESIGN: A computerized search without language restriction was conducted using PubMed and SCOPUS. An article was considered eligible for inclusion in the systematic review if it reported data on patient(s) with intestinal involvement in Kawasaki disease. Our case was also included in the analysis.
RESULTS: Thirty-three articles reporting 48 cases of Kawasaki disease with intestinal involvement were considered. Fever, abdominal pain, and vomiting were the most frequent symptoms observed and typical Kawasaki disease signs and symptoms appeared after intestinal complaints in all cases. Plain radiographs, ultrasonography, and computed tomography showed pseudo-obstruction as the most frequent sign of gastrointestinal involvement; 25 patients underwent surgery. Cardiac involvement was documented in 21 cases. All but three patients received medical treatment with immunoglobulin intravenous or aspirin. The outcome was good in 28 patients; 7 patients showed persistence of coronary artery abnormalities; 1 patient developed cyanosis, and later, left hand and forefoot gangrene; 3 patients died.
CONCLUSIONS: The diagnosis and treatment of Kawasaki disease might be delayed if intestinal symptoms appear before the characteristic clinical features of Kawasaki disease, thus, increasing the risk of cardiac complications. Furthermore, patients may undergo unnecessary invasive procedures. Pediatricians and pediatric surgeons, therefore, should consider Kawasaki disease among diagnoses in children with fever, abdominal symptoms, and radiologic findings of pseudo-obstruction.

Cowling, B. J., et al. (2018). "Influenza-like illness and viral aetiology in Hong Kong children." Hong Kong medical journal = Xianggang yi xue za zhi **24**(5 Supplement 6): 12-15.

Dionne, A. and N. Dahdah (2018). "Myocarditis and Kawasaki disease." International Journal of Rheumatic Diseases **21**(1): 45-49.
Kawasaki disease (KD) is the most common vasculitis of childhood. Coronary artery aneurysms and myocarditis are common cardiovascular complications of KD. While evidence of myocarditis can be found in all patients with KD on histology specimens, only a minority of patients are clinically symptomatic. Occasionally children can present with KD shock syndrome and hemodynamic instability as a result of decreased systolic function and vasoplegia. Several children with KD have depressed shortening fraction on echocardiography. Increased end-systolic and end-diastolic dimensions, strain abnormalities and diastolic dysfunction are also found in a significant proportion of patients. Echocardiographic signs of myocarditis improve after the acute phase and do so more quickly in patients who have received intravenous immunoglobulins, as opposed to those given only aspirin. Normalization of systolic function is typically observed over long-term follow-up; however, more subtle abnormalities (strain, diastolic function) may persist. It is noteworthy that myocarditis associated with KD can occur in absence of coronary artery abnormalities. KD myocarditis can result in long-term sequelae.

Elfving, K., et al. (2018). "Pathogen Clearance and New Respiratory Tract Infections Among Febrile Children in Zanzibar Investigated With Multitargeting Real-Time Polymerase Chain Reaction on Paired Nasopharyngeal Swab Samples." The Pediatric infectious disease journal **37**(7): 643-648.
BACKGROUND: New molecular methods have revealed frequent and often polymicrobial respiratory infections in children in low-income settings. It is not known whether presence of multiple pathogens is due to prolonged infections or to frequent exposure. The aim of this study was to analyze short-term pathogen clearance from nasopharynx and the rate of new respiratory tract infections in febrile preschool children. METHOD(S): Children (n = 207) with uncomplicated acute febrile illness 2-59 months of age presenting to a health center in Zanzibar, Tanzania, April-July 2011, were included. Paired nasopharyngeal swab samples, collected at enrolment and after 14 days, were analyzed by multiple real-time polymerase chain reaction for Adenovirus, bocavirus, Bordetella pertussis, Chlamydophila pneumoniae, Coronaviruses, Enterovirus, influenza A and B virus, metapneumovirus, measles virus, Mycoplasma pneumoniae, parainfluenza virus,

Parechovirus, respiratory syncytial virus and Rhinovirus. An age-matched and geographically matched healthy control group (n = 166) underwent nasopharyngeal sampling on 1 occasion. RESULT(S): At baseline, 157/207 (76%) patients had at least 1 pathogen detected, in total 199 infections. At follow-up (day 14), 162/199 (81%) of these infections were not detected, including >95% of the previously detected infections with Enterovirus, influenza A virus, influenza B virus, metapneumovirus or parainfluenza virus. Still 115 (56%) children were positive for at least 1 pathogen at follow-up, of which 95/115 (83%) were not found at baseline. Detection of influenza B on day 14 was significantly associated with fever during follow-up. CONCLUSION(S): The results suggest that children with acute febrile illness in Zanzibar rapidly clear respiratory tract infections but frequently acquire new infections within 14 days.

Fabi, M., et al. (2018). "Gastrointestinal presentation of kawasaki disease: A red flag for severe disease?" PLoS ONE **13**(9).
Background Kawasaki disease (KD) is a febrile systemic vasculitis of unknown etiology and the main cause of acquired heart disease among children in the developed world. To date, abdominal involvement at presentation is not recognized as a risk factor for a more severe form of the disease. Objective To evaluate whether presenting abdominal manifestations identify a group at major risk for Intravenous immunoglobulin (IVIG)-resistance and coronary lesions. Methods Retrospective study of KD patients diagnosed between 2000 and 2015 in 13 pediatric units in Italy. Patients were divided into 2 groups according to the presence or absence of abdominal manifestations at onset. We compared their demographic and clinical data, IVIG-responsiveness, coronary ectasia/aneurysms, laboratory findings from the acute and subacute phases. Results 302 patients (181 boys) were enrolled: 106 patients with, and 196 patients without presenting abdominal features. Seasonality was different between the groups (p = 0.034). Patients with abdominal manifestations were younger (p = 0.006) and more frequently underwent delayed treatment (p = 0.014). In the acute phase, patients with abdominal presentation had higher platelet counts (PLT) (p = 0.042) and lower albuminemia (p = 0.009), while, in the subacute phase, they had higher white blood cell counts (WBC) and PLT (p = 0.002 and p < 0.005, respectively) and lower red blood cell counts (RBC) and hemoglobin (Hb) (p = 0.031 and p 0.009). Moreover, the above mentioned group was more likely to be IVIG-resistant (p < 0.005) and have coronary aneurysms (p = 0.007). In the multivariate analysis, presenting abdominal manifestations, age younger than 6 months, IVIG- resistance, delayed treatment and albumin concentration in the acute phase were independent risk factors for coronary aneurysms (respectively p<0.005, <0.005, = 0.005 and 0.009). Conclusions This is the first multicenter report demonstrating that presenting gastrointestinal features in KD identify patients at higher risk for IVIG-resistance and for the development of coronary aneurysms in a predominantly Caucasian population. © 2018 Fabi et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Gamez-Gonzalez, L. B., et al. (2018). "Kawasaki disease shock syndrome: Unique and severe subtype of Kawasaki disease." Pediatrics International **60**(9): 781-790.
Background: Kawasaki disease shock syndrome (KDSS) is an uncommon presentation of Kawasaki disease (KD). KDSS has been associated with more severe markers of inflammation, coronary abnormalities and i.v. immunoglobulin (IVIG) resistance. Methods: A retrospective, descriptive study of children with KDSS in two hospitals was performed. Relevant articles about KD and shock were collected, and demographic data, clinical presentation, laboratory variables, echocardiogram findings, treatment and special features were analyzed when available. Twelve patients diagnosed with KDSS were retrospectively reviewed from two centers in Mexico, along with 91 additional cases from the literature. Results: Seventy-two patients presented with complete KD (69.9%), and 30.1% (31/103) had unusual KD manifestations. The most frequent diagnosis at the time of admission was toxic shock syndrome (TSS; n = 20). Sixteen of the 20 had coronary artery abnormalities. Overall, abnormalities in the coronary arteries were

documented in 65% of the patients. The mortality rate was 6.8%. Conclusion: The presence of coronary aneurysms was significantly and positively correlated with male gender, IVIG resistance, inotrope treatment, cardiac failure, abdominal pain and neurological symptoms. IVIG-resistant patients had higher neutrophil : lymphocyte ratio. Abdominal symptoms, hypoalbuminemia and elevated C-reactive protein were present in almost all of the patients. Multisystem involvement with atypical presentation in KDSS is frequent. An important differential diagnosis is TSS. Mechanical ventilation, gastrointestinal and neurological symptoms were associated with IVIG resistance and the presence of coronary aneurysms. The first line of treatment includes IVIG and pulse corticosteroids; in severe cases, infliximab, anakinra, cyclosporine or plasmapheresis are alternative treatment options. © 2018 Japan Pediatric Society

Goh, Y. G., et al. (2018). "Coronary manifestations of Kawasaki Disease in computed tomography coronary angiography." Journal of cardiovascular computed tomography **12**(4): 275-280.
Coronary arteritis in Kawasaki disease can lead to serious complications such myocardial infarction and sudden death. The identification of coronary manifestations with a method that is minimally invasive and of low radiation exposure is therefore important in paediatric patients with Kawasaki disease. Coronary CT angiography can be an attractive alternative to invasive coronary angiography. This paper describes imaging techniques for coronary CT angiography in pediatric patients and demonstrates the spectrum of cardiovascular manifestations in patients with Kawasaki disease.

Huang, X., et al. (2018). "Is aspirin necessary in the acute phase of Kawasaki disease?" Journal of Paediatrics and Child Health **54**(6): 661-664.
Aim: To explore whether aspirin is necessary for treatment in the acute phase of Kawasaki disease (KD). Methods: Nine hundred ten patients who fulfilled the criteria of KD and maintained follow-up for 2 years were included in this retrospective study. All patients initially received a single dose of intravenous immunoglobulin (IVIG, 2 g/kg) in the acute phase. Patients were classified into three groups according to the doses of aspirin. Group 1 included 152 cases treated with IVIG only in the acute phase. Group 2 included 672 cases treated with IVIG plus 3–5 mg/kg/day aspirin as the low-dose group, and group 3 included 86 cases treated with IVIG plus 30–50 mg/kg/day aspirin as the moderate-dose group. Changes in inflammatory indices and platelet count after treatment were compared by one-way analysis of variance or analysis of covariance to analyse the clinical effect of aspirin in acute KD. The relationship between aspirin use and coronary artery lesion complications was analysed by logistic regression. Results: There was no significant difference among the three groups in terms of the anti-inflammation effect revealed by C-reactive protein level, white blood cell count, percentage of neutrophils in white blood cells, decreasing platelet count or prevention of the formation of coronary artery lesion. Conclusions: The role of aspirin in the treatment of the acute phase of KD should be questioned as a definite benefit has not been shown in our study. Further prospective studies incorporating large multicentre samples of patients are needed to confirm this finding. © 2017 Paediatrics and Child Health Division (The Royal Australasian College of Physicians)

Jeudy, J., et al. (2018). "Spectrum of Coronary Artery Aneurysms: From the Radiologic Pathology Archives." Radiographics **38**(1): 11-36.
Advances in medical diagnosis reveal that coronary artery aneurysms (CAAs) may develop in several clinical scenarios and manifest variable symptoms, imaging appearances, and outcomes. Aneurysms are pathologically classified into three groups: atherosclerotic, inflammatory, and noninflammatory. The last category is associated with congenital, inherited, and connective tissue disorders. Overlap exists among the groups, because secondary atherosclerotic change may be present in an aneurysm of any cause. Atherosclerosis is the most common cause of CAAs in adults, and inflammation is considered the underlying mechanism. In children, Kawasaki disease is the most likely cause of CAAs. In both conditions, the aneurysms are usually multiple and affect more than one coronary artery. Mycotic (infectious), iatrogenic, and cocaine-induced CAAs

are also well documented. Most CAAs are discovered incidentally, but potential cardiovascular complications include thrombosis, occlusion, fistula formation, rupture, myocardial infarction, and cardiac tamponade. Imaging modalities to evaluate a suspected CAA include transthoracic echocardiography, angiographic cardiac catheterization, electrocardiographically gated computed tomographic angiography, cardiac magnetic resonance (MR) imaging, and MR angiography. Management is usually individualized, and options include surveillance, anticoagulant therapy, percutaneous stent or coil placement, surgical resection, and coronary artery bypass grafting.

Juliusson, P. B., et al. (2018). "Real-world safety data in a cohort of children with noonan syndrome treated with growth hormone: Final results from nordinet international outcome study (IOS) and answer program." Hormone Research in Paediatrics **90 (Supplement 1)**: 505-506.
Objectives: Current safety data do not indicate an association of GH therapy with increased risk for development/progression of tumours, or worsening of congenital cardiac conditions in individuals with Noonan syndrome (NS); however, data are limited. This report describes real-world safety data on GH therapy in paediatric patients with NS. Method(s): Two complementary non-interventional, multicentre studies, NordiNet IOS (NCT00960128) and ANSWER Program (NCT01009905), evaluated long-term effectiveness and safety of Norditropin (somatropin; Novo Nordisk A/S) as prescribed by treating physicians in a real-world clinical setting. Safety events (serious adverse events not related to therapy [SAEs], non-serious and serious adverse reactions [NSARs/SARs]) were evaluated in GH-treated patients with NS (n=412) enrolled in these studies. Result(s): Baseline characteristics [% or mean (SD)]: female, 29.1%; age at treatment start, 9.48 (3.92) years; height standard deviation score (SDS), -2.65 (0.95); weight SDS, -2.03 (1.31); IGFI SDS, -1.13 (1.62); IGF-binding protein-3 SDS, -0.91 (1.72); GH dose (mug/kg/day), 43.9 (13.7); GH na?ve (68.5%). Mean (SD) followup time on GH treatment, 3.1 (2.6) years and mean GH dose (mug/ kg/day) during treatment, 46.6 (13.6). A total of 35 (8.5%) patients were diagnosed with cardiovascular (CV) comorbidities prior to GH start, with pulmonary valve stenosis (n=19) and atrial septal defect (n=5) being most frequent. After start of GH treatment, five patients were diagnosed with (potentially pre-existing) CV comorbidities: unspecified CV disease (n=3), ruptured abdominal aortic aneurysm (n=1), pulmonary valve stenosis (n=1). Overall, 31 safety events were reported in 21 patients (#events/#patients): NSARs, 21/15; SARs, 2/1; SAEs, 8/5. Most patients with a safety event reported one occurrence (16/21). For patients with safety events, mean (SD) age at treatment start was 9.90 (4.13) years and baseline height SDS was -3.14 (0.82). The most common NSARs were headache (six events/six patients) and arthralgia (five events/ three patients). Two SARs (brain neoplasm; metastases to spine) were reported in one patient. The SAEs reported: giant cell epulis (one patient), scoliosis and spinal fusion surgery (both in one patient), moyamoya disease (one patient), glioneuronal tumour (one patient), and aggravated glioneuronal tumour and epilepsy (one patient). Glioneuronal tumours have previously been associated with Noonan syndrome and RASopathies. No cardiac safety events were reported in these patients. Conclusion(s): These data suggest a favourable safety profile of GH therapy in patients with NS, including those with pre-existing cardiovascular comorbidities.

Kim, S. H., et al. (2018). "Clinical aspects of scrub typhus initially misdiagnosed as Kawasaki disease." Iranian Journal of Pediatrics **28**(2).
Objectives: To analyze the clinical characteristics of scrub typhus (ST) initially misdiagnosed as Kawasaki disease (KD) in children. Methods: This study was conducted through a review of medical records of children with ST from March 2005 to June 2015. Results: Among 182 incomplete KD patients, 11 patients were ST. Red lips, strawberry tongue, and BCG site redness were not reported. Presence of eschars was reported in 5 patients. Group 1 patients (n = 6) were initially treated by using intravenous immunoglobulin (IVIG) and among them, one patient had an eschar after IVIG use. Group 2 patients (n = 5) were also initially diagnosed as KD but were not treated because eschar was detected in four patients before use of IVIG. One patient had no eschar but had a positive serologic test before IVIG use. Conclusions: When children have

symptoms similar to KD but without red lips and strawberry tongue, clinicians should search for an eschar and perform serologic tests for ST. © 2018, Iranian Journal of Pediatrics.

Koca, T., et al. (2018). "Kawasaki disease in a 9-year old girl presenting with febrile cholestasis: case report and review of literature." International Journal of Rheumatic Diseases **21**(11): 2046-2049.
Kawasaki disease is a systemic vasculitis that develops during childhood, especially in those younger than 5 years. Gastrointestinal involvement does not belong to the classic diagnostic criteria. We reported here, a 9-year old girl who presented with febrile cholestasis, and developed a medium right coronary artery aneurysm despite intravenous immunoglobulin administration on the 9th day of fever. Hepatobiliary ultrasonographic evaluation revealed normal findings. Seroimmunologic markers of cholestasis were negative. Her clinical feature was ameliorated shortly after a second dose of intravenous immunoglobulin administration. We consider that a high index of suspicion of Kawasaki disease could prevent delayed diagnosis and complications.

Li, X., et al. (2018). "Predictors of intravenous immunoglobulin-resistant Kawasaki disease in children: a meta-analysis of 4442 cases." European Journal of Pediatrics **177**(8): 1279-1292.
The purpose of this study was to identify the clinical features and laboratory factors that are predictive of intravenous immunoglobulin (IVIG)-resistant Kawasaki disease. Multiple databases were searched for relevant studies on IVIG-resistant Kawasaki disease published from January 2002 to April 2017. Eligible studies were retrieved by manual review of the references. Stata 12 was used for the meta-analysis. Weighted mean differences and odds ratios with 95% confidence intervals were calculated for several indices. Twenty-eight studies involving 26,260 patients comprising 4442 IVIG-resistant Kawasaki disease patients and 21,818 IVIG-sensitive Kawasaki disease patients were included. The meta-analysis showed that the erythrocyte sedimentation rate (ESR) in the IVIG-resistant group was significantly higher than that in the IVIG-sensitive group, and that platelet count and hemoglobin levels were significantly lower in the IVIG-resistant group. The patients with oral mucosa alterations, cervical lymphadenopathy, swelling of the extremities, polymorphous rash, and initial administration of IVIG ≤ 4.0 days after the onset of symptoms were more likely to be IVIG resistant. Conclusion: The initial administration of IVIG ≤ 4.0 days after the onset of symptoms increased ESR and decreased hemoglobin and platelet counts, oral mucosa alterations, cervical lymphadenopathy, swelling of the extremities, and polymorphous rash and are the risk factors for IVIG-resistant Kawasaki disease.What is Known:• Recent reports on this topic are about aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transferase, total bilirubin, white blood cells, platelets, erythrocyte sedimentation rate (ESR), polymorphonuclear leukocytes (PMN), C-reactive protein (CRP), pro-brain natriuretic peptide (BNP), albumin, and sodium as the risk factors in the IVIG-resistant Kawasaki disease; however, no studies have been published on clinical features as predictors of IVIG resistance.What is New:• This meta-analysis identified the clinical features, the initial administration of IVIG ≤ 4.0 days after the onset of symptoms, and much more comprehensive laboratory indicators, such as hemoglobin, as predictors of IVIG-resistant Kawasaki disease. © 2018, The Author(s).

Liu, Y. C., et al. (2018). "State-of-the-art acute phase management of Kawasaki disease after 2017 scientific statement from the American Heart Association." Pediatrics & Neonatology **59**(6): 543-552.
Kawasaki disease (KD) has become the most common form of pediatric systemic vasculitis. Although patients with KD received intravenous immunoglobulin (IVIG) therapy, coronary arterial lesions (CALs) still occurred in 5%-10% of these patients during the acute stage. CALs may persist and even progress to stenosis or obstruction. Therefore, CALs following KD are currently the leading cause of acquired heart diseases in children. The etiology of CALs remains unknown despite more than four decades of research. Two unsolved problems are IVIG unresponsiveness and the diagnosis of incomplete KD. The two subgroups of KD patients with these problems have

a high risk of CAL. In April 2017, the American Heart Association (AHA) updated the guidelines for the diagnosis, treatment, and long-term management of KD. Compared with the previous KD guidelines published in 2004, the new guidelines provide solutions to the aforementioned two problems and emphasize risk stratification by using coronary artery Z score systems, as well as coronary severity-based management and long-term follow-up. Therefore, in this study, we merged the AHA Scientific Statement in 2017 with recent findings for Taiwanese KD patients to provide potential future care directions for Taiwanese patients with KD.

Marchesi, A., et al. (2018). "Kawasaki disease: Guidelines of Italian Society of Pediatrics, part II - Treatment of resistant forms and cardiovascular complications, follow-up, lifestyle and prevention of cardiovascular risks." Italian Journal of Pediatrics **44**(1).
This second part of practical Guidelines related to Kawasaki disease (KD) has the goal of contributing to prompt diagnosis and most appropriate treatment of KD resistant forms and cardiovascular complications, including non-pharmacologic treatments, follow-up, lifestyle and prevention of cardiovascular risks in the long-term through a set of 17 recommendations. Guidelines, however, should not be considered a norm that limits the treatment options of pediatricians and practitioners, as treatment modalities other than those recommended may be required as a result of peculiar medical circumstances, patient's condition, and disease severity or individual complications. © 2018 The Author(s).

Marrani, E., et al. (2018). "How Should We Classify Kawasaki Disease?" Frontiers in Immunology **9**: 2974.
The exact classification of Kawasaki disease (KD) has been debated. Infectious disease specialists have claimed it as an infection with a classic immune responses to an as yet unidentified pathogen that localizes to the coronary arteries. Others have favored an autoreactive hypothesis that KD is triggered by an antigen that shares homology with structures in the vascular wall, and molecular mimicry resulting in an immune response directed to that tissue. Rheumatologists have classified it as a systemic vasculitis, while some immunologists have stressed the robust nature of the innate immune response that causes both systemic inflammation as well as damage to the coronary arterial wall and questioned whether KD falls within the spectrum of autoinflammatory diseases. This review will describe the evidences available up to now regarding these hypotheses.

McCrindle, B. W. and B. Cifra (2018). "The role of echocardiography in Kawasaki disease." International Journal of Rheumatic Diseases **21**(1): 50-55.
Kawasaki disease (KD) is an acute, self-limited vasculitis affecting young children. It can result in coronary artery abnormalities in a significant proportion of patients, especially if the diagnosis is missed or treatment gets delayed. Echocardiography is the imaging modality of choice for detection of coronary artery abnormalities and assessment of myocardial function. It is also useful for characterization and risk stratification of patients with KD. Echocardiography should be performed at the time of diagnosis and then again at 1-2 weeks and 4-6 weeks after treatment, for uncomplicated cases who do not have significant coronary artery involvement. Use of a standardized imaging protocol is necessary to detect and characterize coronary artery abnormalities, including standardization of measurements (Z scores). For patients with evolving abnormalities, more frequent assessment is necessary in order to detect thromboses in aneurysms. Long-term prognosis and management is dependent on both the maximal and current Z scores of aneurysms. Patients with large or giant aneurysms (i.e., Z score >= 10) are at the highest risk of both thrombosis and stenosis. Such patients need careful follow-up for subsequent cardiovascular events. Many of them would be candidates for advanced cardiovascular imaging and may require revascularization therapy. Serial echocardiography plays a key role in surveillance. In addition, stress echocardiography has proven useful as a modality to assess for inducible myocardial ischemia. Intravascular ultrasound has been recommended for functional and structural assessment of coronary arteries in children with KD.

Miura, M. (2018). "Role of glucocorticoids in Kawasaki disease." International Journal of Rheumatic

Diseases **21**(1): 70-75.
Although treatment with intravenous immunoglobulin (IVIg) with aspirin is the standard of care for children with Kawasaki disease (KD), 15-20% of patients fail to respond and experience persistent or recurrent fever after completion of IVIg administration. These IVIg non-responders are at high risk for coronary artery lesions (CAL), and may need alternative or supplemental therapy. Based on retrospective studies (albeit with low evidence levels), glucocorticoid therapy was hitherto thought to worsen CAL. However, subsequent prospective studies have shown that prednisolone or IV methylprednisolone pulse as the initial or rescue therapy is effective in reducing CAL. A clinical trial known as the Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for KD (RAISE) Study, demonstrated the efficacy of prednisolone with initial IVIg, especially in predicted IVIg non-responders. Several meta-analyses have also supported the use of glucocorticoids for patients with severe forms of KD. Glucocorticoids can be considered as pre-emptive therapy for children with severe KD and as rescue therapy for initial non-responders. However, routine use of glucocorticoids in KD remains a contentious issue and would need further study.

Nakamura, Y. (2018). "Kawasaki disease: epidemiology and the lessons from it." International Journal of Rheumatic Diseases **21**(1): 16-19.
A half of century has passed since Dr. Tomisaku Kawasaki reported his 50 cases with Kawasaki disease (KD) in 1967. Since then, more than 300 000 cases have been reported to the nationwide epidemiologic surveys in Japan. However, the etiology and risk factors of the disease are still unknown. In this paper, the author emphasizes that the epidemiology of KD may indicate an infectious agent to be a potential trigger of disease in susceptible children.

Onouchi, Y. (2018). "The genetics of Kawasaki disease." International Journal of Rheumatic Diseases **21**(1): 26-30.
Kawasaki disease (KD) is a complex disorder which affects genetically susceptible infants and children. Several susceptibility genes (e.g., ITPKC, CASP3, CD40 and ORAI) and chromosomal regions have been identified through genome-wide association and genome-wide linkage studies to have association with KD. Knowledge of susceptibility genes involved in the pathogenesis of KD may provide new insights into diagnosis and treatment of this condition. However, there is much that we still do not know about the genetic basis of KD.

Pintos Pascual, I., et al. (2018). "[Flu virus and respiratory virus infections]." Medicine **12**(56): 3291-3297.
In general, respiratory infections are benign and self-limiting, but occasionally they can cause severe symptoms and become a major cause of mortality and morbidity, especially in the more vulnerable population groups. Flu epidemics occur annually, and there can be pandemics every few years, such as those caused by types H1N1 or H3N2. The main clinical manifestations are respiratory symptoms associated with fever, and complications such as pneumonia can arise. Nasopharyngeal swab and RT-PCR should be performed to confirm the diagnosis, which can yield results for other viruses as well. Treatment is generally symptomatic, reserving neuraminidase inhibitors for the more serious cases. The best preventive measure is annual vaccination of the population at risk. The coronavirus is also particularly relevant, due to its potential prognostic implications, and the respiratory syncytial virus and parainfluenza virus should be borne in mind in children.

Pisareva, M. M., et al. (2018). "Etiological structure of influenza and other ARVI in St. Petersburg during epidemic seasons 2012-2016. [Russian]." Voprosy virusologii **63**(5): 233-239.
The etiological structure of influenza and other acute respiratory viral infections including their rate of incidence in St. Petersburg and Leningrad region during 4 epidemic seasons has been studied. Seasonality of some respiratory viruses was shown and peaks of circulation of RSV, adenovirus, parainfluenza viruses, rhinovirus, bocavirus, metapneumovirus and coronavirus were

marked. The interference of influenza A viruses and RSV, RSV and rhinoviruses was highlighted. A high incidence of adenovirus infection in organized communities and RSV infection in children was revealed.

Poole, C., et al. (2018). "Hospital-acquired viral respiratory infections (HA-VRI) in a Tertiary Neonatal Intensive Care Unit (NICU)." Journal of the Pediatric Infectious Diseases Society **7 (Supplement 2)**: S89.
Background. Viral respiratory infections are increasingly recognized as important hospital-acquired infections (HAI) in neonatal intensive care units (NICU). Guidelines to direct testing in this setting are lacking and infections are likely underdiagnosed. We conducted a prospective surveillance study of HA-VRI in a tertiary NICU. Method. Single-center tertiary NICU was site of study. Enrollment from October 4, 2016 to March 21, 2017. A weekly nasal swab was collected during hospitalization and stored at -80degreeF. Swabs collected on infants hospitalized for >= 4 weeks were tested for 16 viruses using a polymerase chain reaction assay. Clinical data were collected from the medical records. P-values calculated using Fisher exact and Exact Wilcoxon two-sample test. Results. Seventy-four infants enrolled; of which, 41 were hospitalized for >=4 weeks. Five (12%) of infants tested positive for a VRI. There was no difference in gender, race, gestational age (mean 28 weeks), birth weight (mean 1,200 g), and number of siblings in VRI (+) and VRI (-) infants. VRI (+) infants had a longer length of stay (98 days vs. 59 days, P = 0.04) and were more likely to develop bronchopulmonary dysplasia (P = 0.02). Excluding infants with necrotizing enterocolitis, VRI (+) infants approached significantly longer respiratory support (median 18 days vs. 2 days, P = 0.07), and days of antibiotics (median 8 days vs. 4 days, P = 0.06). No VRI (+) infants had bacterial coinfections at the time of VRI. All 5 VRI (+) infants had respiratory symptoms, only 3 were identified as virus infected by treating physician, and the other 2 remained unrecognized. Study samples obtained on these infants were negative for a virus before the clinically positive sample. One infant was reintubated at the time of rhinovirus infection and died at the time of coronavirus OC43 coinfection. Conclusion. This study confirms prior findings that respiratory viruses are a cause of HAI, they occur in excess of clinical suspicion and are associated with negative outcomes.

Prill, M. M., et al. (2018). "Surveillance for viral respiratory infections in pediatric chronic care facilities." Open Forum Infectious Diseases **5 (Supplement 1)**: S377-S378.
Background. Residents of pediatric chronic care facilities (PCCFs) are vulnerable to acute respiratory infections (ARIs) due to their underlying medical conditions and infection control challenges in congregate living. Methods. We conducted active, prospective surveillance for ARIs (defned as >2 new signs/symptoms of respiratory illness) among all residents in three PCCFs near New York City from December 7, 2016 to May 7, 2017. The parents/guardians of some residents also provided consent for research specimen collection at the start of the study. In that subset, nasopharyngeal swabs were obtained <=4 days of ARI symptom onset and weekly for 4 weeks of follow-up to assess viral shedding. Infuenza, respiratory syncytial virus (RSV), rhinovirus (RV), coronavirus (229E, NL63, OC43, HKU1), parainfuenzavirus (PIV 1-4), metapneumovirus (MPV), adenovirus (AdV), bocavi-rus (BoV), enterovirus, parechovirus, and M. pneumoniae were tested by the Fast Track Diagnostics Respiratory Pathogens 21 real-time RT-PCR panel. Results. Subset with research specimen collection: Among 79 residents (aged 0-20 years, median = 8), 60 ARIs were reported in 37 (47%) residents. Swabs were obtained at illness onset for 53/60 ARI episodes; among these, there were 25 single-virus detections and fve co-detections. An additional 33 single- and fve co-detections occurred in 175 follow-up swabs (table). Molecular typing of 32 RV+ specimens iden-tifed 13 RV types. All residents: During the 2016-2017 infuenza season, 308/322 (96%) age-eligible residents received infuenza vaccine and 168/364 (46%) received prophylactic antivi-rals for infuenza exposures. Although infuenza was not detected in research swabs, it was detected in 3/200 tests conducted for clinical purposes. Conclusion. ARIs were common among residents of three PCCFs, and a variety of respiratory viruses were detected. The rarity of infuenza may refect strong infection control practices in

these facilities, including vaccination and prophylactic use of antivirals.

Randall, R. S., et al. (2018). "Resolution of obstructive sleep apnea after mandibular distraction osteogenesis in setting of delayed tongue-lip adhesion takedown A case report." Medicine (United States) **97 (42) (no pagination)**(e12853).
Rationale: There is a high prevalence of obstructive sleep apnea (OSA) in patients with Pierre Robin sequence (PRS), and treatment approaches are highly variable. One approach is a temporary tongue-lip adhesion (TLA) that acts as a temporizing measure while the mandible continues to grow and is usually taken down at 1 year of age. Patient concerns: Side effects of prolonged tongue-lip adhesion and optimal workup and treatment of persistent OSA in the setting of a tongue-lip adhesion. Diagnoses: Pierre Robin sequence (PRS), persistent obstructive sleep apnea (OSA), and tongue-lip adhesion (TLA). Intervention(s): Mandibular distraction osteogenesis (MDO), adenotonsillectomy, and tongue-lip adhesion takedown. Outcome(s): Resolution of OSA. Lessons: This case puts into question the efficacy of isolated TLA in infants with Pierre Robin sequence and OSA, and places emphasis on the importance of considering an earlier workup of other potential causes of obstruction and the potential need for MDO as a primary or adjunctive approach to treatment. Copyright © 2018 the Author(s).

Rowley, A. H. (2018). "Is Kawasaki disease an infectious disorder?" International Journal of Rheumatic Diseases **21**(1): 20-25.
Although the etiology of Kawasaki disease (KD) is largely unknown, a large body of clinical, epidemiologic, immunologic, pathologic and ultrastructural evidence suggests that an infectious agent triggers a cascade that causes the illness. However, this elusive infectious agent remains unidentified at present. Increasingly sensitive molecular methods for identifying microbial nucleic acids and proteins in tissue samples continue to rapidly emerge, and these methods should be utilized in studies on KD etiology as they become available. Identifying the etiology of this enigmatic disease remains the single most important research goal in the field, and accomplishing this goal is the best means to improve diagnosis, treatment and prevention of this potentially fatal childhood disease.

Rowley, A. H. and S. T. Shulman (2018). "The Epidemiology and Pathogenesis of Kawasaki Disease." Frontiers in Pediatrics **6**: 374.
Epidemiologic and clinical features of Kawasaki Disease (KD) strongly support an infectious etiology. KD is worldwide, most prominently in Japan, Korea, and Taiwan, reflecting increased genetic susceptibility among Asian populations. In Hawaii, KD rates are 20-fold higher in Japanese ethnics than in Caucasians, intermediate in other ethnicities. The age distribution of KD, highest in children < 2 yo, lower in those < 6 months, is compatible with infection by a ubiquitous agent resulting in increasing immunity with age and with transplacental immunity, as with some classic viruses. The primarily winter-spring KD seasonality and well-documented Japanese epidemics with wave-like spread also support an infectious trigger. We hypothesize KD pathogenesis involves an RNA virus that usually causes asymptomatic infection but KD in a subset of genetically predisposed children. CD8 T cells, oligoclonal IgA, and upregulation of cytotoxic T cell and interferon pathway genes in the coronaries in fatal KD also support a viral etiology. Cytoplasmic inclusion bodies in ciliated bronchial epithelium identified by monoclonal antibodies made from oligoclonal IgA heavy chains also supports a viral etiology. Recent availability of "second generation" antibodies from KD peripheral blood plasmablasts may identify a specific viral antigen. Thus, we propose an unidentified ("new") RNA virus infects bronchial epithelium usually causing asymptomatic infection but KD in a subset of genetically predisposed children. The agent persists in inclusion bodies, with intermittent respiratory shedding, entering the bloodstream via macrophages targeting coronaries. Antigen-specific IgA plasma cells and CD8 T cells respond but coronaries can be damaged. IVIG may include antibody against the agent. Post infection, 97-99% of KD patients are immune to the agent, protected against recurrence. The agent can spread either from those with asymptomatic primary infection in

winter-spring or from a previously infected contact who intermittently sheds the agent.

Sederberg-Olsen, J. F., et al. (2018). "Grommets in otitis media: a 25-year follow up." Acta Oto-Laryngologica **138**(12): 1057-1060.
Background: This study is unique as it is the first study which can describe the long term sequelae of treatment of otitis media with effusion (OME) with insertion of grommets in the Primary Health Sector in Denmark. Objective(s): Eardrum pathology and hearing acuity 25 years after treatment of OME by insertion of grommets, in a private ear-, nose-, and throat practice. Material(s) and Method(s): 262 children with OME were treated from 1975 to 1978. The patients were re-examined by otomicroscopy, tympanometry and pure tone audiometry after 7.5, 12, and 25 years. Result(s): Hearing level, flaccida retraction and incudo pexi was equivalent. For atrophy and myringosclerosis no equivalence was shown using 95% confidence intervals. Tympanometry was fairly unchanged. Conclusion and significance: The insertion of a grommet in treating OME has no influence on hearing acuity in the long term. The prevalence of myringosclerosis and atrophy was unchanged in 70-80% of the eardrums. Most important is that the small increase in myringosclerosis and atrophy does not seem to influence the hearing acuity. We show that long term sequelae from the Primary Health Sector are similar to those from the Secondary Health sector. Copyright © 2019, © 2019 Acta Oto-Laryngologica AB (Ltd).

Singh, S., et al. (2018). "Diagnosis of Kawasaki disease." International Journal of Rheumatic Diseases **21**(1): 36-44.
Kawasaki disease (KD) is a medium vessel vasculitis with predilection for coronary arteries. Due to lack of a reliable confirmatory laboratory test, the diagnosis of KD is based on a constellation of clinical findings that appear in a typical temporal sequence. These diagnostic criteria have been modified from time to time and the most recent guidelines have been proposed by the American Heart Association (AHA) in 2017. However, several children may have incomplete or atypical forms of KD and the diagnosis can often be difficult, especially in infants and young children. In this review, we have detailed the steps involved in arriving at a diagnosis of KD and also highlight the important role of echocardiography in diagnosis and management of children with KD.

Smith, J. M., et al. (2018). "Evaluation of options for rodent health surveillance in ventilated cages and conventional housing." Journal of the American Association for Laboratory Animal Science **57 (5)**: 582-583.
Heath surveillance in rodent facilities typically uses live sentinel animals euthanized at periodic intervals for serology, parasitology, and necropsy evaluation. Recent literature has suggested the number of animals needed could be reduced by PCR testing flters or fecal and fur swabs from colony animals instead of sacrifcing sentinels. To evaluate this in our facilities, we compared PCR testing of flter tops from sentinel cages (SPF), room exhaust flters (conventional), and random fecal and fur swabs from colony animals to results obtained from sentinel sacrifce. Our hypothesis was that the alternative testing would provide equivalent results to sentinels. Two mouse rooms and 1 rat room with commercially available positive pressure IVC cages with rack fltered incoming air and exhaust through the cage top flter to the plenum were evaluated. Six rack sides were evaluated in each room. The sentinel cage flter top was marked and not changed for 8 wk. After 8 wk a 1 x 1-in piece of each flter was submitted for PCR testing. Fecal and fur swabs were also taken from colony animals by sampling animals in 1 cage/row. Samples from each rack side were pooled 10 samples/test. In conventional rooms, sections of room exhaust flters were also submitted for PCR. Serology and PCR were sent to a commercial laboratory, with in-house necropsy and parasitology for sentinels. SPF mice historically were positive for mouse norovirus and Helicobacter. Conventional mice were positive for these plus mouse hepatitis virus, mouse parvovirus, epizootic diarrhea of infant mice, pinworms, and fur mites. SPF rats were positive for rat theilovirus (RTV) and Helicobacter. Our results showed that flters consistently picked up Helicobacter, but not mouse norovirus (MNV) or RTV. However, the results of direct

colony sampling for mice matched the sentinel results and did not pick up any additional agents. For rats, the direct samples were negative for agents found by sentinels. We thus concluded that by holding mouse sentinels for longer intervals and adding direct random colony sampling we could reduce animal numbers while not compromising our ability to detect rodent pathogens. Further evaluation may be needed for rats.

Su, E. J., et al. (2018). "Reye's syndrome arising from the treatment of Kawasaki disease." Hong Kong Journal of Paediatrics **23**(2): 185-187.
We report on a 20-month-old girl who presented with vomiting and lethargy after being discharged from the ward following treatment for Kawasaki disease. The symptoms occurred after five days of aspirin therapy. The clinical features and laboratory tests proved the presence of Reye's syndrome and she recovered after intensive treatment. In addition, we collected three similar reported cases. All the patients came from East Asia and the mortality rate reached 50%. Since salicylate is an effective and imperative treatment for Kawasaki disease, paediatricians and emergency physicians can consider using a low dose of aspirin (3-5 mg/kg) as maintenance therapy, discontinuing aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics, and having a high index of suspicion of Reye's syndrome in patients with Kawasaki disease.

Sun, Q., et al. (2018). "Gallbladder Hydrops Associated With Kawasaki Disease: A Case Report and Literature Review." Clinical Pediatrics **57**(3): 341-343.

Toizumi, M., et al. (2018). "Viral Acute Respiratory Illnesses in Young Infants Increase the Risk of Respiratory Readmission." Pediatric Infectious Disease Journal **37**(12): 1217-1222.
Background: Respiratory viruses cause acute respiratory illness (ARI) in early childhood, but their effect on subsequent ARI admissions is not fully understood. This study aimed to determine the association between initial ARI admission because of viruses including human rhinovirus (HRV), respiratory syncytial virus (RSV), human adenovirus (HAdV) and human metapneumovirus (hMPV) and the risk of ARI readmission in children. Method(s): Clinical information and nasopharyngeal swab samples were collected from children <2 years old at their initial ARI admission in Nha Trang, Vietnam, from January 2007 to April 2012. The incidence of ARI readmission during the follow-up period (initial admission to 5 years of age) was compared between children with and without 1 of 13 respiratory viruses (influenza virus A, influenza virus B, RSV, hMPV, parainfluenza virus-1, parainfluenza virus-2, parainfluenza virus-3 and parainfluenza virus-4, HRV, human coronavirus-229E, human coronavirus-OC43, HAdV and human bocavirus) at initial admission. Result(s): A total of 1941 children were enrolled in the study. Viruses were detected in 1254 (64.6%) children at enrollment; HRV, RSV, HAdV and hMPV were detected in 499 (25.7%), 439 (22.6%), 156 (8.0%) and 47 (2.4%) children, respectively. During the follow-up period (4572.7 person-years), 277 children were readmitted with ARI. Virus-related ARI initial admission was associated with an increased risk of ARI readmission for children who were initially admitted before 6 months of age (adjusted rate ratio, 1.6; 95% confidence interval: 1.1-2.5). HAdV (4.6; 1.8-11.9), hMPV (20.4; 6.2-66.9) and HRV (1.6; 1.0-2.4) were independently associated with the outcome. These associations were not observed for children whose initial admission occurred after 6 months of age. Conclusion(s): HAdV-, hMPV- and HRV-related initial ARI admissions, when occurring during early infancy, increased the risk of subsequent ARI-related readmission.

Tremoulet, A. H. (2018). "Adjunctive therapies in Kawasaki disease." International Journal of Rheumatic Diseases **21**(1): 76-79.
Despite the administration of intravenous immunoglobulin (IVIg) at a dose of 2 g/kg, approximately 3-5% of children with acute Kawasaki disease (KD) may develop coronary artery aneurysms. IVIg-resistance, defined as recrudescence of fever more than 36 h after IVIg

completion, is a risk factor for coronary artery abnormalities. Thus, several adjunctive therapies are being evaluated for use in IVIg-resistant KD patients and in patients with coronary artery abnormalities. In this review the role of some of these adjunctive therapies in treatment of children with KD is discussed.

Varghese, L., et al. (2018). "Epidemiology and clinical features of human coronaviruses in the pediatric population." Journal of the Pediatric Infectious Diseases Society **7**(2): 151-158.
Background. The epidemiology and clinical features of human coronaviruses (HCoVs) in children are not fully characterized. Methods. A retrospective study of children with HCoV detected by reverse-transcriptase polymerase chain reaction (RT-PCR) was performed for a community cohort and a children's hospital in the same community from January 2013 to December 2014. The RT-PCR assay detected HCoV 229E, HKU1, NL63, and OC43 in nasal swabs from symptomatic children <=18 years. Factors associated with increased severity of illness in hospitalized children were assessed by multivariable logistic regression. Results. Human coronavirus was detected in 261 children, 49 and 212 from the community and hospital, respectively. The distribution of HCoV types and seasonal trends were similar in the community and hospital. Community cases were older than hospitalized cases (median age, 4.4 versus 1.7 years, respectively; P < .01), and a minority of community cases (26.5%) sought medical attention. Among the hospitalized children with HCoV detected, 39 (18.4%) received respiratory support and 24 (11.3%) were admitted to the pediatric intensive care unit (PICU). Age <2 years (odds ratio [OR] = 5.0; 95% confidence interval [CI], 1.9-13.1) and cardiovascular (OR = 3.9; 95% CI, 1.6-9.5), genetic/congenital (OR = 2.8; 95% CI, 1.1-7.0), and respiratory chronic complex conditions ([CCCs] OR = 4.5; 95% CI, 1.7-12.0) were associated with receiving respiratory support. Genetic/congenital (OR = 2.8; 95% CI, 1.1-7.4) CCCs were associated with PICU admission. Severity of illness was similar among hospitalized children with different HCoV types. Conclusions. Children in the community with HCoV detected generally had mild illness as demonstrated by few medically attended cases. In hospitalized children, young age and CCCs, but not HCoV type, were associated with increased severity of illness.

Vervoort, D., et al. (2018). "Pitfalls in the diagnosis and management of Kawasaki disease: An update for the pediatric dermatologist." Pediatric Dermatology **35**(6): 743-747.
Kawasaki disease is easily diagnosed when it presents in its complete form, but because not all characteristic symptoms are always present at the same time, and the diagnosis of incomplete and atypical Kawasaki disease is often challenging, a delay in diagnosis or misdiagnosis often occurs. We present the diagnostic approach to Kawasaki disease with common pitfalls and explain how to avoid them. We also describe current practice and new trends in treatment.

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Agarwal, S. and D. K. Agrawal (2017). "Kawasaki disease: etiopathogenesis and novel treatment strategies." Expert Review of Clinical Immunology **13**(3): 247-258.
INTRODUCTION: Kawasaki disease is an acute febrile systemic vasculitis that predominantly occurs in children below five years of age. Its etiopathogenesis is still not clear, but it is thought to be a complex interplay of genetic factors, infections and immunity. Areas covered: This review article discusses in detail Kawasaki disease, with particular emphasis on the recent updates on its pathogenesis and upcoming alternate treatment options. Though self-limiting in many cases, it can lead to severe complications like coronary artery aneurysms and thrombo-embolic occlusions, and hence requires early diagnosis and urgent attention to avoid them. Intravenous immunoglobulin (IVIG) with or without aspirin has remained the sole treatment option for these cases, but 10-15% cases develop resistance to this treatment. Expert commentary: There is a

need to develop additional treatment strategies for children with Kawasaki disease. Targeting different steps of pathogenesis could provide us with alternate therapeutic options.

Ariga, S., et al. (2017). "Infantile incomplete Kawasaki disease mimicking cervical purulent lymphadenitis with coronary artery aneurysm." Pediatrics International **59**(9): 1020-1022.

Del Principe, D., et al. (2017). "Pathogenetic determinants in Kawasaki disease: the haematological point of view." Journal of Cellular & Molecular Medicine **21**(4): 632-639.
Kawasaki disease is a multisystemic vasculitis that can result in coronary artery lesions. It predominantly affects young children and is characterized by prolonged fever, diffuse mucosal inflammation, indurative oedema of the hands and feet, a polymorphous skin rash and non-suppurative lymphadenopathy. Coronary artery involvement is the most important complication of Kawasaki disease and may cause significant coronary stenosis resulting in ischemic heart disease. The introduction of intravenous immunoglobulin decreases the incidence of coronary artery lesions to less than 5%. The etiopathogenesis of this disease remains unclear. Several lines of evidence suggest that an interplay between a microbial infection and a genetic predisposition could take place in the development of the disease. In this review, we summarize the state of the art of pathogenetic mechanisms of Kawasaki disease underscoring the relevance of haematological features as a novel field of investigation.

Denby, K. J., et al. (2017). "Management of Kawasaki disease in adults." Heart **103**(22): 1760-1769.
Kawasaki disease is the most common childhood vasculitis in the USA and the most common cause of acquired cardiac disease in children in developed countries. Since the vast majority of Kawasaki disease initially presents at <5 years of age, many adult cardiologists are unfamiliar with the pathophysiology of this disease. This vasculitis has a predilection for coronary arteries with a high complication rate across the lifespan for those with medium to large coronary artery aneurysms. An inflammatory cascade produces endothelial dysfunction and damage to the vascular wall, leading to aneurysmal dilatation. Later, pseudonormalisation of the vascular lumen occurs through vascular remodelling and layering thrombus, but this does not necessarily indicate resolution of disease or reduction of risk for future complications. There is a growing prevalence of Kawasaki disease, making it increasingly relevant for adult cardiologists as this population transitions into adulthood. As the 2017 American Heart Association (AHA) and 2014 Japanese Circulation Society (JCS) guidelines emphasise, Kawasaki disease requires rigorous follow-up with cardiac stress testing and non-invasive imaging to detect progressive stenosis, thrombosis and luminal occlusion that may lead to myocardial ischaemia and infarction. Due to differences in disease mechanisms, coronary disease due to Kawasaki disease should be managed with different pharmacological and non-pharmacological treatment algorithms than atherosclerotic coronary disease. This review addresses gaps in the current knowledge of the disease and its optimal treatment, differences in the AHA and JCS guidelines, targets for future research and obstacles to transition of care from adolescence into adulthood.

Dietz, S. M., et al. (2017). "Dissecting Kawasaki disease: a state-of-the-art review." European Journal of Pediatrics **176**(8): 995-1009.
Kawasaki disease (KD) is a pediatric vasculitis with coronary artery aneurysms (CAA) as its main complication. The diagnosis is based on the presence of persistent fever and clinical features including exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosae and extremities. Although the etiology remains unknown, the current consensus is that it is likely caused by an (infectious) trigger initiating an abnormal immune response in genetically predisposed children. Treatment consists of high dose intravenous immunoglobulin (IVIG) and is directed at preventing the development of CAA. Unfortunately, 10-20% of all patients fail to respond to IVIG and these children need additional anti-inflammatory treatment. Coronary artery lesions are diagnosed by echocardiography in the acute and subacute phases. Both absolute arterial diameters and z-scores, adjusted for height and weight, are used as criteria for CAA.

Close monitoring of CAA is important as ischemic symptoms or myocardial infarction due to thrombosis or stenosis can occur. These complications are most likely to arise in the largest, so-called giant CAA. Apart from the presence of CAA, it is unclear whether KD causes an increased cardiovascular risk due to the vasculitis itself.
CONCLUSION: Many aspects of KD remain unknown, although there is growing knowledge on the etiology, treatment, and development and classification of CAA. Since children with previous KD are entering adulthood, long-term follow-up is increasingly important. What is known: * Kawasaki disease (KD) is a pediatric vasculitis with coronary artery damage as its main complication. * Although KD approaches its 50th birthday since its first description, many aspects of the disease remain poorly understood. What is new: * In recent years, multiple genetic candidate pathways involved in KD have been identified, with recently promising information about the ITPKC pathway. * As increasing numbers of KD patients are reaching adulthood, increasing information is available about the long-term consequences of coronary artery damage and broader cardiovascular risk.

Hartz, J. and S. Clauss (2017). "Treatment strategies for hypercholesterolemia." Current Pediatric Reviews **13**(4): 243-254.
Background: Atherosclerotic disease is a leading cause of morbidity and mortality in adults and is generally thought of as only affecting adults. However, the pathologic changes in vessels leading to atherosclerosis, and an increased risk of cardiovascular disease, have been shown to begin in early adolescence. Objectives: There is a growing body of literature suggesting that earlier treatment, through lifestyle changes and pharmacotherapy, can help reduce this risk. A growing number of children are presenting with elevated cholesterol because of the increased prevalence of obesity and diabetes mellitus. Methods: In addition, an increasing number of children are living with previously fatal diseases that increase the risk of atherosclerosis, either because of the disease process or as adverse effect of the treatment, such as human immunodeficiency virus, Kawasaki disease, and cardiac transplantation. Result and Conclusion: In addition, specific disorders of cholesterol metabolism, such as Familial Hypercholesterolemia (FH) may be encountered in a pediatric practice. © 2017 Bentham Science Publishers.

Huang, Y. H. and H. C. Kuo (2017). "Anemia in Kawasaki Disease: Hepcidin as a Potential Biomarker." International Journal of Molecular Sciences **18**(4): 12.
Kawasaki disease (KD) is an autoimmune-like disease and acute childhood vasculitis syndrome that affects various systems but has unknown etiology. In addition to the standard diagnostic criteria, anemia is among the most common clinical features of KD patients and is thought to have a more prolonged duration of active inflammation. In 2001, the discovery of a liver-derived peptide hormone known as hepcidin began revolutionizing our understanding of anemia's relation to a number of inflammatory diseases, including KD. This review focuses on hepcidin-induced iron deficiency's relation to transient hyposideremia, anemia, and disease outcomes in KD patients, and goes on to suggest possible routes of further study.

Jiao, F., et al. (2017). "The emergence of Kawasaki disease in India and China." Global Cardiology Science & Practice **2017**(3): e201721.
Kawasaki disease (KD) is recognized as a leading cause of acquired heart disease in children in developed countries. Although global in distribution, Japan records the highest incidence of KD in the world. Epidemiological reports from the two most populous countries in the world, namely China and India, indicate that KD is now being increasingly recognized. Whether this increased reporting is due to increased ascertainment, or is due to a true increase in incidence, remains a matter of conjecture. The diagnosis and management of KD in developing countries is a challenging proposition. In this review we highlight some of the difficulties faced by physicians in managing children with KD in resource-constrained settings.

Kuo, H. C. (2017). "Preventing coronary artery lesions in Kawasaki disease." Biomedical Journal **40**(3):

141-146.
A form of systemic vasculitis that affects mostly small and medium-sized vessels, Kawasaki disease (KD) is most commonly found in children under the age of 5 years old. Though its etiology is unknown, KD has been the most frequent acquired heart disease in developing countries. Its incidence has increased over recent decades in many centuries, including Japan, Korea, and China. The most severe complications of KD are coronary artery lesions (CAL), including dilation, fistula, aneurysm, arterial remodeling, stenosis, and occlusion. Aneurysm formation has been observed in 20-25% of KD patients that do not receive intravenous immunoglobulin (IVIG) treatment, and in 3-5% that do receive it. Coronary artery dilation has been found in about 30% of KD patients in the acute stage, although mostly in the transient form. Diminishing the occurrence and regression of CAL is a vital part of treating KD. In this review article, I demonstrate the clinical method to prevent CAL formation used at the Kawasaki Disease Center in Taiwan.

Lewnard, J., et al. (2017). "Transmission dynamics of respiratory viruses in a congregated military population: Prospective cohort study." Open Forum Infectious Diseases **4 (Supplement 1)**: S238.
Background. Human coronaviruses (HCoVs), rhinoviruses, and non-polio enteroviruses (NPEVs) are leading causes of seasonal acute respiratory infections among children and adults, posing significant health and economic burden annually. Despite this, little is known about their epidemiological dynamics, including the role of asymptomatic shedding in transmission; the durations of virus incubation and shedding; and the effect of immune responses on risk for re-infection during the same season. We studied respiratory virus shedding in military recruits, and used mathematical models to measure pathogen-specific transmission rates and durations of incubation, shedding, and immune protection. Methods. We tested for shedding of HCoVs, rhinoviruses, and NPEVs in nasal samples collected from 78 military recruits entering basic training and then at staggered, biweekly visits over 65 days during winter 2017. We developed a continuous- time Markov chain model for virus acquisition and clearance, and used Bayesian methods to estimate model parameters for each of HCoV-229E, HCoV-OC43, rhinoviruses, and NPEVs. Results. We observed widespread transmission of HCoV-229E, rhinoviruses, and NPEVs within the first week after entry into basic training, and a subsequent phase of transmission predominantly involving HCoV-OC43 during the second month (Figure). We estimated pre-epidemic reproductive numbers ranging from 1.97 (95% credible interval: 1.49, 2.60) for HCoV-OC43 to 5.69 (3.92, 7.98) for HCoV-229E (Table). Subjects re-acquired HCoV-229E, rhinoviruses, and NPEVs despite previous exposure; for these pathogens, we estimated reversion to pre-infection susceptibility to occur, on average, 28.5 (15.8, 49.7) days, 52.2 (22.3, 151.1), and 144.7 (61.3, 812.5) days, respectively, following clearance of viral shedding. Conclusion. Asymptomatic shedding is a source of transmission of common respiratory viruses in the close-contact basic training environment. Protection against re-acquisition is short-lived, and may be inadequate to prevent re-infection by rhinoviruses and NPEVs within a season. Estimated durations of shedding and incubation periods provide a basis for modeling pathogen spread and informing isolation protocols. (Figure Presented) .

Lin, M. T. and M. H. Wu (2017). "The global epidemiology of Kawasaki disease: Review and future perspectives." Global Cardiology Science & Practice **2017**(3): e201720.
Kawasaki disease (KD) is one of the most common childhood vasculitides and may lead to coronary arterial complications. KD has been reported in more than 60 countries over five continents. Previous publications have provided a comprehensive description of the epidemiologic features of KD including incidence, age of onset, seasonal trends, and rates of cardiac lesions. However, the interactions among the KD patients, time (seasons) and place have been less well studied. We review the current global epidemiology of KD and focus on the longitudinal changes in incidence, seasonality and response to intravenous immunoglobulin (IVIG) therapy.

McCrindle, B. W., et al. (2017). "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association." Circulation **135**(17): e927-e999.
BACKGROUND: Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in =25% of untreated cases. It has been reported worldwide and is the leading cause of acquired heart disease in children in developed countries.
METHODS AND RESULTS: To revise the previous American Heart Association guidelines, a multidisciplinary writing group of experts was convened to review and appraise available evidence and practice-based opinion, as well as to provide updated recommendations for diagnosis, treatment of the acute illness, and long-term management. Although the cause remains unknown, discussion sections highlight new insights into the epidemiology, genetics, pathogenesis, pathology, natural history, and long-term outcomes. Prompt diagnosis is essential, and an updated algorithm defines supplemental information to be used to assist the diagnosis when classic clinical criteria are incomplete. Although intravenous immune globulin is the mainstay of initial treatment, the role for additional primary therapy in selected patients is discussed. Approximately 10% to 20% of patients do not respond to initial intravenous immune globulin, and recommendations for additional therapies are provided. Careful initial management of evolving coronary artery abnormalities is essential, necessitating an increased frequency of assessments and escalation of thromboprophylaxis. Risk stratification for long-term management is based primarily on maximal coronary artery luminal dimensions, normalized as Z scores, and is calibrated to both past and current involvement. Patients with aneurysms require life-long and uninterrupted cardiology follow-up.
CONCLUSIONS: These recommendations provide updated and best evidence-based guidance to healthcare providers who diagnose and manage Kawasaki disease, but clinical decision making should be individualized to specific patient circumstances.

Merckx, J., et al. (2017). "Asthma exacerbations and risk of emergency department management failure: Burden and impact of various respiratory pathogens in a pediatric population." Open Forum Infectious Diseases **4 (Supplement 1)**: S695-S696.
Background. In asthmatic children, 60-80% of exacerbations are triggered by respiratory pathogens and represent an important burden of illness. The impact of pathogens on exacerbation severity and treatment response remains unclear. Our aim was to describe the prevalence of respiratory pathogens in children presenting to the emergency department (ED) and investigate the association between pathogens and (i) exacerbation severity on presentation and (ii) ED treatment failure. Methods. We performed a secondary analysis of the DOORWAY study, a prospective multi-center cohort of children (1-17 years) presenting to the ED with moderate or severe asthma exacerbation. All received per protocol oral corticosteroids and bronchodilators. Nasopharyngeal (NPA) secretions were analyzed by RT-PCR for 30 different pathogens. Linear and logistic multivariate regression models were used to estimate absolute risks and risk differences (RD) with their 95% CI representing average marginal effects. Results. Of 958 patients with NPA specimens, 591 (61.7%) were positive for >= 1 pathogens; human rhinovirus (HRV) was the most prevalent (29.4%). Non-HRV infection (RD -12.9%; 95% CI -19.5; -6.3), human metapneumovirus (RD -13.6%; 95% CI -23.0%; -4.3%) and parainfluenza virus (PIV) (RD -31.7%; 95% CI -44.5%; -18.9%) were negatively associated with severity; no association was found between severity and the presence of any pathogen, co-infection, or the specific viruses HRV-A, HRV-B, HRV-C, respiratory syncytial virus, influenza (INF), enterovirus serotype D68, adenovirus or coronavirus. The risk of treatment failure in the absence of a pathogen was 12.5% (95% CI 9.0%; 16.0%). The presence of any pathogen (RD 8.2%; 95% CI 3.3%; 13.1%) and non-HRV infection as a group (RD 13.1%; 95% CI 6.4%; 19.8%), and of INF and PIV specifically (RD 24.9%; 95% CI 4.7%; 45.1% and RD 34.1%; 95% CI 7.5%; 60.7%) were positively associated with treatment failure. Conclusion. In this large cohort of children with moderate or severe exacerbation, no single respiratory pathogen was associated with higher severity on presentation. However, in addition to any pathogen and non-HVR infection, INF and

PIV were specifically associated with higher treatment failure in the ED, supporting the need for influenza prevention, pathogen identification at presentation and exploration of pathogen-therapy interaction.

Newburger, J. W. (2017). "Kawasaki disease: State of the art." Congenital Heart Disease **12**(5): 633-635.
Kawasaki disease is an acute febrile arteritis of childhood that can result in coronary artery aneurysms if untreated in the first 10 and ideally 7 days of illness. Kawasaki disease begins as a necrotizing arteritis with neutrophilic infiltrate, followed by subacute/chronic changes and luminal myofibroblastic proliferation that can cause coronary artery stenosis. Manifestations include the presence of >=5 days of fever, together with clinical criteria of extremity changes, rash, conjunctivitis, oral changes, and unilateral cervical lymphadenopathy. Echocardiography should be performed at the time of diagnosis, then 1-2 weeks and 4-6 weeks later, with more frequent studies in individuals with coronary artery dilation or persistent fever. Coronary artery dimensions are characterized both as z-scores and absolute measurements, and coronary architecture evolves over time in children who have aneurysms in the first weeks of illness. Systematic follow-up and therapies are tailored to the degree of coronary disease and to coronary ischemia.

Petrarca, L., et al. (2017). "Difficult diagnosis of atypical kawasaki disease in an infant younger than six months: A case report." Italian Journal of Pediatrics **43**(1).
Background: Kawasaki disease (KD) is an acute inflammatory vasculitis of unknown origin. Case presentation: We report the case of a 5-month-old child with an atypical form of KD, characterized by undulating symptoms, who developed an aneurysm of the right coronary artery and an ectasia of the left anterior descending coronary artery. Conclusion: This case report underlines the difficulties in recognizing incomplete forms of the illness in young infants, who are at higher risk of cardiac complications. © 2017 The Author(s).

Qureshi, A. M. and H. Agrawal (2017). "Catheter-based anatomic and functional assessment of coronary arteries in anomalous aortic origin of a coronary artery, myocardial bridges and Kawasaki disease." Congenital Heart Disease **12**(5): 615-618.
Most diagnostic testing in patients with anomalous aortic origins of coronary arteries, myocardial bridges, and coronary artery changes after Kawasaki disease are performed with the use of noninvasive techniques. In some cases, however, further diagnostic information is needed to guide the clinician in treating these patients. In such instances, cardiac catheterization with invasive anatomic and functional testing is an invaluable tool. Moreover, interventional treatment in the cardiac catheterization laboratory may be performed in a small subset of these patients. As the diagnosis of these conditions is now becoming more common, it is important for pediatric interventional cardiologists to be familiar with these techniques. In this article, the role of angiography, intravascular ultrasound, fractional flow reserve, and optical coherence tomography in these patients is reviewed.

Rajput, S., et al. (2017). "Getting warmer." Journal of Hospital Medicine (Online) **12**(1): 52-56.
The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

Sakulchit, T., et al. (2017). "Acetylsalicylic acid for children with Kawasaki disease." Canadian Family Physician **63**(8): 607-609.
Question A 7-year-old child in my office was recently discharged from the hospital after receiving intravenous immunoglobulin for Kawasaki disease. Should I continue treatment with acetylsalicylic acid (ASA), and if so, what is the appropriate dose? Answer The role of ASA for Kawasaki disease during the acute febrile phase has recently been called into question.

According to several studies, ASA might reduce the duration of fever but it does not appear to directly reduce the incidence of coronary artery complications. However, with no high-quality randomized controlled trials, the evidence is scarce and more studies with good methodology are needed to determine the value of ASA in the treatment of Kawasaki disease. Currently, guidelines recommending the use of ASA should be followed.

Sharma, D., et al. (2017). "A child with X-linked agammaglobulinemia and Kawasaki disease: an unusual association." Rheumatology International **37**(8): 1401-1403.
An association of X-linked agammaglobulinemia (XLA) with Kawasaki disease (KD) is very uncommon. Only two case reports are available so far in pediatric literature. Patients with XLA have recurrent infections and physical examination have absent lymph nodes and tonsils. Laboratory investigations reveal hypogammaglobulinemia and reduced or absent B cells on flow cytometry. KD is a medium vessel vasculitis. Here, we report a 12 year old boy with X-linked agammaglobulinemia on regular replacement intravenous immunoglobulin who developed KD on follow-up. This is an uncommon occurrence.

Taddio, A., et al. (2017). "Describing Kawasaki shock syndrome: results from a retrospective study and literature review." Clinical Rheumatology **36**(1): 223-228.
Kawasaki shock syndrome (KSS) is a rare manifestation of Kawasaki disease (KD) characterized by systolic hypotension or clinical signs of poor perfusion. The objectives of the study are to describe the main clinical presentation, echocardiographic, and laboratory findings, as well as the treatment options and clinical outcomes of KSS patients when compared with KD patients. This is a retrospective study. All children referred to two pediatric rheumatology units from January 1, 2012, to December 31, 2014, were enrolled. Patients were divided into patients with or without KSS. We compared the two groups according to the following variables: sex, age, type of KD (classic, with less frequent manifestations, or incomplete), clinical manifestations, cardiac involvement, laboratory findings, therapy administered, response to treatment, and outcome. Eighty-four patients with KD were enrolled. Of these, five (6 %) met the criteria for KSS. Patients with KSS had higher values of C-reactive protein ($p = 0.005$), lower hemoglobin levels ($p = 0.003$); more frequent hyponatremia ($p = 0.004$), hypoalbuminemia ($p = 0.004$), and coagulopathy ($p = 0.003$); and increase in cardiac troponins ($p = 0.000$). Among the KSS patients, three had a coronary artery involvement, but none developed a permanent aneurysm. Intravenous immunoglobulin resistance was more frequent in the KSS group, although not significantly so (3/5, 60 % vs. 23/79, 30 %, P = NS). None of the five cases was fatal, and all recovered without sequelae. KSS patients are more likely to have higher rates of cardiac involvement. However, most cardiovascular abnormalities resolved promptly with therapy.

Teraura, H., et al. (2017). "The serum concentration of soluble interleukin-2 receptor in patients with Kawasaki disease." Annals of Clinical Biochemistry **54**(2): 209-213.
Kawasaki disease is a febrile disease of childhood that is associated with increased inflammatory cytokines and immunoregulatory abnormalities. While the serum concentrations of soluble IL-2 receptor can change under such pathologies, the relevance of the soluble IL-2 receptor concentration in patients with Kawasaki disease has not been specified. We aimed to summarize the existing studies that reported the soluble IL-2 receptor concentrations in patients with Kawasaki disease. Original articles that were published up to July 2016 were collected using a PubMed/Medline-based search engine. A total of nine articles that reported the serum soluble IL-2 receptor concentrations in acute-phase Kawasaki disease were eligible. All of the articles described a high soluble IL-2 receptor concentration in patients with Kawasaki disease relative to the level of controls or the reference range. Two of five articles on patients with coronary artery aneurysms described a significantly higher soluble IL-2 receptor concentration in patients with coronary artery aneurysms than patients without. Two articles on patients with intravenous immunoglobulin therapy described a significant decrease of the soluble IL-2 receptor concentration after the therapy. Accordingly, the serum soluble IL-2 receptor can be a potent

marker of disease activity and therapeutic effects in patients with Kawasaki disease; further studies are thus warranted for its use in the clinical setting.

Tsumura, Y., et al. (2017). "[Prolonged optic disc swelling in Kawasaki disease - A case report and literature review]." Nihon Rinsho Meneki Gakkai Kaishi **40**(5): 377-381.
Kawasaki disease (KD), an acute childhood panvasculitis, presents a variety of ocular complications as well as conjunctival injection among the principal symptoms. However, most pediatricians are unfamiliar with the ophthalmological complications of KD. A 2-year-old girl was referred to us from the ophthalmology department due to injected bulbar conjunctivae and optic disc swelling. She had familial exudative vitreoretinopathy as an underlying disease and the ocular findings had been made by chance while the patient was receiving an eye examination. Although she was afebrile at the time of her first medical interview, KD was diagnosed based on the presence of four of the principal symptoms including fever and dilatation of the coronary arteries. Intravenous immunoglobulin (IVIG) therapy was administered on Day 15 from the onset of fever. After IVIG administration, her laboratory test results showed rapid improvement but her optic disc swelling continued for six months. Eye complications in KD generally occur in the anterior segment, and recovery occurs within two months. Past reports have shown that in three of seven KD cases with optic disc involvement, optic disc swelling lasted over two months. This is the second case in which the condition lasted six months.

Williams, K. (2017). "Preventing Long-Term Cardiac Damage in Pediatric Patients With Kawasaki Disease." Journal of Pediatric Health Care **31**(2): 196-202.
Kawasaki disease is currently the leading cause of long-term cardiac damage in pediatric patients in the United States. Kawasaki disease is diagnosed based on symptomatology and by ruling out other etiology. There is a significant need for an improved, standardized treatment protocol for patients diagnosed with Kawasaki disease and a more rapid initiation of treatment for these patients. Decreasing the cardiac damage caused by Kawasaki disease with timely diagnosis and treatment needs be a principal goal.

2016 (23)

Chang, H. K., et al. (2016). "Kawasaki Disease: An Autopsy Case Series and Review of the Literature." American Journal of Forensic Medicine & Pathology **37**(3): 183-186.
INTRODUCTION: Kawasaki disease (KD) is a major cause of acquired heart disease in children, and there is limited information on postmortem findings in the pediatric population in Canada.
CASES: For a 15-year time span (January 2000-March 2015), we had 2 cases of KD presented to the Department of Forensic Pathology at Hamilton General Hospital.
DISCUSSION: There were common cardiac findings including presence of giant coronary artery aneurysms and microscopic changes occurring within the coronary arteries and the myocardium. Evidence of old infarction was present in both heart specimens, but acute infarction was noted in one of the specimens.
CONCLUSIONS: This case series documents postmortem findings that outline cardiac complications of KD including aneurysms, thrombotic events, and infarcts. In addition to addressing the medical complications of KD, it is also important to address the psychosocial effect due to its impact on quality of life.

Chen, S., et al. (2016). "Coronary Artery Complication in Kawasaki Disease and the Importance of Early Intervention : A Systematic Review and Meta-analysis." JAMA Pediatrics **170**(12): 1156-1163.
Importance: The timing and selection of patients with Kawasaki disease for corticosteroid use to prevent coronary artery complications remain controversial.
Objective: To evaluate the effect of corticosteroid therapy in KD.
Data Sources: Databases of Medline, The Cochrane Library, and the Clinicaltrials.gov website until July

2015. We used the key words ["Kawasaki disease"] and ["steroid" OR "corticosteroid"] to retrieve potentially relevant studies in the databases of Medline, the Cochrane Library, and the Clinicaltrials.gov website until July 2015. Both English and non-English literature was identified. Titles and abstracts were reviewed by 2 authors (S.C. and Y.D.) to determine suitability for inclusion. Relevant articles were reassessed by reviewing the full text. Discrepancies in study inclusion were resolved by consensus (M.G.K.).

Study Selection: Clinical studies that compared corticosteroids plus intravenous immunoglobulin (IVIG) therapy with IVIG therapy alone in treating patients with KD. Studies either using corticosteroids as initial therapy or as rescue therapy were included.

Data Extraction and Synthesis: Investigators independently extracted the data information. Data were quantitatively synthesized using random-effects analysis.

Main Outcomes and Measures: Rate of coronary artery abnormalities.

Results: Sixteen comparative studies characterizing 2746 patients were analyzed. The duration of illness before corticosteroids therapy was significantly shorter in the initial corticosteroids subset than in the rescue corticosteroids subset. The rate of coronary artery abnormalities was significantly lower in adjunctive corticosteroids therapy than in IVIG therapy (odds ratio [OR], 0.424; 95% CI, 0.270-0.665). Meta-regression based on known variables demonstrated that the overall efficacy was negatively correlated with the duration of illness before corticosteroid therapy ($P < .001$). Subgroup analysis, including studies using corticosteroids plus IVIG as initial therapy, showed a more advantageous effect than IVIG alone regarding coronary artery abnormality prevention (OR, 0.320; 95% CI, 0.183-0.560), whereas this benefit was not found in a subgroup of studies using corticosteroids as rescue therapy. Further analysis found that patients predicted at baseline to be at high risk of IVIG resistance seemed to obtain the greatest benefit from adjunctive corticosteroid therapy regarding coronary artery abnormality prevention (OR, 0.240; 95% CI, 0.123-0.467). The fever duration was significantly reduced in the corticosteroids group. The favorable effects of corticosteroids were conferred without an increased risk of adverse events.

Conclusions and Relevance: This study highlights the importance of timing to prevent coronary artery complication in treating KD. High-risk patients with KD benefit greatly from a timely and potent adjunctive corticosteroid therapy strategy.

Chou, C. P., et al. (2016). "A male infant had subdural effusion and paroxysmal supraventricular tachycardia during the febrile episode of Kawasaki disease: a case report and literature review." BMC Pediatrics **16**: 71.

BACKGROUND: Kawasaki disease is an acute, febrile, self-limiting, inflammatory systemic vasculitis seen in early childhood, most commonly in those below 5 years of age. In Kawasaki disease, the coronary arteries are most commonly affected, which may lead to asymptomatic coronary artery ectasia or formation of an aneurysm. Paroxysmal supraventricular tachycardia(PSVT) is a severe and rare cardiovascular complication of Kawasaki disease. A case of Kawasaki disease presenting with unusual findings, including subdural effusion and PSVT is reported.

CASE PRESENTATION: This is a 4-month-10-day-old boy presents with anterior fontanelle bulging and moderate bilateral subdural effusion at the acute stage of Kawasaki disease and PSVT at the subacute stage of Kawasaki disease. The subdural effusion was resolution after intravenous immunoglobulin(IVIG) administration. And the PSVT was subsided after administered 3 doses of adenosine, 1 dose of amiodarone loading and Propranolol twice per day use. At 1-year follow-up has made a complete recovery with no arrhythmia episodes, developmental effects or abnormal neurologic findings.

CONCLUSION: Subdural effusion in the acute stage of Kawasaki disease may be an inflammatory response. It may resolves spontaneously after anti-inflammatory treatment such as IVIG infusion. PSVT is a severe cardiovascular complication of Kawasaki disease. In those who taking aspirin, we need to carefully observe the heart rhythm and PSVT side effects, especially in the first month.

Cohen, E. and R. Sundel (2016). "Kawasaki Disease at 50 Years." JAMA Pediatrics **170**(11): 1093-1099.
Importance: Kawasaki disease (KD) is the most recognized vasculitis of childhood. The condition's characteristic high fever, rash, mucositis, conjunctivitis, lymphadenopathy, and extremity changes are superficially unexceptional, and resolve spontaneously within a mean of 12 days. It is the acuity and the potential for life-changing damage to the coronary arteries that distinguish KD from conditions that mimic it and exemplify the unique aspects and challenges of vascular inflammation in children.
Observations: Although KD is an orphan disease, its role as a leading cause of acquired heart disease in children has led to significant efforts to determine its etiology, optimize diagnosis, and customize treatment according to individuals' needs. The result is that KD can now be controlled without sequelae in more than 95% of cases. Furthermore, advances in stratifying patients according to measurable risk factors allow therapy to be personalized in increasingly effective ways. High-risk patients, such as infants younger than 6 months, those with early evidence of coronary artery dilatation, and those with extreme abnormalities in laboratory test results, are often identified at presentation. This early identification allows them to be treated with corticosteroids in addition to intravenous immunoglobulin to improve their outcomes. Children with similar findings on laboratory tests and echocardiography may be treated based on algorithms for managing "incomplete KD" despite falling short of fulfilling classic diagnostic criteria. Children who do not respond to intravenous immunoglobulin are the focus of trials to minimize the duration of inflammation and thereby protect their coronary arteries in ways never before considered.
Conclusions and Relevance: Kawasaki disease is a hybrid condition at the junction of infectious diseases, immunology, rheumatology, and cardiology. Rather than being left an orphan disease, KD is bringing disciplines together to identify its genetic, pathophysiological, and hemodynamic features. In turn, this work promises to shed light on many other inflammatory conditions as well.

Esposito, S., et al. (2016). "Vaccines and Kawasaki disease." Expert Review of Vaccines **15**(3): 417-424.
The distinctive immune system characteristics of children with Kawasaki disease (KD) could suggest that they respond in a particular way to all antigenic stimulations, including those due to vaccines. Moreover, treatment of KD is mainly based on immunomodulatory therapy. These factors suggest that vaccines and KD may interact in several ways. These interactions could be of clinical relevance because KD is a disease of younger children who receive most of the vaccines recommended for infectious disease prevention. This paper shows that available evidence does not support an association between KD development and vaccine administration. Moreover, it highlights that administration of routine vaccines is mandatory even in children with KD and all efforts must be made to ensure the highest degree of protection against vaccine-preventable diseases for these patients. However, studies are needed to clarify currently unsolved issues, especially issues related to immunologic interference induced by intravenous immunoglobulin and biological drugs.

Gitomer, S. A., et al. (2016). "Pediatric lymphedema caused by diffuse cervical lymphadenopathy: A case report and review of the literature." International Journal of Pediatric Otorhinolaryngology **87**: 67-70.
Pediatric head and neck lymphedema is rare and there have not been any reported cases in children. Here we discuss severe, diffuse head and neck lymphedema in a child caused by compression of the internal jugular veins by lymphadenopathy from Kawasaki's disease. With steroid and intravenous immunoglobulin treatment, the lymphadenopathy improved and facial edema slowly resolved. In review of the literature, complications of head and neck lymphedema including airway obstruction and blindness are discussed. This case highlights the importance of the pediatric otolaryngologist considering lymphedema as a cause for facial swelling and monitoring for complications of lymphedema.

Gordon, J. B., et al. (2016). "The Spectrum of Cardiovascular Lesions Requiring Intervention in Adults

after Kawasaki Disease." JACC: Cardiovascular Interventions **9**(7): 687-696.
Objectives The aim of this study was to characterize the range of management issues raised by adults with cardiovascular sequelae from Kawasaki disease (KD) in childhood. Background Aneurysms resulting from vascular inflammation associated with KD in childhood may remain clinically silent until adulthood. Adults with large aneurysms, unstable angina, or myocardial infarction following KD in childhood present unique challenges to interventional cardiologists and cardiothoracic surgeons. Methods In an observational study of adults with histories of KD in childhood, data were collected regarding the medical histories and outcomes of 154 adult KD patients, of whom 21 underwent either percutaneous interventions or surgery. Results Of the 21 subjects with interventions, 11 had been diagnosed with KD in childhood, and 10 had histories of KD-compatible illnesses. Seventeen subjects were asymptomatic until experiencing acute cardiovascular symptoms: acute myocardial infarction (n = 12), angina (n = 2), end-stage congestive heart failure requiring cardiac transplantation (n = 1), and claudication (n = 2). Conclusions Cardiovascular complications in these subjects illustrate the following points: 1) even small to moderate-sized aneurysms that "normalize" on echocardiography in childhood can lead to stenosis and thrombosis decades after the acute illness; 2) coronary interventions without intravascular ultrasound may result in clinically significant underestimation of vessel luminal diameter; 3) failure to assess the extent of calcification may lead to suboptimal procedural outcomes; and 4) patients with symptomatic peripheral aneurysms may benefit from endarterectomy or resection. Interventional cardiologists should be aware of the potential challenges in treating this growing population of adults. © 2016 American College of Cardiology Foundation.

Hara, T., et al. (2016). "Kawasaki disease: a matter of innate immunity." Clinical & Experimental Immunology **186**(2): 134-143.
Kawasaki disease (KD) is an acute systemic vasculitis of childhood that does not have a known cause or aetiology. The epidemiological features (existence of epidemics, community outbreaks and seasonality), unique age distribution and clinical symptoms and signs of KD suggest that the disease is caused by one or more infectious environmental triggers. However, KD is not transmitted person-to-person and does not occur in clusters within households, schools or nurseries. KD is a self-limited illness that is not associated with the production of autoantibodies or the deposition of immune complexes, and it rarely recurs. Regarding the underlying pathophysiology of KD, innate immune activity (the inflammasome) is believed to play a role in the development of KD vasculitis, based on the results of studies with animal models and the clinical and laboratory findings of KD patients. Animal studies have demonstrated that innate immune pathogen-associated molecular patterns (PAMPs) can cause vasculitis independently of acquired immunity and have provided valuable insights regarding the underlying mechanisms of this phenomenon. To validate this concept, we recently searched for KD-specific PAMPs and identified such molecules with high specificity and sensitivity. These molecules have structures similar to those of microbe-associated molecular patterns (MAMPs), as shown by liquid chromatography-tandem mass spectrometry. We propose herein that KD is an innate immune disorder resulting from the exposure of a genetically predisposed individual to microbe-derived innate immune stimulants and that it is not a typical infectious disease.

Hu, P., et al. (2016). "Incomplete Kawasaki disease induced by measles in a 6-month-old male infant." International Journal of Dermatology **55**(1): e34-36.

Kim, K. Y. and D. S. Kim (2016). "Recent Advances in Kawasaki Disease." Yonsei Medical Journal **57**(1): 15-21.
Kawasaki disease (KD) is characterized with acute systemic vasculitis, occurs predominantly in children between 6 months to 5 years of age. Patients with this disease recover well and the disease is self-limited in most cases. Since it can lead to devastating cardiovascular complications, KD needs special attention. Recent reports show steady increases in the

prevalence of KD in both Japan and Korea. However, specific pathogens have yet to be found. Recent advances in research on KD include searches for genetic susceptibility related to KD and research on immunopathogenesis based on innate and acquired immunity. Also, search for etiopathogenesis and treatment of KD has been actively sought after using animal models. In this paper, the recent progress of research on KD was discussed.

Kim, W. and M. D. Stevenson (2016). "Temporal trends in testing for respiratory pathogens among infants <= 60 days of age who undergo lumbar puncture in the emergency department." Pediatrics. Conference: National Conference on Education **141**(1).
Purpose Febrile young infants often undergo an evaluation for serious bacterial infection with lumbar puncture in the emergency department setting yet a viral infection is often the source of fever. Since the advent of rapid laboratory testing for respiratory pathogens, little has been published regarding the prevalence of such testing and frequency of infection. The purpose of this study was to evaluate temporal trends in prevalence of testing for respiratory pathogens (RP) among infants <= 60 days who undergo lumbar puncture in the ED and describe the frequency of RP detection and concomitant bacterial infection. Methods We performed a retrospective chart review using microbiology data from the ED and inpatient settings of a single urban pediatric hospital. All infants <= 60 days who underwent lumbar puncture and had a cerebrospinal fluid (CSF) culture obtained in the ED between January 1, 2010 and December 31, 2014 were eligible. Blood, urine, and CSF culture results were recorded and pathogens were identified using standard criteria. Any results from rapid respiratory syncytial virus (RSV), rapid influenza, or multiplex PCR respiratory pathogen testing within 48 hours of the ED visit were also collected. Data were analyzed via descriptive statistics and logistic regression modeling was used to evaluate trends over time. Result(s): Among 1665 infants, the mean age was 27.8 days (SD=16.2) and 10 (0.6%) had a pathogen isolated on CSF culture; 26/1608 (1.6%) grew a pathogenic bacterium on blood culture, while 127/1603 (7.9%) had a positive urine culture. During the ED visit, 561 infants (34%) underwent any RP testing, while 779 infants (47%) had RP testing +/- 48 hours of the visit. On rapid antigen tests, 12/204 (5.8%) were positive for influenza and 50/414 (12.1%) were positive for RSV. On multiplex PCR testing, 130/404 infants (32%) tested positive for a RP. After adjustment for age, increasing year of visit was associated with viral testing within 48 hours of the ED visit (aOR 1.18 [95% CI 1.1, 1.27]. Among infants with any positive RP test, 12/188 (6.4%) had a positive urine culture and 2/188 (1.6% [95% CI: 0, 3.4%]) had bacteremia due to group B streptococcus at 46 and 53 days of life despite testing positive for coronavirus and influenza, respectively. Conclusion Testing for respiratory pathogens in young infants who undergo lumbar puncture in the ED is increasing, and detection of a respiratory pathogen occurs in approximately 1/3 of tested infants. Although the prevalence of bacteremia among infants <= 60 days who test positive for a respiratory pathogen is low, a positive test for a respiratory pathogen does not rule out bacteremia and the frequency of concomitant bacteriuria remains appreciable.

Kim, Y., et al. (2016). "Pathogens associated with febrile respiratory illnesses in Haitian children." Pediatrics. Conference: National Conference on Education **141**(1).
Background: There are limited data available on etiology of febrile respiratory illnesses in Haitian children. One of the most recent study of Caribbean countries by the Caribbean Epidemiology Centre showed significant incidence of respiratory syncytial virus (RSV) and influenza A virus in the Caribbean counties. However, this study did not include Haiti and was not focused on children. A recent Haitian study of children being admitted to the hospital showed significant morbidity and mortality from respiratory illnesses. Given the recent earthquake in Haiti and numerous international aid workers traveling to Haiti who may introduce new pathogens, determining the distribution of pathogens associated with febrile respiratory illness in Haitian children is important in optimizing their care. Objective(s): To determine the pathogens associated with febrile respiratory illnesses in Haitian children. Method(s): We have established a cohort of students attending schools run by the Christianville Foundation in the Gressier region of

Haiti. During the 2013-2014 and 2014-2015 academic year, nasal swabs were obtained from children presenting with febrile respiratory illness. The swabs were stored in -20C. Nucleic acid was isolated from these swabs using the nucleic acid isolation kit (Stratec) and real time PCR was performed using the Respiratory pathogens 21 plus kit (Fast-track Diagnostics). Result(s): The virus detected in order of frequency was rhinovirus 35.7%, influenza H1N1 13.7%, Adenovirus 6.6%, Enterovirus 6.0%, influenza B 4.9%, Coronavirus 43 3.8%, Human metapneumovirus 3.3%, influenza A 2.8%, Parainfluenza 4 2.7%, RSV 2.2%, Parainfluenza 2 2.2%, Bocavirus 1.6%, Parainfluenza 3 1.6%, Coronavirus 22 1.1%, Coronavirus HKU 1.1%, Parechovirus 0.5%, Parainfluenza 1 0%, and Coronavirus 63 0%. 27.4% of patients were positive for multiple viruses. As for bacteria detected, Streptococcus Pneumoniae 57%, Staphylococcus Aureus at 22%, Haemophilus influenza B 3.8%, Mycoplasma pneumonia 2.2%, and Chlamydia pneumonia 0.5%.18.7% of patients were positive for multiple bacteria. Conclusion(s): Rhinovirus was the most commonly detected virus of febrile respiratory illness in Haitian children. However, compared to other studies in the Caribbean region and other tropical countries, RSV incidence was low at only 2.2%. This may be due to the population studied with the youngest patient being 2 years of age and RSV being frequently detected in patients 2 years and younger. There was high frequency of Streptococcus Pneumoniae in this population at 57% but majority of these cases likely represent asymptomatic carrier status rather than the etiology of the febrile respiratory illness. Given the lack of immunization for Streptococcus Pneumoniae in Haiti, the rate of colonization is in line with previously published rates in unvaccinated countries. Haiti has started an initiative to vaccinate for Streptococcus Pneumoniae this year. Further studies will be required to validate the findings of this study and the efficacy of the vaccination program in Haiti.

Koibuchi, H., et al. (2016). "Endothelial dysfunction by flow-mediated dilation assessed ultrasonically in patients with Kawasaki Disease." Minerva Pediatrica **68**(2): 143-147.
Kawasaki Disease (KD) is a febrile disorder seen in infants and young children. One of the most serious complications of the disease is coronary aneurysm. Endothelial dysfunction is considered to underlie the etiopathology of coronary aneurysm. Flow-mediated dilation (FMD), as assessed ultrasonically, is used to observe the endothelial function. The current paper summarizes, by providing a systematic review, the clinical studies that have examined endothelial dysfunction by determining the FMD ultrasonically in patients with KD. A PubMed-based search found eight articles published until 2013. Six studies reported the FMD level to be significantly lower in the patients with KD compared to controls, while two studies reported no significant difference in the FMD level between those with and without KD. Although patients with KD appeared to have endothelial dysfunction in the current summary, most reports have been associated with limitations, such as a small size and no prospective design for vascular outcomes. Further studies are therefore needed to draw definite conclusions regarding whether patients with KD suffer from endothelial dysfunction as determined by the FMD and/or whether this determination can be useful for understanding and managing vascular complications in these patients.

Otheo, E., et al. (2016). "Low co-infection rate in children with community-acquired pneumonia in Spain." Open Forum Infectious Diseases. Conference: ID Week **3**(Supplement 1).
Background. Areas of priority research include defining the epidemiology of community- acquired pneumonia (CAP) after the development of the molecular diagnostic tests. Previous studies have reported high rates of combined infection (8-51%). Our objective is to describe the etiology of CAP in hospitalized children, with a focus on the incidence of co-infections. Methods. From April 2012 until March 2015, hospitalized children with CAP were recruited in two hospitals of Madrid, Spain. An extensive microbiological work-up was performed, including: blood cultures, S. pneumoniae by PCR in blood, S. pneumoniae antigen in urine, paired serum for M. pneumoniae, C. pneumoniae and L. pneumophila, and PCR for 16 viruses, M. pneumoniae and C. pneumoniae in nasopharyngeal aspirate (NPA). Culture and S. pneumoniae antigen in pleural fluid was added if thoracentesis was performed. Organisms were considered the causative agents of pneumonia in the following situations: any bacteria in blood culture or S. pneumoniae by PCR in blood,

urinary S. pneumoniae antigen plus C-reactive protein >100 mg/ L and/or procalcitonin >1.5 ng/mL, seroconversion to any agent, presence of nucleic acids of M. pneumoniae, C. pneumoniae, RSV, hMPV, ADV, PIV or flu virus on NPA, and any bacteria on culture or S. pneumoniae antigen detection in pleural fluid. Following recent recommendations, rhinovirus, enterovirus, bocavirus and coronavirus were excluded as causality, if detected. Results. We recruited 151 patients. They had a median age of 41 months (range 2- 201), and 53% were male. Two-thirds were under 60 months. A total of 93% were fully immunized against Hib, and 64% of them had received one or more dose of PCV13. One or more pathogens were documented in 66%: typical bacteria in 24 (16%, 23 [90%] of them S. pneumoniae), atypical bacteria in 31 (20%) (28 of them M. pneumoniae) and significant viruses in 60 (40%). Of note, half of the patients with M. pneumoniae were under 60 months. There were only 19 patients (13%) with co-infection with more than an agent. If we included non-significant viruses, 81% of patients had more than one organism identified and the co-detection rate raised up to 31%. Conclusion. Viruses are the main etiological agents of CAP in children. Considering significant etiological agents only, the co-infection rate was not as high as reported elsewhere. M. pneumoniae is not uncommon in children under 5 years.

Rigante, D., et al. (2016). "Critical Overview of the Risk Scoring Systems to Predict Non-Responsiveness to Intravenous Immunoglobulin in Kawasaki Syndrome." International Journal of Molecular Sciences **17**(3): 278.
Kawasaki syndrome (KS) is the most relevant cause of heart disease in children living in developed countries. Intravenous immunoglobulin (IVIG) has a preventive function in the formation of coronary artery abnormalities and a poor strictly-curative action in established coronary damage. More than two decades ago, the Harada score was set to assess which children with KS should be subject to administration of IVIG, evaluating retrospectively a large cohort of patients with regard to age, sex and laboratory data. Nowadays, high dose IVIG is administered to all children with a confirmed diagnosis of KS, but a tool for predicting non-responsiveness to the initial infusion of IVIG has not been found. The prediction of IVIG resistance is a crucial issue, as recognising these high-risk patients should consent the administration of an intensified initial treatment in combination with IVIG in order to prevent coronary injuries. Few reports have focused on factors, referring to both clinical parameters and laboratory data at the onset of KS, in order to predict which patients might be IVIG non-responsive. We have analysed three different risk scores which were formulated to predict IVIG resistance in Japanese children with typical KS, but their application in non-Japanese patients or in those with incomplete and atypical patterns of the disease has been studied in a fragmentary way. Overall, our analysis showed that early and definite ascertainment of likely IVIG non-responders who require additional therapies reducing the development of coronary artery involvement in children with KS is still a challenge.

Rodo, X., et al. (2016). "Revisiting the role of environmental and climate factors on the epidemiology of Kawasaki disease." Annals of the New York Academy of Sciences **1382**(1): 84-98.
Can environmental factors, such as air-transported preformed toxins, be of key relevance to the health outcomes of poorly understood human ailments (e.g., rheumatic diseases such as vasculitides, some inflammatory diseases, or even severe childhood acquired heart diseases)? Can the physical, chemical, or biological features of air masses be linked to the emergence of diseases such as Kawasaki disease (KD), Henoch-Schonlein purpura, Takayasu's aortitis, and ANCA-associated vasculitis? These diseases surprisingly share some common epidemiological features. For example, they tend to appear as clusters of cases grouped geographically and temporarily progress in nonrandom sequences that repeat every year in a similar way. They also show concurrent trend changes within regions in countries and among different world regions. In this paper, we revisit transdisciplinary research on the role of environmental and climate factors in the epidemiology of KD as a paradigmatic example of this group of diseases. Early-warning systems based on environmental alerts, if successful, could be implemented as a way to better

inform patients who are predisposed to, or at risk for, developing KD. Further research on the etiology of KD could facilitate the development of vaccines and specific medical therapies.

Sanderson, S. K., et al. (2016). "Laboratory-confirmed human coronavirus infections among children: Does type matter?" Open Forum Infectious Diseases. Conference: ID Week **3**(Supplement 1). Background. Human coronaviruses (HCoV) cause illness ranging from the common cold to life-threatening pneumonia. However, the reported clinical epidemiology and burden of HCoV infection is confounded by frequent codetection with other respiratory viruses. Although different types of HCoV can be detected by laboratory testing, few data exist describing single HCoV infection by type in children. Methods. We conducted a retrospective cohort study of children <18 years with single HCoV detection from December 2012 to February 2016 at Primary Children's Hospital (PCH), Salt Lake City, UT. Demographic, clinical, and financial data of children with moderate to severe single HCoV infection (hospitalized >=24 hours) were evaluated by HCoV type (HKU1, OC43, 229E, NL63). Testing was performed using the FilmArray Respiratory panel (BioFire Diagnostics, LLC, Salt Lake City, UT). Results. Over the study period, a respiratory virus was detected in 11 714 of 19 150 (61%) children undergoing respiratory viral testing at PCH, with HCoV accounting for 1267 (11%) of detected viruses. Of these, single HCoV infection occurred in 534 children (42% of HCoV detections) comprising the study cohort; 207 (39%) were hospitalized >=24 hours. The overall median age was 14 months (interquartile range [IQR], 3-46). A chronic medical condition was present in 62 (30%) children, with 69 (33%) requiring intensive care unit (ICU) admission and 28 (14%) requiring mechanical ventilation. The median length of stay (LOS) was 2.5 days (IQR, 1.5-4.7), and hospital cost was $6502 (IQR, $3708-$14 280) (table). Chronic medical conditions were noted more frequently in children with HCoV NL63 (32; 43%) compared with HCoV OC43 (14; 18%) (P = 0.008). Intensive care unit admission, mechanical ventilation, median hospital LOS, and cost were comparable among the different HCoV types. Death from HCoV (3; 1%) was rare among children with moderate to severe single HCoV infection. Conclusion. Human coronavirus infection is a common cause of respiratory illness among children. Among children with single HCoV detection, 35% to 42% of each type required hospitalization for >=24 hours. Outcomes in children with HCoV infection alone were comparable to each other and associated with a substantial clinical and economic burden for all of the HCoV types.

Singh, S., et al. (2016). "Kawasaki Disease: Issues in Diagnosis and Treatment - A Developing Country Perspective." Indian Journal of Pediatrics **83**(2): 140-145.
Kawasaki disease (KD) is a common vasculitis in children and is the commonest cause of pediatric acquired heart disease in children in Japan and countries in North America and the European Union. It is now being increasingly reported from several developing countries, including China and India. Diagnosis of KD is based on a set of clinical criteria, none of which is individually pathognomonic for this condition. Further, these clinical features appear sequentially over a few days and all findings may not be present at a given point of time. Like many other vasculitides, there is no confirmatory laboratory test for KD. Treatment of KD involves use of intravenous immunoglobulin (IVIg) and aspirin. IVIg is an expensive product and poses several difficulties for patients in developing countries who may find it difficult to access therapy even if a diagnosis of KD has been made in time. In this review, the authors discuss some of these challenges that pediatricians have to face while managing KD in resource constrained settings. © 2015, Dr. K C Chaudhuri Foundation.

Singh, S., et al. (2016). "Recent Advances in Kawasaki Disease - Proceedings of the 3rd Kawasaki Disease Summit, Chandigarh, 2014." Indian Journal of Pediatrics **83**(1): 47-52.
Kawasaki disease (KD) is the most common cause of acquired heart disease in children in Japan, North America and Europe. It is now being increasingly recognized from the developing countries as well. If not diagnosed and treated in time, KD can result in coronary artery abnormalities in approximately 15-25% cases. The long-term consequences of these abnormalities may manifest

in adults as myocardial ischemia and congestive heart failure. Intravenous immunoglobulin (IVIg) remains the drug of choice for treatment of KD, but several new agents like infliximab, cyclosporine, glucocorticoids and statins are now being increasingly used in these patients. While echocardiography has been the preferred imaging modality hitherto, CT coronary angiography has emerged as an exciting new supplementary option and provides an entirely new dimension to this disease. The incidence of KD has shown a progressive increase in several countries and it is likely that this disease would impact public health programmes in the near future even in the developing countries.

Soderman, M., et al. (2016). "Frequent respiratory viral infections in children with febrile neutropenia - A prospective follow-up study." PLoS ONE **11 (6) (no pagination)**(e0157398).
Objective Febrile neutropenia is common in children undergoing chemotherapy for the treatment of malignancies. In the majority of cases, the cause of the fever is unknown. Although respiratory viruses are commonly associated with this condition, the etiologic significance of this finding remains unclear and is therefore the subject of this study. Study design Nasopharyngeal aspirates were collected during 87 episodes of febrile neutropenia in children age 0-18 years, being treated at a children's oncology unit between January 2013 and June 2014. Real-time polymerase chain reaction was used to determine the presence of 16 respiratory viruses. Follow-up samples were collected from children who tested positive for one or more respiratory viruses. Rhinoviruses were genotyped by VP4/ VP2 sequencing. Fisher's exact test and Mann-Whitney U test were used for group comparisons. Results At least one respiratory virus was detected in samples from 39 of 87 episodes of febrile neutropenia (45%), with rhinoviruses the most frequently detected. Follow-up samples were collected after a median of 28 days (range, 9-74 days) in 32 of the 39 virus-positive episodes. The respiratory viral infection had resolved in 25 episodes (78%). The same virus was detected at follow-up in one coronavirus and six rhinovirus episodes. Genotyping revealed a different rhinovirus species in two of the six rhinovirus infections. Conclusion The frequency of respiratory viral infections in this group of patients suggests an etiologic role in febrile neutropenia. However, these findings must be confirmed in larger patient cohorts.

Whitin, J. C., et al. (2016). "A novel truncated form of serum amyloid a in kawasaki disease." PLoS ONE **11**(6).
Background Kawasaki disease (KD) is an acute vasculitis in children that can cause coronary artery abnormalities. Its diagnosis is challenging, and many cytokines, chemokines, acute phase reactants, and growth factors have failed evaluation as specific biomarkers to distinguish KD from other febrile illnesses. We performed protein profiling, comparing plasma from children with KD with febrile control (FC) subjects to determine if there were specific proteins or peptides that could distinguish the two clinical states. Materials and Methods Plasma from three independent cohorts from the blood of 68 KD and 61 FC subjects was fractionated by anion exchange chromatography, followed by surface-enhanced laser desorption ionization (SELDI) mass spectrometry of the fractions. The mass spectra of KD and FC plasma samples were analyzed for peaks that were statistically significantly different. Results A mass spectrometry peak with a mass of 7,860 Da had high intensity in acute KD subjects compared to subacute KD ($p = 0.0003$) and FC ($p = 7.9 \times 10\text{-}10$) subjects. We identified this peak as a novel truncated form of serum amyloid A with N-terminal at Lys-34 of the circulating form and validated its identity using a hybrid mass spectrum immunoassay technique. The truncated form of serum amyloid A was present in plasma of KD subjects when blood was collected in tubes containing protease inhibitors. This peak disappeared when the patients were examined after their symptoms resolved. Intensities of this peptide did not correlate with KD-associated laboratory values or with other mass spectrum peaks from the plasma of these KD subjects. Conclusions Using SELDI mass

spectrometry, we have discovered a novel truncated form of serum amyloid A that is elevated in the plasma of KD when compared with FC subjects. Future studies will evaluate its relevance as a diagnostic biomarker and its potential role in the pathophysiology of KD.

Yun, H. W., et al. (2016). "Comparison of cervical-lymph-node-first presentation of Kawasaki disease and typical Kawasaki disease." Pediatric Infection and Vaccine **23**(1): 10-17.
Purpose: The diagnosis of Kawasaki disease depends on clinical symptoms, which makes it difficult to diagnose early in patients with only cervical lymphadenopathy. The purpose of this study is to understand the clinical characteristics of cervical-lymph-node-first presentation of Kawasaki disease and compare them with those of typical Kawasaki disease. Methods: We surveyed 283 patients who were admitted to Hallym Sacred Heart Hospital and were diagnosed with Kawasaki disease from January 2012 to December 2014. The patients were divided into two groups: cervical-lymph-node-first presentation of Kawasaki disease (LKD, N=24) and typical Kawasaki disease (KD, N=259). The medical records were retrospectively reviewed. Results: The mean age of the LKD group was higher than that of the KD group (P =0.04). At admission, the LKD patients had on average 1.62 out of 5 symptoms, whereas the KD patients had 3.47. The time from fever to diagnosis and administration of IV immunoglobulin was longer in the LKD group than in the KD group (P <0.001). The mean C-reactive protein of the LKD group was higher than that of the KD group (P = 0.01). There were no statistical differences in the presence of coronary artery complications between the two groups at two weeks or at two months after diagnosis (P =0.52, P =0.08). Conclusions: The Kawasaki disease patients with fever and cervical lymphadenopathy usually do not present obvious clinical symptoms, which makes it hard to diagnose in the early phase of disease. Clinician must pay attention when examining these patients.

Zhang, H., et al. (2016). "Meta-analysis of risk factors associated with atherosclerosis in patients with Kawasaki disease." World Journal of Pediatrics **12**(3): 308-313.
BACKGROUND: Kawasaki disease (KD) has now become the leading cause of acquired heart disease among children in developed countries. This study investigated whether patients with KD have an increased risk of atherosclerosis.
METHODS: Electronic databases, including PubMed, Embase and Springer link, were searched through June 1, 2015, for eligible studies. Studies were included when they met the following criteria: 1) an observational study focusing on evaluating the risk factors for atherosclerosis in patients with KD; 2) KD was diagnosed clinically according to the Japan Kawasaki Disease Research Committee or American Heart Association's diagnostic criteria; 3) the study subjects were KD patients without coronary heart disease or related cardiovascular disease (KD group) and non-KD patients as control (control group), and 4) investigation of important atherosclerosis risk factors, total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides (TG), systolic blood pressure (SBP), and flowmediated dilatation (FMD). The methodological quality of the included studies was evaluated using the Newcastle- Ottawa Scale. Mean difference (MD) and relative risk (RR) and corresponding 95% confidence intervals (CI) were used to calculate the pooled results.
RESULTS: Sixteen studies were included with a total of 870 patients, including 421 KD patients and 449 non-KD controls. Differences in TG and SBP between KD patients and controls were not significant; in contrast, TC and LDL levels were significantly higher in KD patients than the controls, whereas FMD in the KD patients was significantly lower.
CONCLUSIONS: KD patients may have an increased risk of developing atherosclerosis.

Abrams, J. Y., et al. (2015). "Childhood vaccines and Kawasaki disease, Vaccine Safety Datalink, 1996-2006." Vaccine **33**(2): 382-387.
Background: Kawasaki disease is a childhood vascular disorder of unknown etiology. Concerns have been raised about vaccinations being a potential risk factor for Kawasaki disease. Methods: Data from the Vaccine Safety Datalink were collected on children aged 0-6 years at seven managed care organizations across the United States. Defining exposure as one of several time periods up to 42 days after vaccination, we conducted Poisson regressions controlling for age, sex, season, and managed care organization to determine if rates of physician-diagnosed and verified Kawasaki disease were elevated following vaccination compared to rates during all unexposed periods. We also performed case-crossover analyses to control for unmeasured confounding. Results: A total of 1,721,186 children aged 0-6 years from seven managed care organizations were followed for a combined 4,417,766 person-years. The rate of verified Kawasaki disease was significantly lower during the 1-42 days after vaccination (rate ratio. = 0.50, 95% CL. = 0.27-0.92) and 8-42 days after vaccination (rate ratio. = 0.45, 95% CL. = 0.22-0.90) compared to rates during unexposed periods. Breaking down the analysis by vaccination category did not identify a subset of vaccines which was solely responsible for this association. The case-crossover analyses revealed that children with Kawasaki disease had lower rates of vaccination in the 42 days prior to symptom onset for both physician-diagnosed Kawasaki disease (rate ratio. = 0.79, 95% CL. = 0.64-0.97) and verified Kawasaki disease (rate ratio. = 0.38, 95% CL. = 0.20-0.75). Conclusions: Childhood vaccinations' studied did not increase the risk of Kawasaki disease; conversely, vaccination was associated with a transient decrease in Kawasaki disease incidence. Verifying and understanding this potential protective effect could yield clues to the underlying etiology of Kawasaki disease. © 2014 .

Bagheri, M. M., et al. (2015). "Is alopecia a clinical symptom in Kawasaki disease?" Journal of Kerman University of Medical Sciences **22**(1): 112-116.
A 20-months-old infant was admitted with prolonged fever, bilateral non-purulent conjunctivitis, strawberry tongue, lip cracking and maculopapular rash. Left branch coronary aneurysm formation was detected in Color-Doppler echocardiography. The diagnosis was Kawasaki disease. After 6 weeks, he had alopecia totalis. Although, alopecia areata has been seen in Kawasaki disease, but alopecia totalis is very rare with unknown etiology. © 2015, Kerman University of Medical Sciences. All rights reserved.

Dietz, S. M., et al. (2015). "Peripheral Endothelial (Dys)Function, Arterial Stiffness and Carotid Intima-Media Thickness in Patients after Kawasaki Disease: A Systematic Review and Meta-Analyses." PLoS ONE [Electronic Resource] **10**(7): e0130913.
BACKGROUND: Kawasaki disease (KD) is a systemic pediatric vasculitis. Its main complication is the development of coronary arterial aneurysms (CAA), causing an increased risk for ischemia and myocardial infarction. It is unclear whether KD patients, apart from the presence of CAA, have an increased cardiovascular disease (CVD) risk due to the previous systemic vasculitis. The aim of this study was to systematically review and meta-analyse the literature regarding surrogate markers for CVD risk in KD patients.
METHODS: Medline and Embase were searched for articles comparing endothelial dysfunction (flow-mediated dilation, nitroglycerin-mediated dilation and peripheral arterial tonometry), vascular stiffness (stiffness index, pulse wave velocity) and carotid intima-media thickness (cIMT) between patients and controls. Two investigators assessed the articles for eligibility and evaluated quality.
RESULTS: Thirty studies were included. For all outcomes, moderate to high heterogeneity between studies was found. Most studies reported a decreased flow-mediated dilation in the whole KD- and CAA-positive group compared to controls, while data on CAA-negative patients were conflicting. The stiffness index was increased in the majority of studies evaluating the whole KD- and CAA-positive group, but not in most studies on CAA-negative patients. Mean cIMT was neither significantly increased in the whole KD-group nor in the CAA-positive group nor in most

studies studying CAA-negative patients. Studies measuring maximum cIMT were conflicting.
CONCLUSION: Literature suggests that surrogate markers for CVD risk in KD patients are increased in CAA-positive but not in CAA-negative patients. This may indicate that CAA-positive patients should be monitored for CVD in later life. The results of this review have to be interpreted with care due to substantial heterogeneity between studies and methodological limitations, as well as the lack of long-term follow-up studies.

Ding, Y., et al. (2015). "Profiles of responses of immunological factors to different subtypes of Kawasaki disease." BMC Musculoskeletal Disorders **16**(1).
Background: The responses of immunological factors to different subtypes of Kawasaki disease (KD) remain poorly understood. Methods: We recruited 388 patients with KD, 160 patients with infectious febrile disease and 85 normal children who served as control subjects. Both the levels and percentages of T lymphocyte subsets, natural killer cells (NK cells) and B cells were analyzed via flow cytometry. The levels of serum IgG, IgM, IgA and C3, C4 were assessed via velocity scatter turbidimetry. Results: The most significant differences noted between the patients with infectious febrile disease and the normal children were the elevated levels of B cells, C3 and the ratio of CD4/CD8, and the decreased levels of CD8+ T cells and NK cells, as well as the moderate increase in the absolute value of the CD3+ cells. The decreased T cell levels and the elevated B cell levels were helpful in distinguishing typical KD from atypical KD; the elevated T cell levels, the elevated NK cell and B cell levels and the decreased B cell levels were helpful in predicting the effectiveness of IVIG; low C3 and C4 levels were linked with prodromal infections. Conclusions: Lymphocytes subsets and complement markers may be useful in differentiating among the different subtypes of KD and in helping clinicians understand the pathophysiology of KD.

Dinulos, J. G. (2015). "What's new with common, uncommon and rare rashes in childhood." Current Opinion in Pediatrics **27**(2): 261-266.
PURPOSE OF REVIEW: Children with rashes account for many of the outpatient visits to a general pediatrician. As such, pediatricians are often the first to identify and treat these rashes. Establishing an approach to common, uncommon and rare pediatric rashes assists in accurate assessment. This review highlights newly identified clinical patterns and disease severity.
RECENT FINDINGS: Group A beta-hemolytic streptococci (GABHS) have been shown to be an important cause of intertrigo and to cause more widespread disease in some instances. Superficial skin infections with GABHS have been associated with strains secreting exfoliating toxins, whereas deeper infections have been associated with superantigen toxins. Hand-foot-and-mouth disease (HFMD) outbreaks have occurred with more virulent strains, causing more widespread disease that may be confused with eczema herpeticum or varicella. Mycoplasma pneumoniae has been shown to be an important cause of common disorders such as urticaria, and less common disorders such as Stevens-Johnson syndrome and Mycoplasma-associated mucositis. Recurrent toxin-mediated erythema is a recently described entity that must be differentiated from Kawasaki disease.
SUMMARY: The number of rashes acquired in childhood is vast, requiring the pediatrician to be able to identify worrisome rashes from those with a more benign course. Key clinical signs may assist in clinical diagnosis and treatment.

Drago, F., et al. (2015). "A Case of Complete Adult-Onset Kawasaki Disease: A Review of Pathogenesis and Classification." Dermatology **231**(1): 5-8.
Kawasaki disease (KD) is an acute systemic vasculitis that occurs primarily in children and rarely in adults, possibly after bacterial or viral infections in genetically susceptible hosts. KD may frequently be undiagnosed especially in adult patients without the presence of all the classical clinical criteria (incomplete or atypical KD). In addition, many differential diagnoses could be considered. Here, we report a case of KD in an adult patient with clinical features characteristic of the classical form. KD requires a long-term management in both paediatric and adult patients, in

order to avoid complications that could follow both the acute and retrospective diagnoses of KD.

Greco, A., et al. (2015). "Kawasaki disease: an evolving paradigm." Autoimmunity Reviews **14**(8): 703-709.
Kawasaki disease (KD) is a self-limited childhood systemic vasculitis that exhibits a specific predilection for the coronary arteries. KD predominantly affects young children between the ages of 6months and 4years. Incidence rates in Asians are up to 20 times higher than Caucasians. The aetiology of KD is not known. One reasonable open hypothesis is that KD is caused by an infectious agent that produces an autoimmune disease only in genetically predisposed individuals. The typical presentation of KD is a young child who has exhibited a high swinging fever for five or more days that persists despite antibiotic and/or antipyretic treatment. The lips are dry and cracked. There is a characteristic strawberry tongue, and a diffuse erythema of oropharyngeal mucosal surfaces. Lymphadenopathy is usually unilateral and confined to the anterior cervical triangle. Coronary aneurysms generally appear during the convalescence phase (beginning during the second week). The absence of any laboratory tests for KD means that the diagnosis is made by the presence of a constellation of clinical features. The aim of echocardiography is to assess the presence of coronary artery dilatation or aneurysm formation. Effective therapies exist for most patients with acute KD, but the exact mechanisms of action are not clear. Treatment with aspirin and intravenous immunoglobulins (IVIG) are first-line therapies. However, options are plentiful for the children who fail this treatment, but these treatments are not as beneficial. Some centres attempt to salvage resistant patients using intravenous pulsed doses of methylprednisolone. Other centres use infliximab or combinations of these approaches.

Kawasaki, T., et al. (2015). "[Three Cases of Moyamoya Disease with a History of Kawasaki Disease]." No Shinkei Geka - Neurological Surgery **43**(11): 1005-1010.
Here, we report three cases of moyamoya disease with a history of Kawasaki disease. A 33-year-old man was found to have stenotic lesions of the internal carotid arteries(ICAs)on both sides at a nearby hospital where he visited complaining of headache and lisping. He had received immunoglobulin therapy for Kawasaki disease at the ages of 1, 2, and 6 years. MRI showed only a chronic ischemic lesion in the white matter. Angiography showed occlusion at the terminal portion of the ICAs on both sides. He was diagnosed with moyamoya disease, but as he had no symptoms and preserved cerebral blood flow (CBF), he was kept under observation. An 8-year-old boy was diagnosed with moyamoya disease and underwent right encephaloduroarteriosynangiosis at a nearby hospital. He had received immunoglobulin therapy for Kawasaki disease at the age of 1 year. His ischemic symptoms worsened. Although MRI detected no apparent ischemic lesion, angiography revealed severe stenosis at the terminal portions of the ICAs on both sides, and 123I-IMP SPECT showed CBF impairment. Bilateral direct bypass was performed. His father was subsequently also diagnosed with moyamoya disease. A 4-year-old girl with epilepsy was diagnosed with moyamoya disease at a nearby hospital. She had been treated with aspirin for Kawasaki disease at the age of 1 year. MRI detected no remarkable ischemic lesions, but angiography revealed mild stenosis at the terminal portions of the ICAs on both sides. Five months later, her ischemic symptoms were worsening with progressing stenotic lesions, and she underwent bilateral direct bypass.

Kontopoulou, T., et al. (2015). "Adult Kawasaki disease in a European patient: a case report and review of the literature." Journal of Medical Case Reports [Electronic Resource] **9**: 75.
INTRODUCTION: Kawasaki disease is an acute necrotising vasculitis of the medium- and small-sized vessels, occurring mainly in Japanese and Korean babies and children, aged 6 months to 5 years. Its main complication is damage of coronary arteries, which has the potential to be fatal. Here we report a rare case of Kawasaki disease that occurred in a 20-year-old Greek adult.
CASE PRESENTATION: A 20-year-old Greek man presented with high fever, appetite loss, nausea and vomiting, headache and significant malaise. He had an erythema of the palms and strikingly red lips and conjunctiva. As he did not respond to broad-spectrum antibiotics and after having

excluded other possible diagnoses, the diagnosis of Kawasaki disease was set. He was treated with intravenous immunoglobulin and oral aspirin on the 10th day since the onset of the illness. His clinico-laboratory response was excellent and no coronary artery aneurysms were detected in coronary artery computed tomography performed 1 month later.
CONCLUSIONS: This report of an adult case of European Kawasaki disease may be of benefit to physicians of various specialties, including primary care doctors, hospital internists, intensivists and cardiologists. It demonstrates that a case of prolonged fever, unresponsive to antibiotics, in the absence of other diagnoses may be an incident of Kawasaki disease. It is worth stressing that such a diagnosis should be considered, even if the patient is adult and not of Asian lineage.

Lee, A. M., et al. (2015). "Role of TGF-beta Signaling in Remodeling of Noncoronary Artery Aneurysms in Kawasaki Disease." Pediatric & Developmental Pathology **18**(4): 310-317.
Coronary artery aneurysms (CAA) remain an important complication of Kawasaki disease (KD), the most common form of pediatric acquired heart disease in developed countries. Potentially life-threatening CAA develop in 25% of untreated children and 5% of children treated with high-dose intravenous immunoglobulin during the acute phase of the self-limited vasculitis. Noncoronary artery aneurysms (NCAA) in extraparenchymal, muscular arteries occur in a minority of patients with KD who also have CAA, yet little is understood about their formation and remodeling. We postulated that activation of the transforming growth factor-beta (TGF-beta) pathway in KD may influence formation and remodeling of aneurysms in iliac, femoral, and axillary arteries, the most common sites for NCAA. We studied a resected axillary artery from one adult and endarterectomy tissue from the femoral artery from a second adult, both with a history of CAA and NCAA following KD in infancy. Histology of the axillary artery aneurysm revealed destruction of the internal elastic lamina and recanalization of organized thrombus, while the endarterectomy specimen showed dense calcification and luminal myofibroblastic proliferation. Immunohistochemistry for molecules in the TGF-beta signaling pathway revealed increased expression of TGF-beta2, TGF-beta receptor 2, and phosphorylated SMAD3. These findings suggest ongoing tissue remodeling of the aneurysms decades after the acute injury and demonstrate the importance of the TGF-beta signaling pathway in this process.

Lin, K. H., et al. (2015). "Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta-analysis." BMJ Open **5**(4): e006703.
OBJECTIVE: To examine the diagnostic value of serum B-type natriuretic peptide (BNP) in acute Kawasaki disease (KD).
DESIGN: Systematic review and meta-analysis.
DATA SOURCES: A systematic literature search strategy was designed and carried out using MEDLINE, EMBASE and the Cochrane Library from inception to December 2013. We also performed manual screening of the bibliographies of primary studies and review articles, and contacted authors for additional data.
STUDY ELIGIBILITY CRITERIA: We included all BNP and NT-pro (N-terminal prohormone) BNP assay studies that compared paediatric patients with KD to patients with febrile illness unrelated to KD. We excluded case reports, case series, review articles, editorials, congress abstracts, clinical guidelines and all studies that compared healthy controls.
PRIMARY AND SECONDARY OUTCOME MEASURES: The performance characteristics of BNP were summarised using forest plots, hierarchical summary receiver operating characteristic (ROC) curves and bivariate random effects models.
RESULTS: We found six eligible studies including 279 cases of patients with KD and 203 febrile controls. Six studies examined NT-proBNP and one examined BNP. In general, NT-proBNP is a specific and moderately sensitive test for identifying KD. The pooled sensitivity was 0.89 (95% CI 0.78 to 0.95) and the pooled specificity was 0.72 (95% CI 0.58 to 0.82). The area under the summary ROC curve was 0.87 (95% CI 0.83 to 0.89). The positive likelihood ratio (LR+ 3.20, 95% CI 2.10 to 4.80) was sufficiently high to be qualified as a rule-in diagnostic tool in the context of high pre-test probability and compatible clinical symptoms. A high degree of heterogeneity was found

using the Cochran Q statistic.
CONCLUSIONS: Current evidence suggests that NT-proBNP may be used as a diagnostic tool for KD. NT-proBNP has high diagnostic value for identifying KD in patients with protracted undifferentiated febrile illness. Prospective large cohort studies are needed to help determine best cut-off values and further clarify the role of NT-proBNP in the diagnosis process of KD.

Parthasarathy, P., et al. (2015). "Upcoming biomarkers for the diagnosis of Kawasaki disease: A review." Clinical Biochemistry **48**(16-17): 1188-1194.
Kawasaki disease (KD) is a major cause of acquired heart disease among children and increases the risk of myocardial infarction. While the biochemical basis of the disease is unclear, the evidence suggests interplay between a microbial infection and a genetic predisposition in the development of the disease. Diagnosis of KD based on clinical observation is not completely reliable and is problematic due to the time-sensitive nature of the disease. Hence, identification of inflammatory, proteomic, and genetic biomarkers may assist in earlier and more effective diagnosis and treatment. This review of observational studies and clinical trials analyzes biomarkers in recent research that may be used to establish a gold standard test for KD diagnosis. 65 articles in the literature are assessed to investigate these new biomarkers in addition to biomarkers presently in use. ESR>=40mm/h, leukocyte count >=16*10(9)/L and increased WBC count are together suggestive of the presence of KD. Among proteomic biomarkers, elevated NT-proBNP and differing levels of several other proteomic biomarkers such as iNOS in monocytes and neutrophils have been observed in KD patients. Genetic polymorphisms of six HLA class I genes have also been linked with the disease, alongside MICA alleles A4 and A5.1. The results suggest that NT-proBNP is currently a very promising biomarker for future investigation; further research is warranted to allow for accurate and early detection of the disease using this biomarker.

Patel, R. M. and S. T. Shulman (2015). "Kawasaki disease: a comprehensive review of treatment options." Journal of Clinical Pharmacy & Therapeutics **40**(6): 620-625.
WHAT IS KNOWN AND OBJECTIVE: Kawasaki disease (KD) is an acute self-limiting systemic vasculitis with specific predilection for the coronary arteries that affects previously healthy young infants and children. It is the leading cause of childhood-acquired heart disease in the developed world. Although the stimulus for the cascade of inflammation in KD is unknown, prompt treatment within 10 days of symptom onset has been shown to improve clinical outcomes and reduce the risk of coronary artery complications. Standard initial therapy is intravenous immunoglobulin (IVIG) and aspirin. Non-responders to initial therapy remain a challenge. This present review summarizes the treatment options for initial and refractory KD, including the role of steroids and other immunosuppressive therapies.
METHODS: Literature search using PubMed database to identify pharmacologic studies in KD using the terms Kawasaki disease, intravenous immunoglobulin, refractory, corticosteroids, infliximab, cyclosporine, methotrexate, high risk from January 1988-May 2015 was performed. Bibliographies of selected references were also evaluated for relevant articles. Results were limited to those published in English. All articles identified from the PubMed searches were evaluated.
RESULTS AND DISCUSSION: Initial IVIG therapy results in rapid resolution of clinical symptoms in 80-90% of patients and has been shown to reduce the risk of coronary disease. Although concomitant aspirin remains the standard of care for the initial management of KD, the evidence to support its efficacy in improving coronary artery outcomes are lacking. Initial therapy with corticosteroids in addition to intravenous immunoglobulin and aspirin improves outcomes in patients in Japan. However, identifying patients at high risk who may benefit from additional corticosteroids in heterogeneous populations has been challenging. Therapeutic options for non-responders to initial therapy are also challenging given the paucity of data. Patients who fail to respond to the first dose of IVIG will most often receive a second dose. Patients who fail to respond to two doses of IVIG present a unique challenge as the appropriate treatment remains

uncertain. Although their effectiveness remains unproven, treatment with infliximab, cyclosporine or methotrexate may be considered in those patients who fail multiple doses of IVIG and steroids.
WHAT IS NEW AND CONCLUSION: The role of steroids in high-risk non-Japanese patients is unclear, with the biggest challenge being early identification of patients at high risk of developing adverse coronary artery outcomes. Limited data evaluating other immunosuppressive agents are available and should be reserved for patients failing two doses of IVIG. Although recent advances in research have broadened our understanding of the epidemiology, genetic susceptibility and pathogenesis of KD, the aetiology of KD remains unclear. Ongoing research will help determine more precise pathogenesis and may assist in developing a diagnostic test as well as identifying new targets for more precise treatment interventions.

Rizk, S. R. Y., et al. (2015). "Acute myocardial ischemia in adults secondary to missed Kawasaki disease in childhood." American Journal of Cardiology **115**(4): 423-427.
Coronary artery aneurysms that occur in 25% of untreated Kawasaki disease (KD) patients may remain clinically silent for decades and then thrombose resulting in myocardial infarction. Although KD is now the most common cause of acquired heart disease in children in Asia, the United States, and Western Europe, the incidence of KD in Egypt is unknown. We tested the hypothesis that young adults in Egypt presenting with acute myocardial ischemia may have coronary artery lesions because of KD in childhood. We reviewed a total of 580 angiograms of patients ≤40 years presenting with symptoms of myocardial ischemia. Coronary artery aneurysms were noted in 46 patients (7.9%), of whom 9 presented with myocardial infarction. The likelihood of antecedent KD as the cause of the aneurysms was classified as definite (n = 10), probable (n = 29), or equivocal (n = 7). Compared with the definite and probable groups, the equivocal group had more traditional cardiovascular risk factors, smaller sized aneurysms, and fewer coronary arteries affected. In conclusion, in a major metropolitan center in Egypt, 6.7% of adults aged ≤40 years who underwent angiography for evaluation of possible myocardial ischemia had lesions consistent with antecedent KD. Because of the unique therapeutic challenges associated with these lesions, adult cardiologists should be aware that coronary artery aneurysms in young adults may be because of missed KD in childhood.

Rowley, A. H. (2015). "The Complexities of the Diagnosis and Management of Kawasaki Disease." Infectious Disease Clinics of North America **29**(3): 525-537.
Kawasaki disease (KD) must be considered in the differential diagnosis of any child with fever for 4 to 5 days and compatible clinical and laboratory features, and in any infant with prolonged fever and compatible laboratory features, even in the absence of the classic clinical signs. Prompt therapy is required, because delayed or unrecognized KD can lead to lifelong heart disease or death in previously healthy children. Most children with KD respond to a single 2 g/kg dose of intravenous gammaglobulin with oral aspirin, but a small subset require additional therapies to resolve the clinical illness.

Saguil, A., et al. (2015). "Diagnosis and management of kawasaki disease." American Family Physician **91**(6): 365-371.
Kawasaki disease is an acute, systemic vasculitis that predominantly affects patients younger than five years. It represents the most prominent cause of acquired coronary artery disease in childhood. In the United States, 19 per 100,000 children younger than five years are hospitalized with Kawasaki disease annually. According to U.S. and Japanese guidelines, Kawasaki disease is a clinical diagnosis. Classic (typical) Kawasaki disease is diagnosed based on the presence of a fever lasting five or more days, accompanied by four out of five findings: bilateral conjunctival injection, oral changes such as cracked and erythematous lips and strawberry tongue, cervical lymphadenopathy, extremity changes such as erythema or palm and sole desquamation, and polymorphous rash. Incomplete (atypical) Kawasaki disease occurs in persons with fever lasting

five or more days and with two or three of these findings. Transthoracic echocardiography is the diagnostic imaging modality of choice to screen for coronary aneurysms, although other techniques are being evaluated for diagnosis and management. Treatment for acute disease is intravenous immunoglobulin and aspirin. If there is no response to treatment, patients are given a second dose of intravenous immunoglobulin with or without corticosteroids or other adjunctive treatments. The presence and severity of coronary aneurysms and obstruction at diagnosis determine treatment options and the need, periodicity, and intensity of long-term cardiovascular monitoring for potential atherosclerosis.

Seaton, K. K. and A. Kharbanda (2015). "Evidence-based management of Kawasaki disease in the emergency department." Pediatric Emergency Medicine Practice **12**(1): 1-20; quiz 21.
Kawasaki disease, also known as mucocutaneous lymph node syndrome, was first described in Japan in 1967. It is currently the leading cause of acquired heart disease in children in the United States. Untreated Kawasaki disease may lead to the formation of coronary artery aneurysms and sudden cardiac death in children. This vasculitis presents with fever for >= 5 days, plus a combination of key criteria. Because each of the symptoms commonly occurs in other childhood illnesses, the disease can be difficult to diagnose, especially in children who present with an incomplete form of the disease. At this time, the etiology of the disease remains unknown, and there is no single diagnostic test to confirm the diagnosis. This issue reviews the presentation, diagnostic criteria, and management of Kawasaki disease in the emergency department. Emergency clinicians should consider Kawasaki disease as a diagnosis in pediatric patients presenting with prolonged fever, as prompt evaluation and management can significantly decrease the risk of serious cardiac sequelae.

Sehgal, S., et al. (2015). "Epidemiology, Clinical Presentation, and Outcomes of Kawasaki Disease among Hospitalized Children in an Inner City Hospital before and after Publication of the American Academy of Pediatrics/American Heart Association Guidelines for Treatment of Kawasaki Disease: An 11-Year Period." Clinical Pediatrics **54**(13): 1283-1289.
The effect of 2004 Kawasaki disease (KD) guidelines on diagnosis and outcome of KD is lacking. We studied the epidemiology of KD in our region and compared the incidence, presentation, and outcome of KD before and after publication of the guidelines. A retrospective chart review was conducted for patients admitted with a diagnosis of KD. Demographics, laboratory data, and clinical data were collected. Comparison was made between 2 groups: prepublication (2000-2004) and postpublication (2005-2009) of guidelines. A total of 312 children were included; 64% were African American, 23% White, and 2% Asian; 61% were boys; 79% were complete KD, and 66% were in winter/spring. There was a significant increase in KD cases over the 11 years. There was no significant difference in clinical findings and outcome between the 2 groups. KD admissions in our region significantly increased during the postpublication period. There was no difference in clinical presentation, laboratory findings, or outcome between the 2 groups. The Author(s) 2015.

Shulman, S. T. and A. H. Rowley (2015). "Kawasaki disease: insights into pathogenesis and approaches to treatment." Nature Reviews Rheumatology **11**(8): 475-482.
This Review summarizes recent advances in understanding of the pathologic processes and pathophysiologic mechanisms leading to coronary arteritis in Kawasaki disease, and describes current approaches to its treatment. Kawasaki disease is the most common cause of acquired heart disease among children in developed countries, in whom the resulting coronary artery abnormalities can cause myocardial ischaemia, infarction and even death. Epidemiologic data strongly suggest an infectious aetiology, although the causative agent has yet to be identified. Genetic factors also increase susceptibility to Kawasaki disease, as indicated by its strikingly high incidence rate in children of Asian ethnicity and by an increased incidence in first-degree family members. The treatment of Kawasaki disease is based on timely administration of intravenous immunoglobulin and aspirin. However, the management of patients who do not respond to this

standard therapy remains challenging; although several options are available, comparative data on which to base treatment decisions are scarce. The added value of adjunctive therapy with corticosteroids in patients at particularly high risk of coronary complications has been demonstrated in Japanese populations, but identification of high-risk patients has proven to be difficult in ethnically diverse populations.

Singh, S., et al. (2015). "The epidemiology of Kawasaki disease: a global update." Archives of Disease in Childhood **100**(11): 1084-1088.
Kawasaki disease (KD) is a childhood vasculitis and the most frequent cause of paediatric acquired heart disease in North America, Europe and Japan. It is increasingly recognised in rapidly industrialising countries such as China and India where it may replace rheumatic heart disease as the most common cause of acquired heart disease in children. We review the current global epidemiology of KD and discuss some public health implications.

Turnier, J. L., et al. (2015). "Concurrent respiratory viruses and Kawasaki disease." Pediatrics **136**(3): e609-e614.
BACKGROUND: The diagnosis of Kawasaki disease (KD) remains challenging without a definitive diagnostic test and currently is guided by using clinical patient characteristics and supported by laboratory data. The role of respiratory viruses in the pathogenesis of KD is not fully understood. METHODS: Charts of patients with KD admitted to Children's Hospital Colorado from January 2009 to May 2013 were retrospectively reviewed. Patients with KD who had a nasopharyngeal wash submitted for multiplex polymerase chain reaction (PCR) viral testing were included. Clinical characteristics, laboratory data, and outcomes of patients with and without positive respiratory viral PCR results were compared. RESULTS: Of 222 patients with KD admitted to the hospital, 192 (86%) had a respiratory viral PCR test performed on or shortly after admission. Ninety-three (41.9%) of the 192 patients with KD had a positive respiratory viral PCR, and the majority were positive for rhinovirus/enterovirus. No statistically significant differences were found in the clinical characteristics and laboratory values between the groups with and without positive respiratory viral PCR findings. Both groups had the same frequency of upper respiratory and gastrointestinal symptoms and had the same incidence of admission to the PICU, intravenous immunoglobulin-resistant disease, and coronary artery lesions. CONCLUSIONS: No differences in clinical presentations or outcomes in children with KD stratified according to positive or negative respiratory viral PCR testing were observed. A positive respiratory viral PCR or presence of respiratory symptoms at the time of presentation should not be used to exclude a diagnosis of KD. © 2015 by the American Academy of Pediatrics.

Wang, W., et al. (2015). "Macrophage activation syndrome in Kawasaki disease: more common than we thought?" Seminars in Arthritis & Rheumatism **44**(4): 405-410.
OBJECTIVES: To analyze the clinical characteristics, treatment, and outcomes of Kawasaki Disease (KD) patients associated with macrophage activation syndrome (MAS) and to compare two diagnostic standards (the HLH 2009 and Ravelli's criteria).
METHODS: All of the studied patients with Kawasaki Disease (KD) were treated at The Children's Hospital, Zhejiang University School of Medicine, during 2007-2010. Clinical and laboratory findings were analyzed.
RESULTS: In 719 KD patients, eight patients (1.11%, 81.3 +/- 49.4 months, all male) were diagnosed by Ravelli's criteria, but only three (0.42%) patients were diagnosed by the HLH 2009 criteria. Aspartate aminotransferase increased significantly in all cases. Alanine aminotransferase, lactate dehydrogenase, and serum ferritin increased significantly in seven cases. Cytopenia and hypertriglyceridemia (>1.5mmol/L) were found in six and five cases, respectively. Hypofibrinogenemia (<1.5g/L) was found in two cases. Three cases showed evidence of hemophagocytosis, but only one case met the HLH 2009 criteria. Ectasia of the coronary arteries occurred in two cases. Seven patients were non-responsive to IVIG. One case died after the combined application of DXM, VP16, and CSA.

CONCLUSIONS: MAS may be a frequently under-recognized complication of KD, because the understanding of complications and diagnostic criteria are still in progress. The HLH 2009 criteria have low sensitivity and specificity for the diagnosis of MAS complicating KD. When hepatosplenomegaly is present in KD patients with abnormal laboratory findings, such as cytopenia, liver dysfunction, hyperferritinemia, elevated serum LDH, hypofibrinogenemia, and hypertriglyceridemia, the presence of MAS should be considered.

Yang, X., et al. (2015). "A meta-analysis of re-treatment for intravenous immunoglobulin-resistant Kawasaki disease." Cardiology in the Young **25**(6): 1182-1190.
OBJECTIVE: To determine the optimal drug therapy for intravenous immunoglobulin-resistant Kawasaki disease.
METHODS: Studies regarding drug therapy for intravenous immunoglobulin-resistant Kawasaki disease were selected from medical electronic databases including PubMed, Medline, Elsevier, and Springer Link. The effectiveness in terms of temperature recovery and coronary artery damage was compared between a second intravenous immunoglobulin treatment and glucocorticosteroid treatment for children with intravenous immunoglobulin-resistant Kawasaki disease using meta-analysis with Review Manager 5.3 software. Indices to evaluate the effects were body temperature, biomarker levels, and coronary artery lesions detected by echocardiography. Results are reported as relative risks or odds ratio with a 95% confidence interval and $p<0.05$.
RESULTS: Meta-analysis included 52 patients in the second intravenous immunoglobulin treatment group and 75 patients in the glucocorticosteroid treatment control group from four studies that met our inclusion criteria. Temperatures of patients who received glucocorticosteroid treatment were effectively controlled compared with those who received a second intravenous immunoglobulin treatment (relative risk=0.73, 95% confidence interval: 0.58-0.92, $p=0.007$). There were no differences, however, in the incidence of coronary artery lesions between the two groups (odds ratio=1.55, 95% confidence interval: 0.57-4.20, $p=0.39$).
CONCLUSIONS: Glucocorticosteroids are more effective in controlling body temperature compared with intravenous immunoglobulin re-treatment in intravenous immunoglobulin-resistant Kawasaki disease children; however, glucocorticosteroids and intravenous immunoglobulin re-treatment showed no difference in the prevention of coronary artery lesions.

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Aldemir-Kocabas, B., et al. (2014). "Recurrent Kawasaki disease in a child with retropharyngeal involvement: a case report and literature review." Medicine **93**(29): e139.
Kawasaki disease (KD) is a multisystemic vasculitic disease. Recurrent KD is rare and generally presents in a similar clinical picture as the first episode, and early diagnosis with prompt treatment is the key point in preventing associated cardiovascular morbidities. A 9-year-old boy, who was diagnosed with KD when he was 1.5 years' old, was referred to our hospital for surgical drainage of retropharyngeal abscess. He had a 7-day history of high fever, sore throat, left-sided neck swelling, and restricted neck movements. Subsequently, he was diagnosed with recurrent KD and retropharyngeal involvement. He was successfully treated with a single dose of intravenous immunoglobulin (IVIG) and acetyl salicylic acid. Recurrence is rare and occurs most commonly in children. Atypical presentation, incomplete disease, short duration of fever, and reduced response to IVIG treatment were found to be the risk factors for recurrence. KD can occasionally present with clinical and radiographic findings of deep neck bacterial infection. Unusual presentations in KD may cause delay in diagnosis and increase the risk of life-threatening complications. We describe a case of recurrent KD presenting with a clinical picture resembling retropharyngeal infection who fully recovered after 1 dose of IVIG instead of surgical drainage and antibiotic use.

Binder, E., et al. (2014). "Kawasaki disease in children and adolescents: Clinical data of Kawasaki patients

in a western region (Tyrol) of Austria from 2003-2012." Pediatric Rheumatology **12**(1).
Background: Kawasaki disease (KD) is a rare vasculitis seen predominantly in children. In developing countries, it is the leading cause of childhood-acquired heart disease. Besides a case report from 1981 there have been no data published dealing with the epidemiology and clinical aspects of KD in Austria. Methods: The purpose of the present study was to investigate the clinical spectrum of KD in a geographically determined cohort of infants, children, and adolescents that were diagnosed and treated at the University Hospital of Innsbruck from 2003-2012. Results: Thirty-two patients were included in the study with a median age of 32.96 months (2-192). 59.4% of the patients were aged between six months and four years. The male-to-female ratio was 1:1.13. Clinical examination revealed non-purulent conjunctivitis and exanthema as the most common symptoms (84.4%). 75% showed oropharyngeal changes, 21.9% had gastrointestinal complaints such as diarrhoe, stomachache or vomiting prior to diagnosis. One third of the patients were admitted with a preliminary diagnosis, whereas 78.1% were pre-treated with antibiotics. The median fever duration at the time of presentation was estimated with 4.96 days (1-14), at time of diagnosis 6.76 days (3-15).75% were diagnosed with complete KD, and 25% with an incomplete form of the disease. There was no significant difference in the duration of fever neither between complete and incomplete KD, nor between the different age groups. Typical laboratory findings included increased C-reactive protein (CRP) (80.6%) and erythrocyte sedimentation rate (ESR) (96%),leukocytosis (48.4%) and thrombocytosis (40.6%) without any significant quantitative difference between complete and incomplete KD. Coronary complications could be observed in six patients: one with a coronary aneurysm and five with tubular dilatation of the coronary arteries. Our patient cohort represents the age distribution as described in literature and emphasizes that KD could affect persons of any age. The frequency of occurrence of the clinical symptoms differs from previous reports - in our study, we predominantly observed non-purulent conjunctivitis and exanthema. Conclusion: KD should always be considered as a differential diagnosis in a child with fever of unknown origin, as treatment can significantly decrease the frequency of coronary complications. © 2014 Binder et al.; licensee BioMed Central Ltd.

Chen, Y. and Y. Yu (2014). "[Value of N-terminal pro-brain natriuretic peptide in the early evaluation of cardiovasculardysfunction in critically ill children]." Zhonghua Erke Zazhi **52**(2): 149-152.

Desforges, M., et al. (2014). "Human respiratory coronaviruses : neuroinvasive, neurotropic and potentially neurovirulent pathogens." Virologie (Montrouge) **18**(1): 5-16.
In humans, viral infections of the respiratory tract are a leading cause of morbidity and mortality worldwide. Among the various respiratory viruses, coronaviruses are important ubiquitous pathogens of humans and animals. Since the late 1960's, human coronaviruses (HCoV) are recognized pathogens of the upper respiratory tract, being mainly associated with mild pathologies such as the common cold. However, in vulnerable populations, (newborns, infants, the elderly and immune-compromised individuals), they can affect the lower respiratory tract, leading to pneumonia, exacerbations of asthma, respiratory distress syndrome or even severe acute respiratory syndrome (SARS). For almost three decades now, the scientific literature has also demonstrated that HCoV are neuroinvasive and neurotropic: neurons are often the target cell in the central nervous system (CNS), inducing neurodegeneration and eventually death. Moreover, HCoV can contribute to an overactivation of the immune system that could lead to autoimmunity in the CNS of susceptible individuals. Given all these properties, it has been suggested that HCoV could be associated with the triggering or the exacerbation of human neurological diseases for which the etiology remains unknown or poorly understood.

Dimitriades, V. R., et al. (2014). "Kawasaki disease: Pathophysiology, clinical manifestations, and management." Current Rheumatology Reports **16**(6).
Kawasaki Disease, a systemic vasculitis of unknown origin with specific predilection for the coronary arteries, is the most common cause of childhood-acquired heart disease in western

countries. Despite its world-wide incidence, the pathophysiology of this enigmatic disease is still under investigation. Diagnosis is made on a clinical basis, with supportive laboratory evidence and imaging. Once identified, timely initiation of treatment is imperative in order to quell the inflammatory response and decrease the incidence of long-term sequelae, specifically coronary artery aneurysms. Finally, longitudinal follow-up should be implemented based on risk stratification and individualized to each patient. © Springer Science+Business Media 2014.

Eleftheriou, D., et al. (2014). "Management of Kawasaki disease." Archives of Disease in Childhood **99**(1): 74-83.
Kawasaki disease (KD) is an acute self-limiting inflammatory disorder, associated with vasculitis, affecting predominantly medium-sized arteries, particularly the coronary arteries. In developed countries KD is the commonest cause of acquired heart disease in childhood. The aetiology of KD remains unknown, and it is currently believed that one or more as yet unidentified infectious agents induce an intense inflammatory host response in genetically susceptible individuals. Genetic studies have identified several susceptibility genes for KD and its sequelae in different ethnic populations, including FCGR2A, CD40, ITPKC, FAM167A-BLK and CASP3, as well as genes influencing response to intravenous immunoglobulin (IVIG) and aneurysm formation such as FCGR3B, and transforming growth factor (TGF) β pathway genes. IVIG and aspirin are effective therapeutically, but recent clinical trials and meta-analyses have demonstrated that the addition of corticosteroids to IVIG is beneficial for the prevention of coronary artery aneurysms (CAA) in severe cases with highest risk of IVIG resistance. Outside of Japan, however, clinical scores to predict IVIG resistance perform suboptimally. Furthermore, the evidence base does not provide clear guidance on which corticosteroid regimen is most effective. Other therapies, including anti-TNFα , could also have a role for IVIG-resistant KD. Irrespective of these caveats, it is clear that therapy that reduces inflammation in acute KD, improves outcome. This paper summarises recent advances in the understanding of KD pathogenesis and therapeutics, and provides an approach for managing KD patients in the UK in the light of these advances.

Gorczyca, D., et al. (2014). "The clinical profile of Kawasaki disease of children from three Polish centers: A retrospective study." Rheumatology International **34**(6): 875-880.
Kawasaki disease (KD) is one of the most common vasculitides of childhood. The aim of this retrospective study is to determine the incidence of KD and to evaluate its presenting symptoms, clinical course, laboratory tests, and treatment in patients with complete KD and incomplete KD at three pediatric rheumatology centers in Poland from January 2011 to December 2012. A total of 27 Caucasian children (12 boys and 15 girls) with median age of 3 years (range 4 months-12 years) were included in this study. The incidence of complete versus incomplete KD was 17 (63%) versus 10 (37%) children, respectively. Patients with incomplete KD significantly less presented cervical lymphadenopathy (20 vs. 88.2%; p = 0.00075), changes in extremities (30 vs. 76.5%; p = 0.04), and bilateral nonpurulent conjunctivitis (60 vs. 100%; p = 0.01). Cardiac assessments show that the majority of patients with KD have not got coronary artery aneurysms (CAA). The median time from the onset of symptoms to intravenous immunoglobulin (IVIG) infusion was 7 days for complete KD and 11 days for incomplete KD. IVIG delay in the incomplete KD had no effect on the incidence of CAA. In conclusion, there were no differences in demographic features, age of onset, and laboratory tests of patients with complete and incomplete KD. Patients with incomplete KD significantly rarely presented cervical lymphadenopathy, changes in extremities, and conjunctival injection. Electrocardiography is a sensitive test to recognize cardiac involvement in the acute phase of KD. Despite the fact that incomplete forms of presentation often delay diagnosis, in most patients treatment with IVIG can avoid complication of CAA. © The Author(s) 2013.

Kato, H. (2014). "[Natural history of Kawasaki disease vasculitis]." Nippon Rinsho - Japanese Journal of Clinical Medicine **72**(9): 1530-1535.
Kawasaki disease is an acute vasculits syndrome of unknown etiology, which mainly affects small

and medium arteries particularly coronary arteries in infants and young children. The cardiovascular problems include coronary artery lesions that develop the aneurysm formation, thrombotic occlusion, progression to coronary artery disease, and pre- mature atherosclerosis. However, the long-term consequences of these cardiovascular problems are still uncertain. In this article the long-term spectrums of Kawasaki disease vasculitis are described by our long-term follow-up study of 2,450 patients from clinical and pathological aspects. We like to emphasize that the long-term cardiovascular prob- lems are important issues not only in children but also in adulthood.

Kawasaki, T. and S. Naoe (2014). "History of Kawasaki disease." Clinical & Experimental Nephrology **18**(2): 301-304.
We describe a short history of Kawasaki disease. In 1967, we published a paper entitled 'Infantile acute febrile mucocutaneous lymph node syndrome with specific desquamation of the fingers and toes. Clinical observation of 50 cases'; this was the first report on what is now called Kawasaki disease. Since then, many reports on cardiology, treatment, epidemiology, pathology and etiology of Kawasaki disease have been published. Furthermore, a recent Chapel Hill Consensus Statement on Kawasaki disease in the classification of vasculitis is given, along with a figure on the relationship and classification of childhood vasculitis by autopsy material.

Krakowski, A. C., et al. (2014). "Transient lingual papillitis associated with confirmed herpes simplex virus 1 in a patient with Kawasaki disease." Pediatric Dermatology **31**(6): e124-e125.
We present a case of transient lingual papillitis associated with confirmed herpes simplex virus 1 that developed after a child received intravenous immunoglobulin and infliximab for acute Kawasaki disease. © 2014 Wiley Periodicals, Inc.

Liu, Y. X., et al. (2014). "Giant coronary artery aneurysm following Kawasaki disease in a child manifesting night waking as a main clinical symptom: A case report." Chinese Journal of Contemporary Pediatrics **16**(11): 1170-1171.

Niedra, E., et al. (2014). "Atorvastatin safety in kawasaki disease patients with coronary artery aneurysms." Pediatric Cardiology **35**(1): 89-92.
Statins (HMG-CoA reductase inhibitors) may decrease inflammation in postacute Kawasaki disease (KD) complicated by coronary artery aneurysm (CAA) and promote vascular remodeling. There are limited data on their safety in young children. Twenty patients with CAAs after KD (median CAA z-score = +25) were treated with 5/10 mg atorvastatin daily for a median of 2.5 years (range 0.5-6.8) starting at a median of 2.3 years (range 0.3-8.9) after acute KD (median age 9.3 years [range 0.7-14.3]). Compliance with treatment was excellent: only one patient reported minor side effects (joint pain, no change in medication). Average total cholesterol before atorvastatin was 3.73 ± 0.84 mmol/L and after atorvastatin was 3.21 ± 0.46 mmol/L (relative decrease -14 %, p = 0.02); low-density lipoprotein cholesterol was 1.99 ± 0.76 mmol/L before and only 1.49 ± 0.27 mmol/L after (relative decrease -20 %, p = 0.04); high-density lipoprotein was 1.39 ± 0.36 mmol/L before and 1.30 ± 0.27 mmol/L after (relative decrease -4 %, p = 0.35); and triglycerides were 0.71 ± 0.28 mmol/L before and 0.71 ± 0.18 mmol/L after (relative decrease -5 %, p = 0.38). Nine of 20 patients (45 %) experienced at least 1 episode of hypocholesterolemia (total cholesterol <3.1 mmol/L), and 2 patients required atorvastatin dose lowering. Transient mild increase of liver enzymes (aspartate aminotransferase/alanine aminotransferase 45-60 U/L) were seen in 7 of 20 (35 %) patients with no patients experiencing more severe increases. Only one patient experienced increased creatine phosphokinase levels (>500 U/L). Serial measurements of age- and sex-specific percentiles of weight (estimated change: 1.4 [2.7] % per year, p = 0.60), height (estimated change: -3.2 [3.2] % per year, p = 0.32), and body mass index (estimated change: 1.0 [2.9] % per year, p = 0.73) showed no association between anthropomorphic growth and atorvastatin treatment. Atorvastatin use in very young children with KD is safe but should be closely monitored. © 2013 Springer

Science+Business Media New York.

Puhakka, L., et al. (2014). "Retropharyngeal involvement in Kawasaki disease--a report of four patients with retropharyngeal edema verified by magnetic resonance imaging." International Journal of Pediatric Otorhinolaryngology **78**(10): 1774-1778.
Kawasaki disease is an acute systemic vasculitis of childhood. The diagnosis is based on clinical criteria. Prognosis with adequate treatment is favorable. Untreated patients, however, may develop coronary manifestations predisposing to acute myocardial infarction. Retropharyngeal edema is a rare but known manifestation of Kawasaki disease. We present a case series of four Kawasaki patients presenting with clinical findings for retropharyngeal abscess and the magnetic resonance imaging findings of these patients, diagnosed during a six week period. To our knowledge, this is the first systematic report of cervical MRI findings of Kawasaki patients.

Rashid, A. K., et al. (2014). "Kawasaki disease and its treatment - an update." Current Rheumatology Reviews **10**(2): 109-116.
AIM: The aim of this review is to update the knowledge about the Kawasaki disease (KD) which includes the way of early detection and latest treatment plan for the disease.
METHOD: A number of literatures were reviewed and latest information about the etiology, diagnosis, laboratory investigation, treatment and outcome of the disease was collected and depicted in the review article.
RESULT: Kawasaki disease is a multisystem vasculitis mainly affecting medium sized blood vessels. It is the second most common cause of vasculitis after Henoch Scholein Purpura (HSP) in children. Etiology of the disease is still unknown. Auto-immunity with genetic influence is thought to associate with the disease. Many physicians are ignorant of the disease. The pediatrician must be aware of the disease and suspect this condition in less than 5 year old children presenting with more than 5 days fever. the number of methods on the basis of criteria is set for the diagnosis of the disease. Latest treatment plan is set up for the disease which reduces the morbidity and mortality to a great extent.
CONCLUSION: Physicians must have consciousness and comprehensive knowledge for the early suspicion of this disease. Any child presenting with fever for more than 5 days should not be ignored and other criteria of KD have to be evaluated by the physician. Early diagnosis and updated treatment are imperative for the prevention of morbidity and mortality for the disease.

Saji, T. (2014). "Guidelines for medical treatment of acute Kawasaki disease: Report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version)." Pediatrics International **56**(2): 135-158.

Smith, K. A. and W. K. Yunker (2014). "Kawasaki disease is associated with sensorineural hearing loss: a systematic review." International Journal of Pediatric Otorhinolaryngology **78**(8): 1216-1220.
CONTEXT: Kawasaki Disease (KD), a systemic vasculitis of unknown etiology, has been associated with the development of sensorineural hearing loss (SNHL). KD is primarily a disease of young children, who are the most susceptible to complications from even minimal hearing loss. If there is a connection between KD and the development of SNHL, a better understanding of this relationship may improve our management of this disease and its complications.
OBJECTIVE: To perform a systematic review according to a standardized guideline to evaluate the possible association between KD and SNHL.
DATA SOURCES: Medline and PubMed online databases were reviewed for appropriate articles.
STUDY SELECTION: All studies available in English discussing KD and SNHL were included.
DATA EXTRACTION: Studies were assessed primarily for the incidence of SNHL. Where possible, they were assessed for the degree and laterality of the loss, length of follow up and change in hearing over time.
RESULTS: 8 studies meeting the criteria were assessed. 3 were case reports, 1 was a case series and the remaining 4 were prospective control trials. 8 patients have been reported as cases, and 240

assessed in PCT. 36% of patients assessed had some degree of SNHL, and overall 14% had evidence of persistent SNHL at follow up.
CONCLUSIONS: This systematic review would suggest there is an association between KD and SNHL. It is important for physicians caring for patients with KD to be aware of this complication and consider screening these patients given possible complications of hearing loss in this age group.

Zambon, M. (2014). "Influenza and other emerging respiratory viruses." Medicine Abingdon **42**(1): 45-51.
Acute lower respiratory tract infections (LRTIs) are a major worldwide health problem, particularly in childhood. About 30-50% of acute LRTIs are viral in origin with influenza A infection a key cause of explosive community outbreaks. Many different influenza A viruses occur naturally in animal reservoirs and present a constant threat of zoonotic infections and global pandemics. Since 2009, when pandemic (H1N1) influenza A emerged from a swine origin, there have been a number of different zoonotic influenza A transmissions into the human population, including H1N1 and H3N2 variant viruses in North America and H7N9 viruses in China. The segmented nature of the influenza A virus genome and the circulation of these viruses in wild bird, domestic poultry and mammalian reservoirs presents a continuous opportunity for reassortment of viral genes and the emergence of a novel pandemic virus. Constant vigilance is required. The emergence of severe acute respiratory syndrome in 2003 and Middle East respiratory syndrome coronavirus in 2012, highlights the fact that other serious respiratory viral infections in humans may originate in animals. Enhanced awareness of the potential for serious human respiratory disease in association with travel, or animal exposure, should form part of clinical assessment. Rapid developments in genomic technology improve the ability to diagnose previously undetected pathogens. Preventative measures for influenza include annual vaccination and treatment with antiviral drugs such as neuraminidase inhibitors, oseltamivir and zanamivir. Subtype-dependent resistance to antivirals can develop and should be closely monitored.

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Assiri, A., et al. (2013). "Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study." The Lancet Infectious Diseases **13**(9): 752-761.
Background: Middle East respiratory syndrome (MERS) is a new human disease caused by a novel coronavirus (CoV). Clinical data on MERS-CoV infections are scarce. We report epidemiological, demographic, clinical, and laboratory characteristics of 47 cases of MERS-CoV infections, identify knowledge gaps, and define research priorities. Methods: We abstracted and analysed epidemiological, demographic, clinical, and laboratory data from confirmed cases of sporadic, household, community, and health-care-associated MERS-CoV infections reported from Saudi Arabia between Sept 1, 2012, and June 15, 2013. Cases were confirmed as having MERS-CoV by real-time RT-PCR. Findings: 47 individuals (46 adults, one child) with laboratory-confirmed MERS-CoV disease were identified; 36 (77%) were male (male:female ratio 3·3:1). 28 patients died, a 60% case-fatality rate. The case-fatality rate rose with increasing age. Only two of the 47 cases were previously healthy; most patients (45 [96%]) had underlying comorbid medical disorders, including diabetes (32 [68%]), hypertension (16 [34%]), chronic cardiac disease (13 [28%]), and chronic renal disease (23 [49%]). Common symptoms at presentation were fever (46 [98%]), fever with chills or rigors (41 [87%]), cough (39 [83%]), shortness of breath (34 [72%]), and myalgia (15 [32%]). Gastrointestinal symptoms were also frequent, including diarrhoea (12 [26%]), vomiting (ten [21%]), and abdominal pain (eight [17%]). All patients had abnormal findings on chest radiography, ranging from subtle to extensive unilateral and bilateral abnormalities. Laboratory analyses showed raised concentrations of lactate dehydrogenase (23 [49%]) and aspartate aminotransferase (seven [15%]) and thrombocytopenia (17 [36%]) and lymphopenia (16 [34%]). Interpretation: Disease

caused by MERS-CoV presents with a wide range of clinical manifestations and is associated with substantial mortality in admitted patients who have medical comorbidities. Major gaps in our knowledge of the epidemiology, community prevalence, and clinical spectrum of infection and disease need urgent definition. © 2013 Elsevier Ltd.

Bayers, S., et al. (2013). "Kawasaki disease: part I. Diagnosis, clinical features, and pathogenesis." Journal of the American Academy of Dermatology **69**(4): 501.e501-511; quiz 511-502.
Kawasaki disease, or mucocutaneous lymph node syndrome, most commonly affects children between 6 months and 5 years of age. Approximately 90% of patients have mucocutaneous manifestations. This article will focus on the epidemiology of Kawasaki disease in the United States as it relates to other countries, the diagnosis of Kawasaki disease, its clinical course, and the currently accepted theories of pathogenesis. A particular focus is given to the various dermatologic manifestations that may occur.

Eladawy, M., et al. (2013). "Kawasaki disease and the pediatric gastroenterologist: A diagnostic challenge." Journal of Pediatric Gastroenterology and Nutrition **56**(3): 297-299.
BACKGROUND AND OBJECTIVES:: Gastrointestinal symptoms and signs are rarely the main clinical presentation of Kawasaki disease (KD). In the present study, we report a series of patients with KD in whom a gastroenterology consult was obtained before consideration of the diagnosis of KD. METHODS:: We retrospectively reviewed all patients with KD admitted to Children's Hospital Colorado from January 2009 through February 2011 with prominent gastrointestinal symptoms, resulting in gastrointestinal service consultation before their diagnosis of KD. RESULTS:: We identified 7 of 118 (6%) patients with KD who met our criteria. All 7 patients were males, and the median age at admission was 9.7 years. All patients had abdominal pain and fever at presentation. Vomiting, diarrhea, and clinical jaundice were present in 70%, 50%, and 43% of patients, respectively. Aminotransferases and/or γ-glutamyl transpeptidase abnormalities were observed in 6 (89%) patients. All of the patients had fever and rash on admission, and 86% had nonexudative conjunctivitis and 71% had mucosal changes. Median duration of illness at gastroenterology consultation was 5 days, whereas median duration of illness at infectious disease consultation was 6 days. One patient developed coronary artery dilation and 2 patients had intravenous immunoglobulin-resistant KD. CONCLUSIONS:: Gastroenterologists should be aware of gastrointestinal presentations of KD. Unexplained gastrointestinal symptoms in the presence of fever, and 1 or 2 of the major clinical signs of KD, should prompt consideration of KD in the differential diagnosis. Copyright © 2013 by ESPGHAN and NASPGHAN.

Falcini, F., et al. (2013). "A four-time-recurring typical complete Kawasaki syndrome successfully treated with intravenous immunoglobulin: a case report with literature review." Rheumatology International **33**(10): 2653-2655.
Kawasaki syndrome (KS) typically strikes children younger than age 5 and presents with persistent high fever for at least 5 days combined with a heterogeneous polymorphous rash, extremity abnormalities, oropharyngitis, non-exudative conjunctivitis and cervical lymphadenitis. Treatment with high-dose intravenous immunoglobulin reduces substantially the risk of potential cardiovascular complications. For the first time, we report a child presenting all the clinical symptoms of KS, which recurred for 4 times in a period of 33 months. Each relapse was characterized by obstinate high fever combined with mucocutaneous signs and was each time successfully treated with intravenous immunoglobulin without the occurrence of any cardiovascular damage.

Fradin, K. N. and H. J. Rhim (2013). "An adolescent with fever, jaundice, and abdominal pain: an unusual presentation of Kawasaki disease." Journal of Adolescent Health **52**(1): 131-133.
A 16-year-old boy presented with a 6-day history of fevers and myalgias and a 4-day history of diffuse crampy abdominal pain. On admission, his sclerae were icteric and he had diffuse

abdominal tenderness. Erythrocyte sedimentation rate was elevated to 40; the gamma-glutamyl transferase level was elevated to 168 U/L; indirect bilirubin was 5.6 mg/dL; and direct bilirubin was 3.3 mg/dL. During the next 2 days, he developed many stigmata of Kawasaki disease (KD), including conjunctivitis, desquamating rash, mucosal changes, swelling of the hands and feet, and lymphadenopathy. KD is commonly seen in young children but can also occur in adolescents and adults. Providers should be aware that these age-groups are at risk for KD and may present with atypical symptoms. Delays in diagnosis can put these adolescents at increased risk of coronary artery aneurysms, and, accordingly, a high index of suspicion is essential.

Golshevsky, D., et al. (2013). "Kawasaki disease--the importance of prompt recognition and early referral." Australian Family Physician **42**(7): 473-476.
BACKGROUND: Kawasaki disease is an acute, febrile vasculitis of childhood that affects medium sized arteries, particularly the coronary arteries. Consequently, it is the leading cause of paediatric-acquired heart disease in developed countries. It is important to have a high index of suspicion for Kawasaki disease in any child with prolonged fever of unknown origin and to refer to a paediatric facility promptly, as timely treatment reduces coronary artery damage.
OBJECTIVE: To provide an evidence based review that will help guide the safe and timely recognition, referral and management of typical and incomplete Kawasaki disease.
DISCUSSION: Kawasaki disease is most common in children aged 6 months to 4 years. A high index of suspicion is needed to consider the diagnosis. There are specific diagnostic criteria, though incomplete Kawasaki disease may occur where the child does not meet all diagnostic criteria. There may be co-existing illnesses, which make the diagnosis more difficult. Persistent fever, skin manifestations and extreme irritability may be some cues to consider the diagnosis. If there is strong clinical suspicion the child should be referred, as early treatment significantly decreases the risk of long term cardiac artery damage.

Iwanczak, B. and O. Krynicka-Scaringella (2013). "[Kawasaki disease in children: epidemiology, clinical symptoms, diagnostics and treatment]." Polski Merkuriusz Lekarski **35**(210): 375-378.
Kawasaki disease is a multisystem inflammatory disease of small- and medium-sized blood vessels with acute and self limiting course. It occurs most frequently in children under five years of age and is characterized by high fever lasting more than five days, conjunctivitis, stomatitis, edema of hands or feet erythema of the palms and soles, epidermic desquamation of the fingers and toes, polymorphic rush and cervical lymphadenopathy. Such symptoms from other organs as cholestatic jaundice, inflammation and hydrops of the gallbladder, pancreatitis, hepatitis and traits of acute abdomen can also be present. The most serious complications of Kawasaki disease are coronary aneurysms. The principal treatment of the disease is intravenous infusion of immunoglobulin and aspirin. Prompt diagnosis with echocardiogram and the treatment with immunoglobulins before 10th day after the first symptoms improve prognosis and diminish life threatening complication such as coronary arteries aneurysms.

Jamieson, N. and D. Singh-Grewal (2013). "Kawasaki Disease: A Clinician's Update." International Journal of Pediatrics **2013**: 645391.
Aims. Kawasaki disease is an acute systemic vasculitis and is the most common cause of acquired heart disease in children in the developed world. This review aims to synthesise recent insights into the disease and provide an update for clinicians on diagnostic and treatment practices. Methods. We conducted a review of the literature exploring epidemiology, aetiology, diagnosis, and management of Kawasaki disease. We searched MEDLINE, Medline In-Process, Embase, Google Scholar, and reference lists of relevant articles. Conclusions . Kawasaki disease is a febrile vasculitis which progresses to coronary artery abnormalities in 25% of untreated patients. The disease is believed to result from a genetically susceptible individual's exposure to an environmental trigger. Incidence is rising worldwide, and varies widely across countries and within different ethnic groups. Diagnosis is based on the presence of fever in addition to four out of five other clinical criteria, but it is complicated by the quarter of the Kawasaki disease patients

with "incomplete" presentation. Treatment with intravenous immunoglobulin within ten days of fever onset improves clinical outcomes and reduces the incidence of coronary artery dilation to less than 5%. Given its severe morbidity and potential mortality, Kawasaki disease should be considered as a potential diagnosis in cases of prolonged paediatric fever.

Kumar, S., et al. (2013). "Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome misdiagnosed as Kawasaki disease: case report and literature review." Rheumatology International **33**(4): 1065-1069.
Patients with systemic onset juvenile idiopathic arthritis (SoJIA) are rarely known to develop coronary artery dilatation. The American heart association (AHA) statement on evaluation of suspected Kawasaki disease (KD) would lead some SoJIA patients (particularly in the early stages of the disease) to be inaccurately classified as KD. In addition to the institution of inappropriate therapy with IVIG, misdiagnosis as KD can delay definitive treatment for these SoJIA patients who probably have a worse predicted outcome. We present a 6-year-old male patient with SoJIA who was initially classified as incomplete KD. The child developed life-threatening macrophage activation syndrome (MAS). Previous literature regarding coronary dilatation in SoJIA is also reviewed.

Li, S. W. and C. W. Lin (2013). "Human coronaviruses: Clinical features and phylogenetic analysis." BioMedicine **3**(1): 43-50.
Strains of human coronavirus (HCoV), namely HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, primarily infect the upper respiratory and gastrointestinal tracts and are the most common cause of non-rhinovirus-induced common cold in humans. Although the manifestations of coronavirus infection (i.e., rhinorrhea, sneezing, cough, nasal obstruction, and bronchitis) are generally self-limiting in healthy adults, certain strains such as HCoV-NL63 and HCoV-HKU1 can cause severe lower respiratory tract infection and febrile seizure, especially in infants, people of advanced age, and immunocompromised hosts. In 2003, a novel HCoV strain was identified as the causative agent of the severe acute respiratory syndrome (SARS) epidemic that began in Asia in 2002. The strain has hence been referred to as SARS-CoV. In addition, as recently as September 2012, another novel HCoV, human betacoronavirus 2c EMC2012, was identified as being the cause of fever, renal failure, pneumonia, and severe respiratory distress in two patients in the Middle East. Phylogenetic analysis has revealed highly conserved sequences of ORF1ab, spike, nucleocapsid, and envelope protein genes, but not membrane protein genes, between human betacoronavirus 2c EMC2012 and SARS-CoV. This review focuses on the differences in the genomes of certain HCoV strains, the pathogenesis of said strains, and recent developments in the establishment of therapeutic agents that might aid in the treatment of patients with such infections.

Mavrogeni, S., et al. (2013). "The emerging role of cardiovascular magnetic resonance in the evaluation of Kawasaki disease." The International Journal of Cardiovascular Imaging **29**(8): 1787-1798.
Kawasaki disease (KD) is a vasculitis affecting the coronary and systemic arteries. Myocardial inflammation is also a common finding in KD post-mortem evaluation during the acute phase of the disease. Coronary artery aneurysms (CAAs) develop in 15-25% of untreated children. Although 50-70% of CAAs resolve spontaneously 1-2 years after the onset of KD, the remaining unresolved CAAs can develop stenotic lesions at either their proximal or distal end and can develop thrombus formation leading to ischemia and/or infarction. Cardiovascular magnetic resonance (CMR) has the ability to perform non-invasive and radiation-free evaluation of the coronary artery lumen. Recently tissue characterization of the coronary vessel wall was provided by CMR. It can also image myocardial inflammation, ischemia and fibrosis. Therefore CMR offers important clinical information during the acute and chronic phase of KD. In the acute phase, it can identify myocardial inflammation, microvascular disease, myocardial infarction, deterioration of left ventricular function, changes of the coronary artery lumen and changes of the coronary artery vessel wall. During the chronic phase, CMR imaging might be of value for risk stratification

and to guide treatment.

Nicholson, G. T., et al. (2013). "Pulmonary hypertension in Kawasaki disease." Pediatric Cardiology **34**(8): 1966-1968.
This report describes the case of two pediatric patients who demonstrated echocardiographic evidence of pulmonary hypertension (PH) during the acute phase of Kawasaki disease. The etiology of PH development in this setting is currently unknown, but the authors hypothesize that pulmonary vasculitis may play a significant role. Fortunately, the PH appeared to be self-limited and resolved in both cases with routine treatment of Kawasaki disease.

Nozaki, F., et al. (2013). "Grisel syndrome as a complication of Kawasaki disease: a case report and review of the literature." European Journal of Pediatrics **172**(1): 119-121.
UNLABELLED: Grisel syndrome is a non-traumatic atlantoaxial subluxation and a rare complication of any inflammatory condition of the upper neck and otolaryngological procedures. Delayed diagnosis causes neurological impairment, ranging from radiculopathy to paralysis and death. Kawasaki disease is a very frequent and important acute febrile vasculitis of childhood that is seen worldwide, and upper neck involvement (cervical lymphadenopathy) is one of the common symptoms of Kawasaki disease. A case of Grisel syndrome that occurred as a complication of Kawasaki disease is reported. This is the first case report, in English, of Grisel syndrome as a complication of Kawasaki disease.
CONCLUSION: Pediatricians should be aware of Grisel syndrome as a possible complication of Kawasaki disease.

O'Byrne, M. L. and M. S. Cohen (2013). "Marked eosinophilia in a patient with history of severe atypical kawasaki disease." Congenital Heart Disease **8**(5): E130-E133.
An infant with recent atypical, treatment-refractory Kawasaki disease presented with marked eosinophilia. Workup failed to identify an etiology. The eosinophilia spontaneously resolved. Eosinophilia has been observed in the acute phase of Kawasaki disease, but has not been reported following recovery. © 2012 Wiley Periodicals, Inc.

Parashar, R., et al. (2013). "Diffuse coronary artery dilatation in a neonate: A case report." Journal of Neonatal-Perinatal Medicine **6**(3): 263-266.
In this case, we describe a newborn that presented on the first day of life with diffuse, bilateral coronary artery dilatation, in the absence of intrauterine hypoxia or other identifiable causes of coronary artery ectasia. The infant's symptoms followed an acute course before spontaneously recovering. Kawasaki disease, though relatively rare in neonates, may present in this population in the absence of classical criteria. If untreated, the cardiac sequelae of this disease can be serious. Through this case, where spontaneously remitting coronary dilatation is the paramount finding, we entertain the possibility that this may represent the earliest known presentation of Kawasaki disease. © 2013-IOS Press.

Ponniah, U. (2013). "Coronary artery thrombus resulting in sudden cardiac death in an infant with Kawasaki disease and giant coronary artery aneurysms." Annals of Pediatric Cardiology **6**(2): 197-199.
We report a case of a six-month-old Hispanic male infant who had Kawasaki disease and coronary artery aneurysms on echocardiography. He died suddenly five months later in spite of aggressive medical therapy. Autopsy showed extensive coronary artery thrombosis. Giant coronary artery aneurysms need diligent follow up as they pose significant risks including risk of thrombus, myocardial infarction and sudden death.

Portman, M. A. (2013). "Kawasaki disease and soy: potential role for isoflavone interaction with Fcgamma receptors." Pediatric Research **73**(2): 130-134.
Kawasaki disease (KD) is a diffuse vasculitis occurring in children and showing predilection for the

coronary arteries. The etiology remains unknown, although some risk factors for susceptibility have been defined. Asian ethnicity is a primary risk factor. Several theories have circulated regarding the differences in KD ethnic incidence. Those theories implicating genetic differences among populations as the cause for this discrepancy have dominated and are areas of active investigation by multiple research groups. Differences in diet between Asians and Westerners are touted as reasons for certain ethnic-related discrepancies in susceptibility to cardiovascular disease and cancer in adults. Surprisingly, these cultural dietary differences have not been previously considered as the source of the discrepancy in KD incidence among these ethnic populations. Recent data from genetic studies have highlighted the role of specific immune receptors in the pathogenesis of KD. Functions of the Fcgamma receptors (FcGRs) are modulated by isoflavones in soy, in particular, genistein. Epidemiological data from Hawaiian populations support an association between soy consumption and KD. These observations form the basis of a hypothesis: isoflavones participate in KD pathogenesis by modulating function of the FcGRs and by disrupting the balance between activation and inhibition of the inflammatory response.

Rowley, A. H. (2013). "Can a systems biology approach unlock the mysteries of Kawasaki disease?" Wiley interdisciplinary reviews. Systems biology & medicine **5**(2): 221-229.
Kawasaki disease (KD) is a systemic inflammatory illness of childhood that particularly affects the coronary arteries. It can lead to coronary artery aneurysms, myocardial infarction, and sudden death. Clinical and epidemiologic data support an infectious cause, and the etiology remains unknown, but recent data support infection with a 'new' virus. Genetic factors influence KD susceptibility; the incidence is 10-fold higher in children of Asian when compared with Caucasian ethnicity. Recent research has identified genes affecting immune response that are associated with KD susceptibility and outcome. A re-examination of the pathologic features of KD has yielded a three process model of KD vasculopathy, providing a framework for understanding the KD arterial immune response and the damage it inflicts and for identifying new therapeutic targets for KD patients with coronary artery abnormalities. The researcher is faced with many challenges in determining the pathogenesis of KD. A systems biology approach incorporating genomics, proteomics, transcriptomics, and microbial bioinformatics analysis of high-throughput sequence data from KD tissues could provide the keys to unlocking the mysteries of this potentially fatal illness of childhood.

Sabatier, I., et al. (2013). "Stroke by carotid artery complete occlusion in Kawasaki disease: case report and review of literature." Pediatric Neurology **49**(6): 469-473.
BACKGROUND: Kawasaki disease is an acute and time-limited systemic vasculitis primarily affecting young children.
PATIENT: We describe an 18-month-old girl with Kawasaki disease who developed cerebral infarction following complete occlusion of her right internal carotid artery.
RESULTS: The occlusion occurred 10 days after the onset of fever, while she was on high-dose aspirin, and the day after she received intravenous immunoglobulin treatment. We present the first literature review on this very rare complication.
CONCLUSION: Stroke is a rare neurological complication in Kawasaki disease. Optimal treatment should be begun as soon as possible after diagnosis. Intravenous immunoglobulins seem to reduce the cerebrovascular complications, but evaluation of hydration status is strongly recommended before performing such treatment.

Sittiwangkul, R., et al. (2013). "Clinical spectrum of incomplete kawasaki disease in thailand." Paediatrics and International Child Health **33**(3): 176-180.
Background: Inadequate diagnostic criteria in incomplete Kawasaki disease (KD) patients may lead to misdiagnosis and delayed treatment. However, the risk of coronary artery aneurysm in these patients remains uncertain. Aim: To investigate differences in clinical, laboratory and echocardiographic variables between patients with incomplete KD and classic KD. Method: The medical records of 208 KD patients treated between January 2001 and December 2009 in the

Department of Pediatrics, Chiang Mai University Hospital were reviewed retrospectively. Patients with three or fewer major criteria were defined as having incomplete KD. Results: Of the 208 KD patients, 61 (29%) had incomplete KD. In those with incomplete KD, a significantly higher proportion were male (73.8% vs 59.2%, P=0.03), the diagnosis was made later [mean (SD) day 9.0 (4.2) vs 7.2 (2.5), P=0.003], there was a higher rate of delayed diagnosis (>10 days, 21% vs 10%, P=0.02) and the presence of five major criteria was less common. The proportion of associated symptoms (irritability, upper respiratory tract symptoms, diarrhoea, vomiting and reactivation of BCG) and laboratory findings (pyuria, haemoglobin level, white blood count, polymorphonuclear cells, platelet count, erythrocyte sedimentation rate and serum albumin) were comparable in patients with incomplete KD and classic KD. The incomplete KD group tended to have a higher proportion of coronary artery abnormalities but the difference was not statistically significant (38% vs 25%, P=0.09). However, a significantly greater proportion of the group with incomplete KD had large aneurysms (10% vs 1%, P=0.009). Conclusions: Incomplete KD and classic KD have the same disease spectrum. Owing to the absence of some major criteria, incomplete KD can be more difficult to diagnose, which can result in delayed diagnosis and a greater risk of large coronary aneurysms.

Sotelo-Cruz, N. (2013). "[A review of Kawasaki disease, a perspective from the articles published in Mexico since January 1977 to May 2012]." Archivos de Cardiologia de Mexico **83**(3): 214-222.
Kawasaki disease was described in 1967 by Tomisu Kawasaki. It affects children aged between one and 5 years, and it evolves with fever and small vessel vasculitis, which leads to cardiovascular complications, including coronary aneurisms, myocarditis, valve injuries, pericardial effusion and myocardial infarction; eventually involving many others organs. The etiology actually is not well known, as the exactly pathogenic mechanisms; however, now there are important advances. If the clinical signs and symptoms are identify early and the children received treatment with aspirin and intravenous immunoglobulin, the patients evolves without sequels. The Kawasaki disease is an infrequent disease in Mexico.

Takeuchi, M., et al. (2013). "Maculopapular rash in the convalescent phase of Kawasaki disease: case series and literature review." European Journal of Pediatrics **172**(3): 405-407.
UNLABELLED: Intravenous immunoglobulin (IVIG) is currently the standard treatment for Kawasaki disease (KD). Although IVIG therapy is generally well tolerated, several minor adverse reactions have been reported. We report a patient with KD treated with IVIG, who developed a cutaneous reaction in the convalescent phase (approximately 10 days after therapy). We identified seven additional KD cases with a similar presentation, accounting for 9.3 % of KD patients at our hospital. We performed a literature review and found that a maculopapular rash could be observed approximately 10 days after IVIG treatment, in patients with and those without KD.
CONCLUSION: Maculopapular rash can occur in nearly 10 % of IVIG-treated children with KD in our cohort, approximately 10 days after treatment. A delayed-onset adverse event of IVIG could be a causative etiology of this unrecognized eruption.

To, L., et al. (2013). "Perioperative considerations of Kawasaki disease." Ochsner Journal **13**(2): 208-213.
Background: Kawasaki disease (KD) is an acute febrile illness that primarily affects young children. Coronary arteritis is an important clinical feature of KD because it is associated with aneurysms and thromboembolic events that can lead to ischemic heart disease, sudden death, and congestive heart failure. KD involvement in multiple organ systems provides a potentially challenging dilemma for clinicians. Methods: This review discusses the pathogenesis of the disease, including diagnosis, clinical features, and treatments. An additional focus is the development of strategies for the successful surgical management of patients with a KD history, emphasizing the preoperative assessment and the operative arena. Conclusion: Although treatments for KD are largely standardized, patients with the disease who require surgical

interventions must be properly assessed to determine the degree of pathogenesis, especially the extent of cardiac involvement. © Academic Division of Ochsner Clinic Foundation.

Yeter, D., et al. (2013). "Mercury promotes catecholamines which potentiate mercurial autoimmunity and vasodilation: Implications for inositol 1,4,5-triphosphate 3-kinase C susceptibility in Kawasaki syndrome." Korean Circulation Journal **43**(9): 581-591.
Previously, we reviewed biological evidence that mercury could induce autoimmunity and coronary arterial wall relaxation as observed in Kawasaki syndrome (KS) through its effects on calcium signaling, and that inositol 1,4,5-triphosphate 3-kinase C (ITPKC) susceptibility in KS would predispose patients to mercury by increasing Ca2+ release. Hg2+ sensitizes inositol 1,4,5-triphosphate (IP3) receptors at low doses, which release Ca2+ from intracellular stores in the sarcoplasmic reticulum, resulting in delayed, repetitive calcium influx. ITPKC prevents IP3 from triggering IP3 receptors to release calcium by converting IP3 to inositol 1,3,4,5-tetrakisphosphate. Defective IP3 phosphorylation resuiting from reduced genetic expressions of ITPKC in KS would promote IP3, which increases Ca 2+ release. Hg2+ increases catecholamine levels through the inhibition of S-adenosylmethionine and subsequently catechol-O- methyltransferase (COMT), while a single nucleotide polymorphism of the COMT gene (rs769224) was recently found to be significantly associated with the development of coronary artery lesions in KS. Accumulation of norepinephrine or epinephrine would potentiate Hg2+-induced calcium influx by increasing IP3 production and increasing the permeability of cardiac sarcolemma to Ca2+. Norepinephrine and epinephrine also promote the secretion of atrial natriuretic peptide, a potent vasodilator that suppresses the release of vasoconstrictors. Elevated catecholamine levels can induce hypertension and tachycardia, while increased arterial pressure and a rapid heart rate would promote arterial vasodilation and subsequent fatal thromboses, particularly in tandem. Genetic risk factors may explain why only a susceptible subset of children develops KS although mercury exposure from methylmercury in fish or thimerosal in pediatric vaccines is nearly ubiquitous. During the infantile acrodynia epidemic, only 1 in 500 children developed acrodynia whereas mercury exposure was very common due to the use of teething powders. This hypothesis mirrors the leading theory for KS in which a widespread infection only induces KS in susceptible children. Acrodynia can mimic the clinical picture of KS, leading to its inclusion in the differential diagnosis for KS. Catecholamine levels are often elevated in acrodynia and may also play a role in KS. We conclude that KS may be the acute febrile form of acrodynia. Copyright © 2013 The Korean Society of Cardiology.

Yim, D., et al. (2013). "Update on Kawasaki disease: epidemiology, aetiology and pathogenesis." Journal of Paediatrics & Child Health **49**(9): 704-708.
Kawasaki disease is an acute systemic vasculitis predominantly affecting young children. It is due to an abnormal host response to as yet unidentified infectious trigger(s). Kawasaki disease may cause coronary artery damage, long-term cardiovascular morbidity and occasionally mortality, especially if the diagnosis is missed or timely treatment is not given. This is the first of two updates on Kawasaki disease. Here we review recent advances in epidemiology, possible aetiologies, host susceptibility and pathogenesis of this fascinating condition.

2012 (16)

Bajolle, F. and D. Laux (2012). "[Kawasaki disease: what you need to know]." Archives de Pediatrie **19**(11): 1264-1268.
Kawasaki disease (KD) is an acute systemic vasculitis syndrome occurring mostly in children younger than 5 years of age. Especially young infants (<1 year) have an increased risk of coronary artery lesions (CAL). Whereas the etiology of KD is still unknown, progress in treatment during its acute phase has decreased the incidence of CAL from 25-30% to 3-5%. In "atypical KD", the clinical picture is dominated by an unusual symptom as seizure, bloody diarrhea,

compressive cervical adenopathy, nephrotic syndrome or hyponatremia. To make a diagnosis in case of "incomplete KD", the supplementary criteria (clinical and biological) suggested by the American Heart Association can be helpful. Once the diagnosis established, the treatment of choice is the intravenous administration of immunoglobulin associated to aspirin at anti-inflammatory dose. However, some patients remain feverish within 36 hours following the end of immunoglobulin administration. This treatment resistance seems increasing in some regions of the globe and can touch up 20% of patients. The unsatisfactory answer to the initial treatment is associated to a higher risk of CAL. Predictive criteria of resistance have been identified and allow to strengthen the medical treatment with a second administration of immunoglobulins. Moreover, methylprednisolone pulse therapy and tumor necrosis factor-alpha blockade (infliximab) appear to be interesting therapeutic options in the future. At last, other treatments have not been the object of controlled studies yet but are alternatives in refractory forms e.g. cytotoxic agents (cyclosporine A, cyclophosphamide, methotrexate), plasmapheresis, plasma exchange or abciximab, especially in patients with aneurysms. Sclerotic vascular changes are often observed in post-Kawasaki disease patients, including those without coronary lesions during the acute phase. Indeed, endothelial dysfunction and risk factors for the development of atherosclerosis, such as dyslipidemia, decreased vascular elasticity, increased C-reactive protein, oxidative stress, and inflammatory cytokines, are known to be present in the late phase of KD. However, it is not clearly established that the survivors of KD carry a higher risk of coronary disease. The epidemiological studies of the next decade should give clearer answers as far as these patients henceforth achieved the age of the atherosclerosis. In conclusion, the diagnosis of KD imposes a strict supervision by a pediatric cardiologist initially. The follow-up is organized according to the existence or non-existence of coronary artery lesions. Late complications as stenosis or coronary thrombosis can occur but remain rare. Thus, it is necessary to be reassuring with the parents, especially for those whose children had no or regressive CAL, while recommending a prevention of the cardiovascular risk factors in the adulthood.

Bakalli, I., et al. (2012). "The approach to incomplete Kawasaki disease in infants." Paediatria Croatica **56**(1): 55-58.
The manifestations of Kawasaki disease in infants are often subtle and many times infants with this condition do not meet full diagnostic criteria. The approach to incomplete Kawasaki disease remains a challenge for physicians because clinical features may be mistaken for symptoms of other conditions. Young infants are at an extremely high risk of developing coronary arterial abnormalities compared to older children, probably due to the delay in diagnosis and the fact that only a small number receive intravenous immunoglobulin (IVIG) during the first 10 days of illness. We present a 5-month-old boy treated at our pediatric intensive care unit. The boy presented with fever lasting for more than five days, unresponsive to antibiotic therapy, changes in extremities (erythema, edema and desquamation), polymorphous rash, changes in the lips and oral cavity, seizures, irritability, pyuria, anemia, leukocytosis and raised titer of acute phase reactants. The presence of rash was initially mistaken for a reaction to antibiotics administered for a presumed urinary tract infection. All bacterial cultures and serologic tests were negative. Echocardiography showed no abnormality, but according to the criteria for incomplete Kawasaki disease published by the American Academy of Pediatrics and American Heart Association, we decided to treat the child with IVIG. With this report, we would like to highlight the importance of a high degree of clinical suspicion of Kawasaki disease in infants in whom the presentation is often incomplete, while prompt IVIG therapy is crucial to avoid serious cardiac complications.

Behniafard, N., et al. (2012). "Autoimmunity in X-linked agammaglobulinemia: Kawasaki disease and review of the literature." Expert Review of Clinical Immunology **8**(2): 155-159.
Although autoimmunity phenotype is surprisingly common in patients with different types of primary antibody deficiency, it is much less frequent in X-linked agammaglobulinemia (XLA). Herein, we report on a 15-month-old boy with XLA who also suffered from Kawasaki disease. The current case presentation is the first report of an association between Kawasaki disease and XLA.

XLA could be considered as a special opportunity to understand autoimmunity in the near absence of immunoglobulins.

Coustasse, A., et al. (2012). "Can Kawasaki disease be managed?" Permanente Journal **16**(2): 70-72.
Kawasaki Disease (KD) is the leading cause of acquired cardiovascular disease among children, but management of KD has received relatively little attention. In the US alone, about 5500 cases were estimated in 2009. KD is most common among Asian and Pacific Islander children but can affect all ethnicities and races. Timely and accurate diagnosis remains critical, but difficult: the etiology of KD is unknown, and no accurate diagnostic laboratory test has been developed. Continuing medical education can help physicians, clinicians, and nurse practitioners accurately diagnose and treat KD. A registry specific to KD or a surveillance system may be necessary to increase awareness among health care professionals and to decrease complications related to misdiagnosis.

Daniels, L. B., et al. (2012). "Kawasaki disease: late cardiovascular sequelae." Current Opinion in Cardiology **27**(6): 572-577.
PURPOSE OF REVIEW: Kawasaki disease was first described in Japanese in 1967, and the first English language report appeared in 1974. Consequently, only recently have Kawasaki disease patients reached adulthood and come to the attention of adult cardiologists. As children with Kawasaki disease grow up, adult cardiologists are likely to see increasing numbers of these patients with cardiovascular complications. The purpose of this review is to highlight recent advances in our understanding of the late cardiac sequelae of Kawasaki disease.
RECENT FINDINGS: Patients with persistent or remodeled coronary aneurysms after Kawasaki disease have a high rate of complications including thrombosis or stenosis leading to myocardial infarction. Whether patients with Kawasaki disease are at risk of accelerated atherosclerosis remains controversial, but there may be persistent inflammation in the arterial wall of coronary aneurysms long after Kawasaki disease, and myofibroblasts likely play a central role in the arterial remodeling process.
SUMMARY: The vasculopathy of Kawasaki disease appears to be distinct from that of atherosclerosis, and optimal management strategies for the two conditions differ. Patients with persistent or remodeled coronary aneurysms or regressed aneurysms after Kawasaki disease are at increased risk and require long-term follow-up by cardiologists knowledgeable about management issues in this patient population.

De Rosa, G., et al. (2012). "Delayed diagnosis of Kawasaki syndrome and thrombosis of a medium-sized aneurysm of the anterior descending coronary artery: case report and literature review." Rheumatology International **32**(3): 809-814.
A 7-year-old child was first admitted for persistent fever of 15-day duration and suspected meningitis. Kawasaki syndrome was lately diagnosed upon the recognition of an extensive diffuse coronary artery damage characterized by medium-sized aneurysms of the epicardial vessels. An eccentric thrombus along the inferior wall of the left anterior descending artery suspected at transthoracic echocardiography was confirmed by coronary computed tomography angiography scan, without significant segmental stenosis. Strict cardiac surveillance and anticoagulant therapy were maintained, and no ischemic complications occurred at a short-term follow-up. This report emphasizes that thrombosis can be observed even in medium-sized aneurysms when the diagnosis of Kawasaki syndrome is delayed.

Diniz, J. C., et al. (2012). "Kawasaki disease and juvenile systemic lupus erythematosus." Lupus **21**(1): 89-92.
Kawasaki disease (KD) is a common vasculitis in childhood. To the authors' knowledge, only one case of juvenile systemic lupus erythematosus (JSLE)-like onset mimicking KD and another case of KD and JSLE association have previously been described. However, the prevalence of this association of the two diseases was not reported. Therefore, over 27 consecutive years, 5419

patients were followed at the Pediatric Rheumatology Unit and 271 (5%) of them met the ACR classification criteria for JSLE. Two (0.7%) of them were female. These also had KD according to European League against Rheumatism / Paediatric Rheumatology European Society (EULAR/PReS) consensus criteria and are described in this report. One case was a 13-year-old who presented all six KD criteria. Echocardiogram showed pericardial effusion, dilatation and tortuosity of right and left coronary, and her symptoms promptly improved after treatment with intravenous immunoglobulin (IVIG). Lupus diagnosis was established a few days later. Another case was a 4-year-old who had also met all six KD criteria, with improvement after IVIG, and lupus diagnosis was made 1 year later. In conclusion, the frequency of the association between these two autoimmune diseases was rare. The occurrence of a second autoimmune systemic disease in a patient with a history of KD should also be considered. Furthermore, the initial presentation of lupus may mimic KD. © The Author(s), 2011.

Ghelani, S. J., et al. (2012). "Increased incidence of incomplete kawasaki disease at a pediatric hospital after publication of the 2004 american heart association guidelines." Pediatric Cardiology **33**(7): 1097-1103.
We sought to study the impact of the 2004 American Heart Association guidelines on diagnosis and treatment of patients with Kawasaki disease (KD). We reviewed patient records from July 2000 to June 2002 (group 1) and July 2007 to June 2009 (group 2) at a tertiary children's hospital. The proportion of patients with incomplete KD in group 2 (56 of 118 [47%]) was significantly higher than that in group 1 (20 of 85 [24%], p = 0.001). Median age (months) and interquartile ranges for group 1 was 26 (range 12.5-52) and for group 2 was 38.5 (range 18-63; p = 0.072). The number of patients diagnosed with KD having just 2 symptoms other than fever was significantly higher in group 2 (2.4 vs. 16.9%, p<0.001). Erythrocyte sedimentation rate, albumin, and alanine aminotransferase levels were obtained in a significantly greater number of patients with KD after the guidelines were published. Thirty-two of the 203 patients studied had coronary artery (CA) involvement (15.8%), 4 of whom had CA aneurysms (2%) and 28 had CA ectasia only (13.8%). CA involvement was seen in 13 of 85 (15.3%) patients in group 1 and 19 of 118 (16.1%; p = 1) patients in group 2. After publication of the 2004 AHA guidelines, diagnoses of incomplete KD and laboratory use increased at our center; however, the rate of CA involvement remained stable. There also was a trend towards older age in children diagnosed with KD. Laboratory parameters and CA involvement between incomplete KD and classic KD were comparable. © Springer Science+Business Media, LLC 2012.

Huang, J. and J. Chen (2012). BP neural network model for early diagnosis of Kawasaki Disease. Advanced Materials Research. **468-471:** 723-726.
In order to diagnose Kawasaki Disease during early phase, clinical symptoms (temperature, rash, conjunctival injection, erythema of thelips, and oral mucosal changes) and laboratory data (white blood cell, neutrophil, platelet, high sensitive c-reactive protein, and erythrocyte sedimentation rate) of 138 children with Kawasaki disease or infectious diseases were used to develop a BP neural network model. 90 random cases were trained using MATLAB software for setting up the BP neural network model. The other 48 cases were analyzed to predict Kawasaki disease using this model. Results showed that the predict accuracy in patients with Kawasaki disease and children with infectious diseases are 95.6% and 88%, respectively. Our result indicates that the BP neural network model is likely to provide an accurate test for early diagnosis of Kawasaki disease. © (2012) Trans Tech Publications.

Hyams, C., et al. (2012). "An unusual case of incomplete kawasaki disease in an adolescent returning from holiday in montana." Pediatric Cardiology **33**(7): 1196-1199.
Here we present an unusual case of incomplete Kawasaki disease in a 15-year-old boy returning from a holiday with his family in Montana. His symptoms were initial diarrhoea and lethargy, with fever, rash, conjunctivitis, and arthralgia developing during the course of his illness. His condition worsened while he was at his local hospital, and he was transferred to the regional tertiary

paediatric hospital. An initial echocardiogram was normal; however, repeat echocardiogram showed dilated coronary arteries with subsequent development of peeling of the skin on the hands and feet. The patient was started on intravenous immunoglobulin and high-dose aspirin and improved clinically. He was discharged home and remains under follow-up by the infectious diseases and cardiology teams. © Springer Science+Business Media, LLC 2012.

Kuo, H. C., et al. (2012). "Kawasaki disease: An update on diagnosis and treatment." Pediatrics and Neonatology **53**(1): 4-11.
Kawasaki disease (KD) is an acute multi-system vasculitis syndrome of unknown etiology occurring mostly in infants and children younger than 5 years of age. In developed countries, it is the leading cause of acquired heart disease in children. However, KD remains a mysterious disease. Some viruses potentially causing the condition have been isolated, but the results have not been able to be reproduced. This article reviews and summarizes different aspects of KD and provides updated information on diagnosis and treatment. The supplementary criteria for incomplete presentation of KD patients suggested by the American Heart Association, treatment (including tumor necrosis factor-alpha antagonist, methylprednisolone pulse therapy, statins, plasma exchange, and cytotoxic agents) for those with intravenous immunoglobulin treatment failure, and other experiences are also included in this review. © 2012, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. All rights reserved.

Lee, K. Y., et al. (2012). "Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system"." Yonsei Medical Journal **53**(2): 262-275.
Kawasaki disease (KD) is a self-limited systemic inflammatory illness, and coronary artery lesions (CALs) are a major complication determining the prognosis of the disease. Epidemiologic studies in Asian children suggest that the etiologic agent(s) of KD may be associated with environmental changes. Laboratory findings are useful for the diagnosis of incomplete KD, and they can guide the next-step in treatment of initial intravenous immunoglobulin non-responders. CALs seem to develop in the early stages of the disease before a peak in inflammation. Therefore early treatment, before the peak in inflammation, is mandatory to reduce the risk of CAL progression and severity of CALs. The immunopathogenesis of KD is more likely that of acute rheumatic fever than scarlet fever. A hypothetical pathogenesis of KD is proposed under the premise of a "protein homeostasis system"; where innate and adaptive immune cells control pathogenic proteins that are toxic to host cells at a molecular level. After an infection of unknown KD pathogen(s), the pathogenic proteins produced from an unknown focus, spread and bind to endothelial cells of coronary arteries as main target cells. To control the action of pathogenic proteins and/or substances from the injured cells, immune cells are activated. Initially, non-specific T cells and non-specific antibodies are involved in this reaction, while hyperactivated immune cells produce various cytokines, leading to a cytokine imbalance associated with further endothelial cell injury. After the emergence of specific T cells and specific antibodies against the pathogenic proteins, tissue injury ceases and a repair reaction begins with the immune cells.

Luca, N. J. and R. S. Yeung (2012). "Epidemiology and management of Kawasaki disease." Drugs **72**(8): 1029-1038.
Kawasaki disease (KD) is an acute systemic vasculitis affecting young children and is rising in incidence worldwide. It is most common in children <5 years of age, males and those of Asian ethnicity. It is an important cause of acquired heart disease in children. Standard treatment with high-dose aspirin (acetylsalicylic acid; ASA) and intravenous immune globulin (IVIG) has been shown to decrease the rate of coronary artery aneurysm development. Anti-coagulation has an important place in the management of KD, although guidance based on evidence is lacking. Treatment of refractory KD is an area under intense study and may include IVIG, corticosteroids and/or tumour necrosis factor (TNF)-alpha inhibitors among immunosuppressive agents. Acute complications of KD include myocarditis/KD shock syndrome and macrophage activation syndrome, which necessitate appropriate awareness in order to initiate proper management.

Onouchi, Y. (2012). "Genetics of Kawasaki disease: what we know and don't know." Circulation Journal **76**(7): 1581-1586.
Kawasaki disease (KD) is a leading cause of acquired heart disease in children in developed countries. Although it has been thought that symptoms of KD are related to hyperactivation of the immune system triggered by infection with some microorganisms, the etiological agent still remains unknown. In this situation, genetic factors underlying the disease pathogenesis, which have been suggested by epidemiological findings, are expected to be clues to the enigma. Recently, susceptibility genes for KD have been identified in succession by studies with a genome-wide approach. Recent advances in genetic studies for KD will be presented.

Uehara, R. and E. D. Belay (2012). "Epidemiology of Kawasaki disease in Asia, Europe, and the United States." Journal of Epidemiology **22**(2): 79-85.
Kawasaki disease (KD) is a systemic vasculitis that mainly affects children younger than 5 years. Although Dr. Tomisaku Kawasaki first reported KD over 40 years ago, the cause of the disease remains unknown. Currently, KD has been diagnosed in more than 60 countries, including those in Asia, the Middle East, Latin America, and Africa, as well as in North America and Europe. The purpose of this review is to describe the epidemiologic features of KD--particularly its incidence, seasonality, and the occurrence of coronary artery abnormalities--primarily in Japan and the United States, but also in Europe and other Asian countries.

Yeom, J. S., et al. (2012). "Initial characteristics of Kawasaki disease with cerebrospinal fluid pleocytosis in febrile infants." Pediatric Neurology **47**(4): 259-262.
To distinguish between febrile infants with cerebrospinal fluid pleocytosis who are finally diagnosed with Kawasaki disease and those with enterovirus meningitis poses a diagnostic challenge. We compared clinical and laboratory features at admission between two groups of infants, aged 30-90 days, to identify markers of Kawasaki disease that initially presented as cerebrospinal fluid pleocytosis. During a 2-year period, 100 patients exhibiting cerebrospinal fluid pleocytosis were studied, including six (6.0%) with Kawasaki disease and 30 (30.0%) with enterovirus meningitis. A longer duration of fever before admission ($P < 0.01$), higher absolute neutrophil count ($P < 0.01$), increased C-reactive protein level ($P < 0.01$), pyuria ($P = 0.02$), and less prominent cerebrospinal fluid pleocytosis ($P = 0.01$) were identified as initial features of infants finally diagnosed with Kawasaki disease. No significant differences were evident in white blood cell count; platelet count; levels of hemoglobin, alanine aminotransaminase, aspartate aminotransferase, albumin, and sodium; cerebrospinal fluid chemistry; or presence of a rash. Our observations may offer early indicators of Kawasaki disease for timely diagnoses in febrile infants with cerebrospinal fluid pleocytosis.

2011 (5)

Alexoudi, I., et al. (2011). "Kawasaki disease: current aspects on aetiopathogenesis and therapeutic management." Autoimmunity Reviews **10**(9): 544-547.
Kawasaki disease (KD) is a vasculitis that affects mainly children of 6 months to 4 years old. It is important to be early recognised so as to limit the inflammatory cascade that may lead to aneurysmatic dilatations of coronary arteries. The causative agent of KD has not been still indentified and the aetiopathogenetic theories are based on epidemiologic, laboratory and histological data. The management of the disease is divided according to the clinical stage and patients' follow up should be continued for years after the disease onset. The exact period is determined by the risk level of the KD.

Rowley, A. H. (2011). "Kawasaki disease: novel insights into etiology and genetic susceptibility." Annual Review of Medicine **62**: 69-77.

Kawasaki disease (KD) is a vasculitis of young childhood that particularly affects the coronary arteries. Molecular analysis of the oligoclonal IgA response in acute KD led to production of synthetic KD antibodies. These antibodies identify intracytoplasmic inclusion bodies in acute KD tissues. Light and electron microscopic studies indicate that the inclusion bodies are consistent with aggregates of viral proteins and RNA. Advances in molecular genetic analysis and completion of the Human Genome Project have sparked a worldwide effort to identify genes associated with KD. A polymorphism of one such gene, ITPKC, a negative regulator of T cell activation, confers susceptibility to KD in Japanese populations and increases the risk of developing coronary artery abnormalities in both Japanese and U.S. children. Identification of the etiologic agent and of genes conferring KD susceptibility are the best means of improving diagnosis and therapy and enabling prevention of this important disorder of childhood.

Takahashi, K., et al. (2011). "Pathogenesis of Kawasaki disease." Clinical & Experimental Immunology **164 Suppl 1**: 20-22.
Kawasaki disease (KD) most frequently affects infants and young children under 5 years of age. This disease is considered a kind of systemic vasculitis syndrome, and primarily invades the medium-sized muscular arteries, including coronary arteries. Diagnosis of KD is based on characteristic clinical signs and symptoms, which are classified as principal clinical findings and other clinical and laboratory findings. Even though the aetiology of KD is unknown, epidemiological data suggest that some kinds of infectious agents are involved in the onset of KD. In addition, the data indicate that host genetics underlie the disease's pathogenesis. Histologically, coronary arteritis begins 6-8 days after the onset of KD, and leads immediately to inflammation of all layers of the artery. The inflammation spreads completely around the artery; as a result, structural components of the artery undergo intense damage; the artery then begins to dilate. Inflammatory cell infiltration continues until about the 25th day of the disease, after which the inflammatory cells gradually decrease in number. KD arteritis is characterized by granulomatous inflammation that consists of severe accumulation of monocytes/macrophages. Aberrant activation of monocytes/macrophages is thought to be involved in the formation of vascular lesions. The lesions in all the arteries are relatively synchronous as they evolve from acute to chronic injury. There is no fibrinoid necrosis nor any mixture of acute inflammatory lesions and scarring lesions, which are characteristics in polyarteritis nodosa in KD.

Thapa, R. (2011). "Facial palsy in a 2-month-old infant with Kawasaki disease." Rheumatology International **31**(2): 277-278.

Young, J. H. M., et al. (2011). "Kawasaki disease presenting as intestinal pseudo-obstruction in a three-year-old boy." Hong Kong Journal of Paediatrics **16**(1): 51-55.
Typical clinical presentations of Kawasaki disease (KD) are well known to paediatricians. Abdominal pain, vomiting, diarrhoea and hydrops of gallbladder are the commonest gastrointestinal presentations of KD, while acute surgical abdomen or severe gastrointestinal complication as a presenting sign is rare. We report a case of a three-year-old previously healthy boy with KD whose gastrointestinal symptoms and signs were present at the onset, which subsequently progressed to intestinal pseudo-obstruction syndrome, and the condition responded to bowel rest, intravenous immunoglobulin and oral aspirin treatment, without any complications. We suggest that KD should be considered a differential diagnosis of a child presenting with fever and intestinal pseudo-obstruction without identifiable cause, and high index of suspicion of atypical KD should be taken as prompt diagnosis and treatment can prevent serious long term consequences.

2010 (14)

Ahn, J. H., et al. (2010). "A ruptured middle cerebral artery aneurysm in a 13-month-old boy with

Kawasaki disease." Journal of Neurosurgery. Pediatrics. **6**(2): 150-153.
This 13-month-old boy, in whom Kawasaki disease had been diagnosed at the age of 6 months, presented with subarachnoid hemorrhage caused by the rupture of a middle cerebral artery aneurysm. The authors performed an emergency craniectomy and clip occlusion of the aneurysm, which was found to be partially thrombosed. The patient was discharged 4 weeks postoperatively without apparent neurological deficit. Intracranial saccular aneurysms in the pediatric population are rare, and are occasionally associated with various systemic disorders. Kawasaki disease is a systemic vasculopathy of unknown origin, but cerebral arteries are usually spared from the disease process. This is the second case report of a ruptured cerebral aneurysm in a patient with Kawasaki disease, providing a novel clinical feature that the authors call Kawasaki syndrome. [References: 15]

Briede, S., et al. (2010). "[Long term effects of Kawasaki disease]." Nederlands Tijdschrift voor Geneeskunde **154**(45): A2121.
Kawasaki Disease (KD) is an acute, self-limiting, vasculitis typically occurring in children under the age of five. Less than 5% of children with KD develop coronary aneurysms and require follow-up by a (paediatric) cardiologist. The majority of patients do not receive follow-up care. However, recent data suggest that the inflammation associated with KD has the potential to affect the entire cardiovascular system. Patients with a history of KD may have an increased risk of long-term cardiovascular sequelae. Therefore KD should be considered a cardiovascular risk factor.

Choueiter, N. F., et al. (2010). "Prospective open-label trial of etanercept as adjunctive therapy for kawasaki disease." Journal of Pediatrics **157**(6): 960-966.e961.
Objective: To determine the safety and pharmacokinetics of etanercept (Amgen, Thousand Oaks, California) a tumor necrosis factor-α receptor blocker, in children with acute Kawasaki disease (KD). Standard therapy of acute KD includes intravenous immunoglobulin (IVIG) and high-dose aspirin, but a substantial number of patients are refractory and require additional treatment. Tumor necrosis factor-α levels are elevated in children with KD, suggesting a role for etanercept in treatment. Study design: We performed a prospective open-label trial of etanercept in patients with KD (age range, 6 months-5 years; n = 17) meeting clinical criteria and with fever ≤10 days. All received IVIG and high-dose aspirin. They received etanercept immediately after IVIG infusion and then weekly two times. For the initial safety evaluation, the first 5 patients received 0.4 mg/kg/dose. Subsequent subjects received 0.8 mg/kg/dose. Results: Fifteen patients completed the study. The pharmacokinetics were similar to that in older children in published series. No serious adverse events related to etanercept occurred. No patient demonstrated prolonged or recrudescent fever requiring re-treatment with IVIG. No patient showed an increase in coronary artery diameter or new coronary artery dilation/cardiac dysfunction. Conclusion: Etanercept appears to be safe and well tolerated in children with KD. The data support performance of a placebo-controlled trial. © 2010 Mosby Inc. All rights reserved.

Dillon, M. J., et al. (2010). "Medium-size-vessel vasculitis." Pediatric Nephrology **25**(9): 1641-1652.
Medium-size-artery vasculitides do occur in childhood and manifest, in the main, as polyarteritis nodosa (PAN), cutaneous PAN and Kawasaki disease. Of these, PAN is the most serious, with high morbidity and not inconsequential mortality rates. New classification criteria for PAN have been validated that will have value in epidemiological studies and clinical trials. Renal involvement is common and recent therapeutic advances may result in improved treatment options. Cutaneous PAN is a milder disease characterised by periodic exacerbations and often associated with streptococcal infection. There is controversy as to whether this is a separate entity or part of the systemic PAN spectrum. Kawasaki disease is an acute self-limiting systemic vasculitis, the second commonest vasculitis in childhood and the commonest cause of childhood-acquired heart disease. Renal manifestations occur and include tubulointerstitial nephritis and renal failure. An infectious trigger and a genetic predisposition seem likely.

Intravenous immunoglobulin (IV-Ig) and aspirin are effective therapeutically, but in resistant cases, either steroid or infliximab have a role. Greater understanding of the pathogenetic mechanisms involved in these three types of vasculitis and better long-term follow-up data will lead to improved therapy and prediction of prognosis.

Gomard-Mennesson, E., et al. (2010). "Kawasaki disease in adults: report of 10 cases." Medicine **89**(3): 149-158.
Kawasaki disease (KD) is an acute multisystemic vasculitis occurring predominantly in children and rarely in adults. Diagnosis is made clinically using diagnostic guidelines; no specific test is available. "Incomplete" KD is a more recent concept, which refers to patients with fever lasting > or =5 days and 2 or 3 clinical criteria (rash, conjunctivitis, oral mucosal changes, changes of extremities, adenopathy), without reasonable explanation for the illness. To describe the clinical and laboratory features of classical (or "complete") KD, and incomplete KD in adults, we report 10 cases of adult KD, including 6 patients who fulfilled the criteria for incomplete KD, diagnosed either at presentation (n = 4) or retrospectively (n = 2). At the time of clinical presentation, complete KD was diagnosed in 4 patients, while 4 patients fulfilled the criteria for incomplete KD. For 3 of the 4 patients with incomplete KD, presence of severe inflammation, laboratory findings (hypoalbuminemia, anemia, elevation of alanine aminotransferase, thrombocytosis after 7 days, white blood cell count > or =15,000/mm, and urine > or =10 white blood cell/high power field), or echocardiogram findings were consistent with the diagnosis. In 2 patients, the diagnosis of KD was made retrospectively in the presence of myocardial infarction due to coronary aneurysms, after an undiagnosed medical history evocative of incomplete KD. Seven patients received intravenous immunoglobulins (IVIG), after a mean delay of 12.5 days, which appeared to shorten the course of the disease. This relatively large series of adult KD highlights the existence of incomplete KD in adults and suggests that the algorithm proposed by a multidisciplinary committee of experts to diagnose incomplete KD in children could be useful in adults. Further studies are needed to determinate whether prompt IVIG may avoid artery sequelae in adult patients with complete or incomplete KD. [References: 85]

Kobayashi, S., et al. (2010). "Anti-neutrophil cytoplasmic antibody-associated vasculitis, large vessel vasculitis and Kawasaki disease in Japan." Kidney & Blood Pressure Research **33**(6): 442-455.
Based on studies comparing the prevalence of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) between Japan and Europe, we have learned that the difference may be due to genetic background and environmental factors, but not to diagnosis or ELISA system for myeloperoxidase and proteinase-3 ANCA. In Japan, microscopic polyangiitis is the most common among AAV, but Wegener's granulomatosis was present in less than 2 per million patients. Also, one study from Hokkaido reported only 16 patients in a 27-year time frame. A recent retrospective study of renal vasculitis between 2000 and 2004 from Miyazaki prefecture in Japan reported an incidence of microscopic polyangiitis of 14.8 per million, but no patients with Wegener's granulomatosis or Churg-Strauss syndrome. In the present review, we focus on ANCA-related vasculitis in Japan: (1) AAV and large vessel vasculitis - Takayasu's arteritis and giant cell arteritis; (2) primary renal vasculitis; (3) epitopes of myeloperoxidase-ANCA in vasculitis in the Japanese population and comparison of ANCA-ELISA systems in Japan and Europe, and finally (4) children with vasculitis in Japan involving Kawasaki disease - a systemic vasculitis.

Liu, Y. C., et al. (2010). "[Atypical kawasaki disease: literature review and clinical nursing]." Hu Li Tsa Chih - Journal of Nursing **57**(6): 104-110.
Kawasaki disease (KD) is an acute febrile multi-systemic vasculitis of unknown etiology that primarily affects children under 5 years of age. KD has been singled out as a main cause of acquired childhood heart disease. Its etiology, genetic background, and immunopathogenesis remain unclear. Diagnosing and providing nursing care to KD patients, especially those suffering from atypical KD, present a challenge for clinicians and nurses. This report is a literature review

covering pathogenesis, clinical presentation, atypical symptoms, differential diagnosis, treatment and nursing of KD and atypical KD. This review provides updated information for clinicians and nurses with care responsibilities for patients with KD and atypical KD.

López, A. I. H., et al. (2010). "Incomplete Kawasaki disease in an adolescent. A case report." Iatreia **23**(2): 178-183.
We report the case of a 12 year old boy with incomplete Kawasaki disease (KD). During the course of his illness he presented with symptoms of acute hepatitis, which delayed the final diagnosis. Although patients with KD may present with elevation of hepatic enzymes and bilirubin, associated acute hepatitis is of rare occurrence in this entity.

Neuwirth, C. A. and H. Singh (2010). "Intercostal Artery Aneurysm in a Child with Kawasaki Disease and Known Coronary Artery Aneurysms." Journal of Vascular and Interventional Radiology **21**(6): 952-953.

Onouchi, Y. (2010). "Identification of susceptibility genes for Kawasaki disease." Nihon Rinsho Meneki Gakkai Kaishi **33**(2): 73-80.
Kawasaki disease is an acute febrile illness of infants and children with unknown etiology. Coronary artery lesions occurring in 20-25% of untreated patients of KD has made KD a leading cause of acquired heart diseases of childhood in developed countries. High prevalence in East Asian countries is one of the epidemiological features of KD and has suggested genetic factors underlying the disease pathogenesis. We tried to identify genetic variants relevant to KD susceptibility by sibpair linkage study and linkage diseuilibrium mapping with SNPs and found that inositol 1,4,5-trisphosphate 3-kianse C gene is a susceptibility gene for KD. We also found the negative regulatory role of ITPKC in TCR signaling and the mechanism by which the responsible SNP in intron 1 of the gene affects transcripts level of ITPKC. Our findings highlighted the importance of Ca(2+)/NFAT pathway in the pathogenesis of KD and shed light on the possibility of immuno-suppressants targeting the pathway as a therapeutic strategy for KD. [References: 25]

Palumbo, E. (2010). "Kawasaki' s syndrome: Recent advances in diagnosis and therapy." Recenti Progressi in Medicina **101**(9): 355-358.
Kawasaki disease is an autoimmune disease that manifests as a multisystemic necrotizing medium vessel vasculitis that is largely seen in children under 5 years of age. It affects many organs, including the skin, lymph nodes, and blood vessel walls, but the most serious effect is on the heart where it can cause severe aneurysmal dilations in untreated children. The aim of this paper is to evidence the recent advances in the diagnosis and therapy of this disease.

Rowley, A. H. and S. T. Shulman (2010). "Pathogenesis and management of Kawasaki disease." Expert Review of Antiinfective Therapy **8**(2): 197-203.
Kawasaki disease (KD) is an acute systemic inflammatory illness of young children that can result in coronary artery aneurysms, myocardial infarction and sudden death in previously healthy children. Clinical and epidemiologic features support an infectious cause, but the etiology remains unknown four decades after KD was first identified by Tomisaku Kawasaki. Finding the cause of KD is a pediatric research priority. We review the unique immunopathology of KD and describe the current treatment. New research has led to identification of viral-like cytoplasmic inclusion bodies in acute KD tissues; this finding could lead to identification of the elusive etiologic agent and result in significant advances in KD diagnosis and treatment. Current management of acute KD is based upon prospective, multicenter treatment trials of intravenous immunoglobulin (IVIG) with high-dose aspirin. Optimal therapy is 2 g/kg IVIG with high-dose aspirin as soon as possible after diagnosis during the acute febrile phase of illness, followed by low-dose aspirin until follow-up echocardiograms indicate a lack of coronary abnormalities. The addition of one dose of intravenous pulse steroid has not been shown to be beneficial. For the 10-15% of patients with

refractory KD, few controlled data are available. Options include repeat IVIG (our preference), a 3-day course of intravenous pulse methylprednisolone, or infliximab (Remicade). Patients with mild-to-moderate coronary abnormalities should receive an antiplatelet agent such as low-dose aspirin (3-5 mg/kg/day) or clopidogrel (1 mg/kg/day up to 75 mg), and those with giant (approximately 8 mm diameter) or multiple coronary aneurysms should receive an antiplatelet agent with an anticoagulant such as warfarin or low-molecular-weight heparin. Acute coronary obstruction requires acute thrombolytic therapy with a surgical or percutaneous interventional procedure. [References: 49]

Takahashi, M. (2010). "Cardiac ischemia in pediatric patients." Pediatric Clinics of North America **57**(6): 1261-1280.
Cardiac ischemia in children is usually not an isolated disease in an otherwise normally formed coronary artery but is part of more complex congenital or acquired diseases. Although cardiac ischemia is not a frequent occurrence, it must be recognized as a serious, life-threatening event. This article lists and characterizes major causes of cardiac ischemia in children, describes signs and symptoms of each, and provides therapeutic considerations.

Yeung, R. S. (2010). "Kawasaki disease: update on pathogenesis." Current Opinion in Rheumatology **22**(5): 551-560.
PURPOSE OF REVIEW: This review will highlight recent advances in our understanding of the pathogenesis of Kawasaki disease, highlighting the molecular players involved in regulation of T-cell activation and their affect on disease incidence and outcome in both humans and mouse.
RECENT FINDINGS: Kawasaki disease is the most common cause of multisystem vasculitis in childhood. The vessels most commonly damaged are the coronary arteries, making Kawasaki disease the number one cause of acquired heart disease in children from the developed world. The contribution of genetics to disease predisposition is clearly implicated, but the mechanisms involved in regulating predisposition to disease susceptibility and outcome are not clearly understood. Two independent approaches have recently identified regulation of T-cell activation as the critical factor in determining susceptibility and severity of Kawasaki disease. Firstly, genetic analysis of affected Japanese children identified ITPKC, 1,4,5-triphosphate 3-kinase C, a kinase involved in regulation of T-cell activation, to be significantly associated with susceptibility to and increased severity of Kawasaki disease. A second independent approach using an animal model of Kawasaki disease has also identified regulation of T-cell activation, specifically costimulation, the second signal regulating optimal T-cell activation as the critical regulator of susceptibility to and severity of disease.
SUMMARY: Understanding the molecular players responsible for dysregulation of the immune response in Kawasaki disease will foster development of improved diagnostic/predictive tools and more rational use of therapeutic agents to improve outcome in affected children.

2009 (10)

Baker, A. L., et al. (2009). "Associated Symptoms in the Ten Days Before Diagnosis of Kawasaki Disease." Journal of Pediatrics **154**(4): 592-595.e592.
Objective: To describe common associated symptoms within the 10 days before diagnosis in subjects enrolled in the Pediatric Heart Network's trial of steroid therapy in Kawasaki disease (KD). Study design: Patients with acute KD were enrolled between days 4 and 10 of illness at 8 centers between 2002 and 2004. We defined common associated symptoms as those occurring in ≥10% of patients. Principal clinical criteria for KD were not included in this analysis. Results: Among 198 patients, irritability was reported in 98 (50%), vomiting in 88 (44%), decreased food/fluid intake in 73 (37%), cough in 55 (28%), diarrhea in 52 (26%), rhinorrhea in 37 (19%), weakness in 37 (19%), abdominal pain in 35 (18%), and joint pain (arthralgia or arthritis) in 29 (15%). One or more gastrointestinal symptom (vomiting, diarrhea, or abdominal pain) was

present in 120 patients (61%) and 69 patients (35%) had ≥ 1 respiratory symptom (rhinorrhea or cough). Conclusions: Nonspecific symptoms occur commonly in children with KD. To reduce delays in diagnosis, clinicians should be educated that such symptoms may comprise a significant component in the chief complaint. © 2009 Mosby, Inc. All rights reserved.

Burns, J. C. (2009). "Kawasaki Disease update." Indian Journal of Pediatrics **76**(1): 71-76.
Kawasaki Disease is rapidly becoming the most common cause of acquired heart disease in children in both the developed and developing world. Its etiology remains a mystery but important progress has been made in characterizing the features of the arterial wall and myocardial pathology and long-term clinical consequences. New treatments aimed at modifying the host immune response are currently under study. The genetic influence on susceptibility and disease outcome is an area of active research. [References: 72]

Gil Veloz, M., et al. (2009). "Kawasaki disease: Clinical behaviour and cardiovascular complications in children in a tertiary-care level hospital." Archivos de Cardiologia de Mexico **79**(1): 11-17.
Objectives: To describe the clinical characteristics, outcome, and treatment response in a series of patients with Kawasaki disease (KD). Methods: Case-series, review of clinical records of children with KD diagnosis cared for from november 1999 to September 2006. Results: 22 patients were included, male:female ratio, 1.4:1, 82% younger than 5 years, 14% with atypical presentation. Of the 22 patients, 10 (45%) received intravenous gammaglobulin (IVGG) in the first 10 days of symptoms onset at the recommended dose; four of them had coronary artery damage but none developed residual aneurysmatic lesions. Eight received IVGG in a different dose or after 10 days, six of them had coronary lesions and in two the damage was permanent. Four patients did not receive IVGG, and two had residual aneurysmatic lesions. None of those who received adequate treatment developed coronary residual damage, in comparison with 33% who received inadequate or no treatment, but difference was not statistically significant (P = .06). Conclusions: KD is a rare clinical entity in our country; even though most of the cases occurred with classic clinical criteria, late referral and delay of treatment worsen the prognosis. © 2007 Instituto Nacional de Cardiología Ignacio Chávez. All rights reserved.

Gordon, J. B., et al. (2009). "When children with Kawasaki disease grow up: Myocardial and vascular complications in adulthood." Journal of the American College of Cardiology **54**(21): 1911-1920.
Kawasaki disease (KD) is an acute, self-limited vasculitis that typically occurs in young children and was first described by Japanese pediatrician Tomisaku Kawasaki in 1967. Although originally thought to be a rare condition, KD has become the most common cause of acquired heart disease in the pediatric age group in developed countries. The majority of patients with KD appear to have a benign prognosis, but a subset of patients with coronary artery aneurysms are at risk for ischemic events and require lifelong treatment. In the 4 decades that have passed since the initial recognition of KD, the number of patients reaching adulthood has continued to grow. Adult cardiologists will be increasingly involved in the management of these patients. Currently, there are no established guidelines for the evaluation and treatment of adult patients who have had KD. We review here the current literature that may be helpful to clinicians who care for adults who experienced KD in childhood. [References: 99]

Hata, A. and Y. Onouchi (2009). "Susceptibility genes for Kawasaki disease: toward implementation of personalized medicine." Journal of Human Genetics **54**(2): 67-73.
Kawasaki disease (KD) is an acute systemic vasculitis syndrome, which primarily affects in children under the age of 5 years. In 20-25% of cases, if untreated, coronary artery lesions develop, making KD the leading cause of acquired heart disease in children in both Japan and the United States. Since 1970, 19 nationwide surveys of KD in Japan have been conducted every 2 years and the data are stored in a database. Even though the etiology of KD remains unknown, despite enthusiastic research spanning more than 40 years, we have learnt a great deal about KD from this enormous database. These 19 epidemiologic studies indicate a strong genetic influence

on the disease susceptibility, prompting us and other researchers to identify the responsible genes for KD by applying either the candidate gene approach or the genome-wide approach. We have employed a genome-wide linkage study using affected sibling pair data of KD in Japan and have identified several susceptibility loci. Further analysis focusing on a region of chromosome 19, where one of the linked loci was detected, identified a predisposing gene, which codes inositol 1,4,5-trisphosphate 3-kinase C (ITPKC). In this review, we summarize the cumulative knowledge regarding KD, and then outline our hypothesis of the role ITPKC plays in KD susceptibility and our trial that aims toward the implementation of personalized medicine for KD. [References: 83]

Jakubowska, B., et al. (2009). "Diagnostic difficulties and Kawasaki disease - 4-month old boy." Pediatria Polska **84**(1): 101-105.
Kawasaki disease - as described by Tomisaku Kawasaki - is an acute generalized inflammation of blood vessels. In the youngest children there is an increased risk of developing coronary aneurysmus. In infants Kawasaki disease runs with stingy symptoms with fever as the only diagnostic sign. Early diagnosis and prompt treatment have a substantial influence for life of young patients and dangerous of complications and decease of child. We present clinical evolution and treatment of Kawasaki disease in a 4-month old boy. © 2009 by Polskie Towarzystwo Pediatryczne.

Kitamura, S., et al. (2009). "Twenty-five-year outcome of pediatric coronary artery bypass surgery for kawasaki disease." Circulation **120**(1): 60-68.
BACKGROUND-: The long-term outcome of pediatric coronary artery bypass for patients with severe inflammatory coronary sequelae secondary to Kawasaki disease is unknown. METHODS AND RESULTS-: One hundred fourteen children and adolescents ranging in age from 1 to 19 (median, 10) years at operation were followed up for as long as 25 years with a median of 19 years. The number of distal anastomoses was 1.7±0.8 per patient, and the internal thoracic artery was used in all but 3, most frequently for left anterior descending artery lesions. Saphenous vein grafts were used in 24 patients, mostly for non-left anterior descending artery lesions. Patients underwent multiple angiograms to evaluate their coronary and graft status. There was no operative or hospital mortality. Both 20- and 25-year survival rates were 95% (95% confidence interval [CI], 88 to 98). Five deaths occurred, all cardiac in origin. Cardiac event-free rates at 20 and 25 years were 67% and 60% (95% CI, 46 to 72), respectively. Percutaneous coronary intervention and reoperation were the most common events. Overall, the 20-year graft patency rate was 87% (95% CI, 78 to 93) for internal thoracic artery grafts (n=154) and 44% (95% CI, 26 to 61) for saphenous vein grafts (n=30) (P<0.001), and the rate for non-left anterior descending artery lesions was also significantly better for arterial grafts (87% [95% CI, 73 to 94]; n=59) than for saphenous vein grafts (42% [95% CI, 23 to 60]; n=27) (P=0.002). Eighty-eight patients (77%) remain on medications, but all 109 survivors are presently symptom free in their daily activities. CONCLUSIONS-: Although the 25-year survival was excellent after pediatric coronary bypass for Kawasaki disease, the event-free rate declined progressively. This reality mandated continued follow-up. Reinterventions successfully managed most cardiac events. An internal thoracic artery graft was the most favorable for children. © 2009 American Heart Association, Inc.

Onouchi, Y. (2009). "Molecular genetics of Kawasaki disease." Pediatric Research **65**(5 Pt 2): 46R-54R.
Kawasaki disease (KD) is a leading cause of acquired cardiac disease of children in the developed countries. The pathogen that triggers this perplexing disease is still unknown after 40 y from the first description. Epidemiologic findings have made us believe that there are considerable genetic components in the etiology and some candidate genetic variations, which confer susceptibility to KD or risk for coronary artery lesions have been identified. However, most of them remain to be definitively confirmed by replication studies with large cohorts. In this article, I review the candidate gene association studies to date. I also introduce our recent findings in genome-wide

approach, which revealed the importance of Ca2+/nuclear factor of activated T-cells pathway in the pathogenesis of KD. [References: 78]

Raith, W., et al. (2009). "How does the time of diagnosis affect the course of disease in children with kawasaki syndrome? a retrospective analysis at one center." Klinische Padiatrie **221**(2): 83-88.
Background: Kawasaki syndrome was described for the first time by Tomisaku Kawasaki in 1967. This disease is characterized by panvasculitis of the small blood vessels of the skin, the mucous membranes, the internal organs and the coronary vessels and has an unclear etiology. Inflammatory changes in the coronary vessels or late diagnosis are prognostically unfavorable for the early and late mortality. Aim of the study: Since two of our patients with Kawasaki syndrome with a short, severe course died despite receiving state-of-the-art treatment, we retrospectively evaluated the medical records of all the children we have treated since October 1978 with regard to the symptoms at the time of diagnosis, intervals between the onset of the disease, diagnosis, beginning of treatment and the result of treatment. Patients: Kawasaki syndrome was diagnosed in 80 patients in the period from October 1978 to October 2007. The patients were grouped according to the phase of the disease and the number of organs affected at the time of diagnosis (Asai-Score) as well as the treatment carried out. The time of the first presentation for diagnosis by the pediatrician was also considered. Method: This is a single-institution retrospective analysis of the medical records, echocardiography and angiography findings of all patients. In view of the change of therapy in that year, patients who had been diagnosed before 1987 were compared with those diagnosed after 1987. Results: Before 1987, the patients were treated solely with high doses of acetylsalicylic acid (50100mg/kg/day p.o. over two to four weeks). Out of a total of 36 patients, 13 showed involvement of the coronary arteries that persisted in seven patients despite treatment. After 1987, all patients received intravenous immunoglobulins (4×0.5g/kg/day resp. 1×2g/kg i.v. over 12 hours). In 18 out of 44 patients, the coronary arteries were affected at the time of diagnosis, but this did not persist in any of the patients. One child died in each group. Comparing the two treatment groups also revealed that a physician was consulted for the first time after a very much shorter duration of the disease in the second treatment period (3±1.8 vs. 6±2.4 days after onset of the illness) and that a pediatrician was consulted much more frequently as the first port of call. This was reflected in a significantly earlier beginning of treatment and a simultaneous significantly lower Asai score. Conclusion: The retrospective evaluation of all medical records did not reveal any plausible explanation for the fatal course of the disease in one child in each of the two treatment periods. Besides the combination therapy with intravenous immunoglobulin and oral administration of acetylsalicylic acid, the greater age and the earlier commencement of treatment appeared to be salient factors resulting in complete cure of the disease in the surviving patients in the second period of treatment. © Georg Thieme Verlag KG Stuttgart New York.

Zhu, Y. G. and J. M. Qu (2009). "Differential characteristics of the early stage of lung inflammation induced by SARS-CoV Nucleocapsid protein related to age in the mouse." Inflammation Research **58**(6): 312-320.
Objective:: Severe acute respiratory syndrome (SARS) is an acute infectious disease of the respiratory system which has newly emerged. Interestingly, it appears to be a disease that predominantly affects adults while the mortality in children is extremely low. However, the pathogenesis of SARS in relation to different characteristics relevant to age remains unclear. Material(s) and Method(s):: To better understand the role of cytokines in the immunopathological processes of SARS, weanling (4 weeks old), young (6 weeks old) and adult (10 weeks old) male BALB/C mice were inoculated intranasally with N-protein of SARS-CoV in this study. Serum or lung homogenate levels of some cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) along with acute injury lung index and histology were also analyzed. Result(s):: Histopathological analysis of adult male BALB/C mice after N-protein infection showed progressive inflammatory reactions, especially pulmonary edema, in accordance with a moderately (~13%) elevated level of W/D ratio at 24 h. Although adult groups underwent

a progressive lung inflammation in the acute phase accompanied by raised levels of TNF-alpha in serum, no significant changes in lung TNF-alpha level were reported simultaneously. Moreover, adult SARS infected BALB/c mice showed elevated levels of IFN-gamma while IFN-gamma levels in weanling and young groups had no obvious association with lung inflammation. Conclusion(s):: Our study supports the observation that adult mice do have progressively greater immune reactions than weanling and adolescent ones over time. The relative immaturity of the immune system in weanlings may confer benefit leading to less impairment of lung function. However, the measurement of TNF-alpha and IFN-gamma levels was not indicative of the severity of lung injury at the early stage of disease.

2008 (13)

Baba, R. (2008). "Effect of immunoglobulin therapy on blood viscosity and potential concerns of thromboembolism, especially in patients with acute Kawasaki disease." Recent Patents on Cardiovascular Drug Discovery **3**(2): 141-144.
Kawasaki Disease (KD) is an acute febrile systemic vasculitis of unknown etiology that primarily affects children younger than five years of age. The most reliable treatment for acute-phase KD is the combination of aspirin and high dose (2g/kg) intravenous immunoglobulin (IVIG) therapy. However, IVIG therapy is occasionally associated with serious thromboembolism, probably because of a rapid increase in plasma IgG concentration. Therefore, patients with KD, who are associated with endothelial impairment, are not free from the risk of thromboembolism associated with IVIG therapy. High levels of IgG, immune complex formation, and increased platelet aggregation could increase blood viscosity after IVIG infusion. Increased serum viscosity reduces arterial and capillary blood flow, leading to thrombosis. We have previously reported that single high-dose IVIG therapy for acute KD raises plasma viscosity. Although there is scarce epidemiological information as to the prevalence of thromboembolism associated with IVIG therapy, the occurrence of these complications must be taken into consideration. This article also includes relevant patents on this topic. [References: 43]

Canino-Rodriguez, A. and R. A. Cox (2008). "Giant coronary aneurysms in a young adult patient with Kawasaki disease." Puerto Rico Health Sciences Journal **27**(4): 382-386.
Kawasaki disease is an acute, self-limited vasculitis of childhood and the principal cause of acquired heart disease in children in several parts of the world. Its major morbidity and mortality is related to the development of coronary aneurysms. The long-term impact of this disease in adults is not known, however, clinically silent coronary artery aneurysms may be recognized after a sudden cardiac event, even death. We report a case of Kawasaki disease in a young asymptomatic Puerto Rican man who presented to our Adult Cardiology Clinic with multiple giant coronary aneurysms. A brief review of the epidemiology, etiology, pathophysiology, clinical features, therapeutic modalities, prognosis and complications of this condition is also included. [References: 29]

Kushner, H. I., et al. (2008). "The two emergencies of Kawasaki syndrome and the implications for the developing world." Pediatric Infectious Disease Journal **27**(5): 377-383.
Kawasaki syndrome (KS) is the most common cause of acquired pediatric heart disease in the developed world. There have been 2 distinctive patterns for the emergence of KS that are likely related to several factors including exposure to the causative agent(s) and host genetics. In Europe and North America where we presume the genetic susceptibility seems to be low, KS has existed in the pediatric population for more than a century and is associated with relatively low incidence. In Japan where genetic susceptibility is presumed to be high, KS seems not to have existed before the early 1950s. This relatively recent exposure has resulted in 3 nationwide epidemics and a high current endemic rate of 200 per 100,000 in children less than 5 years. If our history of alternative patterns of the emergence of KS is valid, it may prove useful as a

predictive tool for countries including India, where clusters of KS cases have been recently reported. This article examines the historical evidence in support of a 2-tiered emergence of KS in Euro-America and Japan and then returns briefly to discuss its implications for the pediatric populations of India and the health care delivery systems in the developing world. [References: 86]

Li, S. T., et al. (2008). "Facial palsy in Kawasaki disease: report of two cases." Acta Paediatrica Taiwanica **49**(1): 24-27.
Facial palsy is an unusual complication associated with Kawasaki disease, with only a few published case reports. We report two patients with typical Kawasaki disease and facial palsy. Both had coronary artery aneurysms and were treated with intravenous immunoglobulin. The facial palsy resolved completely over the next several months in both patients. Coronary artery aneurysms resolved completely in one patient, and the other has not regressed to normal till now. The incidence of coronary artery aneurysm appears to be higher in the handful of reported cases of Kawasaki disease with facial palsy. [References: 24]

Mavrogeni, S., et al. (2008). "How to image Kawasaki disease: a validation of different imaging techniques." International Journal of Cardiology **124**(1): 27-31.
Kawasaki disease contributes to coronary artery aneurysm in 25% of patients. Cardiovascular imaging has an important role in diagnosis and follow-up of these cases. Echocardiography is the bedside technique of choice during the acute phase of the disease. MRI can be a valuable tool especially in adolescents, where sometimes echocardiography fails to detect coronary abnormalities and it has also the advantage of simultaneous perfusion, function and viability evaluation. If MRI is not available, a combination of echocardiography and SPECT gives an overview of anatomy, function and perfusion. MSCT is of limited value for follow-up because of radiation and the misleading data due to coronary calcifications. X-ray coronary angiography is kept mainly for cases where an invasive procedure should be performed. [References: 35]

Mutter, J. and D. Yeter (2008). "Kawasaki's disease, acrodynia, and mercury." Current Medicinal Chemistry **15**(28): 3000-3010.
A superantigen or autoimmunity has been hypothesized to be the main cause of the Kawasaki's Disease but the etiology is unknown. Medical literature, epidemiological findings, and some case reports have suggested that mercury may play a pathogenic role. Several patients with Kawasaki's Disease have presented with elevated urine mercury levels compared to matched controls. Most symptoms and diagnostic criteria which are seen in children with acrodynia, known to be caused by mercury, are similar to those seen in Kawasaki's Disease. Genetic depletion of glutathione S-transferase, a susceptibility marker for Kawasaki's Disease, is known to be also a risk factor for acrodynia and may also increase susceptibility to mercury. Coinciding with the largest increase (1985-1990) of thimerosal (49.6% ethyl mercury) in vaccines, routinely given to infants in the U.S. by 6 months of age (from 75µg to 187.5µg), the rates of Kawasaki's Disease increased ten times, and, later (1985-1997), by 20 times. Since 1990 88 cases of patients developing Kawasaki's Disease some days after vaccination have been reported to the Centers of Disease Control (CDC) including 19% manifesting symptoms the same day. The presented pathogenetic model may lead to new preventive- and therapeutic strategies for Kawasaki's disease.

Ogata, S. and M. Ishii (2008). "[Development of diagnosis]." Nippon Rinsho - Japanese Journal of Clinical Medicine **66**(2): 301-306.
Kawasaki disease (KD) is an acute vasculitis that affects most often in children. This is unknown etiology of KD. Therefore, KD is diagnosed by characteristic symptoms. The standard care of acute KD is high-dose intravenous immunoglobulin(IVIG) treatment and aspirin. IVIG has been observed to reduce both the duration of fever and the incidence of coronary artery aneurysms when given within a few days of the onset KD. However, despite receiving IVIG within the first

10 days of illness, 10-20% of patients are resistant to initial IVIG treatment. And approximately 5% of children with KD have subsequent coronary aneurysms. Recently, it became the problems that adequately diagnose KD and early deject resistant initial IVIG case. [References: 11]

Pinna, G. S., et al. (2008). "Kawasaki disease: an overview." Current Opinion in Infectious Diseases **21**(3): 263-270.
PURPOSE OF REVIEW: Kawasaki disease is an acute, self-limited vasculitis of childhood. The increasing frequency of the disease as well as the deficiency of specific diagnostic means renders its diagnosis and treatment an area of intense investigation. The purpose of this review is to summarize all the known features of Kawasaki disease and also give an insight to the latest findings.
RECENT FINDINGS: Kawasaki disease is one of the leading causes of acquired heart disease in children while its cause remains essentially unknown. Viruses, bacterial conventional as well as superantigens, and genetic polymorphisms have been implicated in the etiology of the disease. Markers of inflammation, such as CCL2 and CCXCL10, contribute to the pathology and the diagnosis of Kawasaki disease. Intravenous administration of immunoglobulin remains the mainstay of therapy for Kawasaki disease. Nevertheless, forms of the disease refractory to intravenous administration of immunoglobulin therapy may respond to aspirin, corticosteroids, cyclophosphamide, and/or plasmapheresis.
SUMMARY: The present review covers evidence regarding the history of Kawasaki disease, the epidemiology, etiology, pathology, genetic influences, and long-term sequela. It also includes an evaluation of contemporary diagnostic techniques and optimal therapeutic approaches with an emphasis on recent publications. [References: 95]

Rowley, A. H., et al. (2008). "Searching for the cause of Kawasaki disease--cytoplasmic inclusion bodies provide new insight." Nature Reviews. Microbiology **6**(5): 394-401.
Kawasaki disease (KD) has emerged as the most common cause of acquired heart disease in children in the developed world. The cause of KD remains unknown, although an as-yet unidentified infectious agent might be responsible. By determining the causative agent, we can improve diagnosis, therapy and prevention of KD. Recently, identification of an antigen-driven IgA response that was directed at cytoplasmic inclusion bodies in KD tissues has provided new insights that could unlock the mysteries of KD.

Schnautz, L. S. and P. Leggett (2008). "Kawasaki disease: a ride for little girls too!" Critical Care Nursing Clinics of North America **20**(3): 265-271.
Kawasaki disease is the leading cause of acquired heart disease in children. Little is known about the origin; however, speculation exists that the disease is associated with the use of carpet cleaner or stagnate water. The disease can have devastating lifelong effects on the heart and cardiovascular system. Early recognition of the clinical manifestations by the health care provider may lead to early treatment and prevention of long-term cardiovascular disease. This article presents a case study, with discussion about the prevalence, incidence, pathophysiology, clinical features, and collaborative clinical management of Kawasaki disease. [References: 11]

Shirai, N., et al. (2008). "[Pathology of Kawasaki disease]." Nippon Rinsho - Japanese Journal of Clinical Medicine **66**(2): 251-257.
Kawasaki disease (KD), an acute febrile disorder with systemic arteritis predominantly in the coronary arteries, is the leading cause of acquired heart disease in childhood. Since many KD patients have reached adulthood, the question arises whether post-KD arteritis lesions can become a risk factor for atherosclerosis of coronary arteries. We immunohistochemically investigated post-KD coronary arteries obtained from autopsied patients. All coronary arteries with KD revealed marked and diffuse intimal proliferation, and occasional sites revealed aneurysmal formation. Coronary arteries, with intervals more than 5 years after the onset, showed distinct atherosclerotic changes of intimal lesions associated with dedifferentiation of

smooth muscle cells. These results strongly suggest that post-KD intimal lesions can become atherosclerotic plaques. [References: 22]

Wang, J. H., et al. (2008). "Bowel obstruction as first symptoms in an infant with incomplete Kawasaki disease." Chinese Journal of Contemporary Pediatrics **10**(5): 674.

Xia, B. and C. R. Li (2008). "[Determination of coronary hemodynamic parameters by Doppler ultrasound in children with Kawasaki disease]." Zhonghua Erke Zazhi **46**(12): 957-959.

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Bayazit, A. K., et al. (2007). "Reno-vascular hypertension in childhood: A nationwide survey." Pediatric Nephrology **22**(9): 1327-1333.
Renovascular disease accounts for 8-10% of all cases of paediatric hypertension, whereas, in adults, its incidence is approximately 1%. The Turkish Paediatric Hypertension Group aimed to create the first registry database for childhood renovascular hypertension in Turkey. Twenty of the 28 paediatric nephrology centres in Turkey responded to the survey and reported 45 patients (27 girls, 18 boys) with renovascular hypertension between 1990 and 2005. The age at presentation ranged from 20 days to 17 years. The mean blood pressure at the diagnosis was 169/ 110 mmHg. Chief complaints of symptomatic patients were headache (38%), seizure (18%), epistaxis (4%), growth retardation (4%), cognitive dysfunction (4%), polyuria (2%), palpitation (2%), and hemiplegia (2%). Renovascular hypertension was found incidentally in 11 children. The diagnosis of renovascular hypertension was established with conventional angiography in 39 patients, MR angiography in three, CT angiography in two, and captopril diethylene triamine penta-acetic acid (DTPA) scintigraphy in one patient. Twenty-one children had bilateral renal artery stenosis and 24 had unilateral renal artery stenosis. Of these, 14 (31%) had fibromuscular dysplasia; 12 (27%) Takayasu's arteritis; six (13%) neurofibromatosis; two (5%) Williams syndrome; one (2%) Kawasaki disease; one (2%) mid-aortic syndrome; one (2%) extrinsic compression to the renal artery, and eight (18%) unspecified bilateral renal artery stenosis. Hypertension was controlled with antihypertensive drugs in 17 patients. Percutaneous transluminal angioplasty (PTRA) or surgery had to be performed in 28 patients: PTRA in 16 patients, PTRA + surgery in one patient and surgery in 11 patients (four nephrectomies). The importance of vasculitic disease, especially Takayasu's arteritis, should not be underestimated in children with renovascular hypertension.

De Lang, A., et al. (2007). "Functional genomics highlights differential induction of antiviral pathways in the lungs of SARS-CoV-infected macaques." PLoS Pathogens **3**(8): 1129-1141.
The pathogenesis of severe acute respiratory syndrome coronavirus (SARS-CoV) is likely mediated by disproportional immune responses and the ability of the virus to circumvent innate immunity. Using functional genomics, we analyzed early host responses to SARS-CoV infection in the lungs of adolescent cynomolgus macaques (Macaca fascicularis) that show lung pathology similar to that observed in human adults with SARS. Analysis of gene signatures revealed induction of a strong innate immune response characterized by the stimulation of various cytokine and chemokine genes, including interleukin (IL)-6, IL-8, and IP-10, which corresponds to the host response seen in acute respiratory distress syndrome. As opposed to many in vitro experiments, SARS-CoV induced a wide range of type I interferons (IFNs) and nuclear translocation of phosphorylated signal transducer and activator of transcription 1 in the lungs of macaques. Using immunohistochemistry, we revealed that these antiviral signaling pathways were differentially regulated in distinctive subsets of cells. Our studies emphasize that the induction of early IFN signaling may be critical to confer protection against SARS-CoV infection and highlight the strength of combining functional genomics with immunohistochemistry to further unravel the pathogenesis of SARS.

Du, L., et al. (2007). "Receptor-binding domain of SARS-CoV spike protein induces long-term protective immunity in an animal model." Vaccine **25**(15): 2832-2838.
Development of effective vaccines against severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) is still a priority in prevention of re-emergence of SARS. Our previous studies have shown that the receptor-binding domain (RBD) of SARS-CoV spike (S) protein elicits highly potent neutralizing antibody responses in the immunized animals. But it is unknown whether RBD can also induce protective immunity in an animal model, a key aspect for vaccine development. In this study, BALB/c mice were vaccinated intramuscularly (i.m.) with 10 mug of RBD-Fc (RBD fused with human IgG1 Fc) and boosted twice at 3-week intervals and one more time at 12th month. Humoral immune responses of vaccinated mice were investigated for up to 12 months at a 1-month interval and the neutralizing titers of produced antibodies were reported at months 0, 3, 6 and 12 post-vaccination. Mice were challenged with the homologous strain of SARS-CoV 5 days after the last boost, and sacrificed 5 days after the challenge. Mouse lung tissues were collected for detection of viral load, virus replication and histopathological effects. Our results showed that RBD-Fc vaccination induced high titer of S-specific antibodies with long-term and potent SARS-CoV neutralizing activity. Four of five vaccinated mice were protected from subsequent SARS-CoV challenge because no significant virus replication, and no obvious histopathological changes were found in the lung tissues of the vaccinated mice challenged with SARS-CoV. Only one vaccinated mouse had mild alveolar damage in the lung tissues. In contrast, high copies of SARS-CoV RNA and virus replication were detected, and pathological changes were observed in the lung tissues of the control mice. In conclusion, our findings suggest that RBD, which can induce protective antibodies to SARS-CoV, may be further developed as a safe and effective SARS subunit vaccine. © 2006 Elsevier Ltd. All rights reserved.

Falcini, F., et al. (2007). "Update on Kawasaki disease: The 25 year experience at the "A. Mayer" Children's Hospital, Florence." Italian Journal of Pediatrics **33**(1): 32-40.
Kawasaki Disease (KD) is an acute febrile systemic vasculitis predominantly affecting children under 5 years of age. Coronary and peripheral artery aneurysms (CAA) develop in about 20% to 35% of untreated patients. Prompt diagnosis and early administration of high dose intravenous gammaglobulin (IVIG) and aspirin reduce the rate of coronary damage, decreasing the rate of affected children to less than 5%. KD is reported as the most common cause of acquired heart disease affecting children in developed countries, and is now considered as an additional risk for adult ischemic heart disease. Since a specific diagnostic test is still lacking, clinical criteria remain the key tools for a definitive diagnosis. Atypical and incomplete cases are a diagnostic challenge for paediatricians and a misdiagnosis, with consequent lack of timely treatment, would confer the children a high risk of developing CAA. This review will focus on the updated approach to the diagnosis and treatment of KD in a cohort of 268 children admitted to "A. Meyer" Children's Hospital in Florence, Italy, from 1982 to 2006. Our aim is to give additional clues for the diagnosis of KD, focussing mainly on atypical and incomplete cases, thus sharing with other clinicians our 25-year long experience in the management of KD patients. Our experience leads us to conclude this take-home message: a child with extreme irritability, persistently high fever and otherwise inexplicably increased indicators of inflammation should alert physicians to consider the diagnosis of KD to prevent the development of CAA by a delay in IVIG administration.

McNicholas, A., et al. (2007). "Post-marketing safety monitoring of a new group B meningococcal vaccine in New Zealand, 2004-2006." Human Vaccines **3**(5): 196-204.
New Zealand introduced a new outer membrane vesicle vaccine in 2004 to combat an epidemic of group B meningococcal disease. An Independent Safety Monitoring Board oversaw intensive safety monitoring, which included hospital surveillance, health professional reporting (passive and active) and mortality monitoring. With over three million doses administered to individuals aged under 20 years, the monitoring results provide consistent evidence supporting the vaccine's

safety. ©2007 Landes Bioscience. AuthorsConclusions:With over three million doses administered to individuals aged under 20 years throughout NZ [New Zealand], the combined safety monitoring activities have provided consistent evidence regarding the safety of the vaccine, and support the safety profile reported from the Phase I and II trials undertaken in NZ "as reported". Although, as with all post-marketing surveillance, we cannot unequivocally rule out the possibility of an excess risk of an undetected, rare adverse event or those with incubation periods longer than the duration of the safety monitoring activities, the ISMB concluded that the combined results of the monitoring undertaken during the period of the Program provide confidence regarding the safety of the vaccine. FreeText:Data on adverse events following immunization (AEFIs) were collected through the following complementary surveillance activities: spontaneous reporting program [health care professionals voluntarily report AEFI to the Center for Adverse Reactions Monitoring (CARM)], intensive vaccine monitoring program (IVMP; CARM collected data from 35 medical centers), and hospital surveillance (identified AEFI of sufficient severity to require hospital admission or emergency department consultation). Pre-selected events, regardless of the patientæs vaccination status, were identified which allowed comparison between vaccinated and unvaccinated individuals. The pre-selected adverse events under surveillance included anaphylaxis, acute flaccid paralysis (AFP), encephalopathy, hypotonic-hyporesponsive episodes, thrombocytopenia (platelet count <50 × 109/L), seizures, simple febrile seizures (SFSs), petechial/purpuric rashes, Henoch-Schonlein purpura (HSP), and Kawasaki disease. Concomitant drugs: other vaccines. AdverseEffects:There were 2107 reports of vaccination reactions in the spontaneous monitoring program including 925 local injection site reactions, 804 skin-related events, 705 fever, 577 gastrointestinal symptoms, 250 headache, 165 musculoskeletal, 122 irritability, 88 syncope/fainting, 81 sleepiness/somnolence, 33 non-febrile seizures, 27 febrile seizures, and 301 hypersensitivity-type reactions (196 urticaria, 35 periorbital edema, 14 angioedema, bronchospasm, 9 anaphylactic-type reactions). There were 516 reports of vaccination reactions in the IVMP. In the hospital surveillance, there were 2 777reports of vaccination reactions including 663 respiratory disease (532 infections), 296 trauma, 50 anxiety related events, 2 acute flaccid paralysis (Guillain-Barre syndrome), 2 acute disseminating encephalomyelitis, 1 hypotonic-hyporesponsive episodes, 7 petechial/purpuric rash, 17 seizures (associated with mild head injury in 3, vomiting and diarrhea in 1, and pyrexia and otitis media in 1), 4 thrombocytopenia, 8 Kawasaki disease, and 6 HSP. Indications:For prevention of meningococcus B infection in 1.1 million subjects. Patients:1.1 million children, age range 4 weeks-19 years. TypeofStudy:An open, retrospective, multicenter study investigating the adverse events associated with MeNZB reported to the Independent Safety Monitoring Board (ISMB) in New Zealand during July 19, 2004 to June 30, 2006. DosageDuration:Dosage not stated, given as 3 single doses. Results:In the spontaneous reporting program, 2212 AEFIs were reported, of which CARM assessed 2107 (95.3%) as including at least one event possibly, probably or definitely associated with vaccination reactions. Local injection site reactions were the most frequently reported adverse events, followed by skin-related events, fever, gastrointestinal symptoms and headache. 277/2107 (13.1%) events were serious hypersensitivity reactions; 24 reports specified 2 different hypersensitivity reactions for a total of 301 reactions. 139 (70.9%) of reported urticaria reactions occurred within 24 hours after immunization, and 21 (10.7%) also had facial/periorbital edema, angioedema or bronchospasm. 6 (2.2%) cases with hypersensitivity reactions also had a hypersensitivity reaction reported following an earlier dose of the vaccine. Of the remaining 271 cases, 155 (57.2%) later received another dose following which no further AEFI was reported. Of the 12 227 vaccination visits identified in the IVMP, 516 (4.2%) resulted in at least 1 reaction in the following 6 weeks. No clinically significant adverse events were reported and the number and distribution of events were similar to that reported in the spontaneous reporting program. Of the 65 000 admissions and emergency department consultations through the hospital surveillance, 3 734 (6%) met the screening criteria used to identify pre-selected events, regardless of vaccination status. Only 1/64 (1.6%) anaphylaxis cases was associated with the meningococcal B vaccine (occurred within 24 hours after vaccination). 50/1726 students (2.9%) experienced anxiety-related events; most commonly reported symptoms were dizziness

(37 cases, or 74.0%), headache (32, or 64.0%) and nausea (30, or 60.0%). 3 (6.0%) cases were treated with adrenaline. None met the pre-defined criteria for anaphylaxis. No relapse was noted when the second and third doses were administered. 1/3 cases of AFP aged under 5 years and 1/6 AFP cased aged 5 years and older were associated with meningococcal B vaccine; both cases were mild Guillain-Barre syndrome with symptom onset 7 days after the second dose and 48 days following the first dose, respectively. Both cases subsequently completed the 3 dose schedule without report of any subsequent AEFI. Of the 15 encephalopathy cases aged under 5 years, 2 had no cause determined and both were diagnosed as acute disseminating encephalomyelitis; 1 had symptom onset 31 days after first dose and received no further doses; the other had symptom onset 6 months after the 3rd dose. Of 3 cases of hypotonic-hyporesponsive episodes, only 1 occurred after meningococcal B vaccination with symptom onset 30 minutes after vaccination. No further doses were administered. 3/577 cases (12%) of petechial/purpuric rash in children aged under 5 years and 4/202 (33.3%) cases in children aged 5 years and older occurred after meningococcal B vaccination with symptom onset within 7 days after vaccination. Of the 925 seizure cases in children aged under 5 years, 533 (57.6%) were SFSs. 17 (1.8%) seizures occurred within 4 days after receiving the meningococcal B vaccine, of which 11 (64.7%) were SFSs. Of the 6 non-SFSs that occurred within 4 days after receiving the meningococcal B vaccine, 3 (50.0%) were associated with mild head injuries, 2 (33.3%) had vomiting and diarrhea and 1 (16.7%) had a prolonged seizure, concurrent pyrexia >38°C and otitis media. In children aged under 5 years, the rate of seizures within 4 days after receiving the meningococcal B vaccine was 1 every 18 600 doses and for SFSs it was 1 every 28 800 doses. Of the 64 cases of thrombocytopenia reported in children aged under 5 years, 3 (4.7%) had no cause determined, and had received the meningococcal B vaccine within the preceding 8 weeks. For 2 of these cases, the platelet count returned to normal without treatment and additional doses were administered without report of any subsequent AEFI. In the 3rd case, the platelet count increased after treatment, but no subsequent doses were administered. Of the 46 cases of thrombocytopenia in hildren aged 5 years and older, only 1 (2.2%) had no cause determined and had received the meningococcal B vaccine within the previous 8-week period. The case received a subsequent dose without report of any subsequent AEFI. There were 46 cases of HSP in children aged under 10 years, of which 6 (13.0%) occurred within 30 days after meningococcal B vaccination; 4/6 (66.7%) cases were subsequently rechallenged with 1 or more doses without report of any subsequent AEFI, while the other 2 (33.3%) developed symptoms after their 3rd dose. Of the 18 cases of Kawasaki disease, only 8 (44.4%) had received a dose of meningococcal B vaccine (onset ranged from 6-258 days after vaccination, mean of 108 days) prior to symptom onset. 3/8 (37.5%) cases subsequently received 1 or more doses without report of any subsequent AEFI. The remaining 5 cases developed Kawasaki disease following the 3rd dose. In the three hospitals where the hospital surveillance took place, there were 1 979 emergency department (ED) consultations and admissions within 7 days after meningococcal B vaccine administration in children aged under 5 years and 798 for persons aged 5 years and older. For the younger group, the largest number of consultations and admissions was for respiratory conditions (663, 33.5%), of which infection-related respiratory infections predominated (532, 80.2% of respiratory conditions). For the older group, the largest number was due to trauma-related events (296, 37.1%). During the period July 19, 2004 to June 30, 2006, a total of 170 deaths occurred within 90 days after receiving the meningococcal B vaccine. Deaths were not attributed to the vaccine.

Satou, G. M., et al. (2007). "Kawasaki disease: diagnosis, management, and long-term implications." Cardiology in Review **15**(4): 163-169.

Kawasaki disease (KD) is an acute inflammatory vasculitis of childhood which was initially described more than 4 decades ago, yet the specific etiology remains unknown. It has become the most common cause of acquired cardiovascular disease in children in the United States. Advances in clinical therapies have reduced, but not eliminated, the incidence of coronary artery abnormalities in affected children. Pathophysiology seems to include an intense elaboration of

cytokines, endothelin, and other vasoactive mediators resulting in the development of vascular endothelial changes that may leave a permanent impact on vascular integrity. Treatment with intravenous immune globulin and aspirin remains the primary management strategy and steroid therapy remains contoversial. In severe circumstances, coronary reperfusion strategies are required, and coronary artery surgery in children with KD has been required, albeit infrequently. KD may be a harbinger for early onset coronary artery disease in adults. Recently developed AHA recommendations have amended diagnostic strategies and indicated a stratified approach to the long-term follow up of this enigmatic yet widespread disease. [References: 45]

Winterberg, D. (2007). "[Kawasaki syndrome, still a mystery]." Nederlands Tijdschrift voor Tandheelkunde **114**(10): 436-439.
Kawasaki disease is an acute vasculitis that occurs especially in young children. Because there is no specific laboratory test available, diagnosis has to be made on the basis of clinical characteristics: prolonged fever, oropharyngeal changes, conjunctival injection, erythema and edema of hands and feet, rash, and cervical lymphadenopathy. Without treatment there is a 25% chance of cardiac complications, especially aneurysms of the coronary arteries. Early treatment with intravenous immunoglobulin reduces this risk to 5%. Accurate diagnosis and therapy is crucial. Kawasaki syndrome has been reported in all racial groups with the highest incidence in Japanese children. Together with the fact that the disease is more common in boys this indicates that genetic factors play an important role in determining susceptibility to a (probably infectious) trigger. In spite of 40 years of intensive scientific research, the cause of Kawasaki disease still remains unknown. [References: 13]

Wolff, A. E., et al. (2007). "Acute Kawasaki disease: not just for kids." Journal of General Internal Medicine **22**(5): 681-684.
Kawasaki Disease is a small-to-medium-vessel vasculitis that preferentially affects children. Kawasaki Disease can occur in adults, but the presentation may differ from that observed in children. Typical findings in both adults and children include fever, conjunctivitis, pharyngitis, and skin erythema progressing to a desquamating rash on the palms and soles. Adults more frequently present with cervical adenopathy (93% of adults vs. 15% of children), hepatitis (65% vs. 10%), and arthralgia (61% vs. 24-38%). In contrast, adults are less frequently affected by meningitis (10% vs. 34%), thrombocytosis (55% vs. 100%), and coronary artery aneurysms (5% vs. 18-25%). We report a case of acute Kawasaki Disease in a 24-year-old man who presented with rash, fever, and arthritis. He was successfully treated with high-dose aspirin and intravenous immunoglobulin (IVIG). Our case highlights the importance of considering Kawasaki Disease in adults presenting with symptoms commonly encountered in a general medical practice. [References: 25]

Wood, L. and R. Tulloh (2007). "Kawasaki disease: diagnosis, management and cardiac sequelae." Expert Review of Cardiovascular Therapy **5**(3): 553-561.
Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown etiology and the most common cause of acquired coronary disease in children aged 6 months to 5 years. The inflammatory process results in coronary arteritis, aneurysmal lesions, arterial thrombotic occlusion or even sudden death. The diagnostic tests are unknown but treatment with immunoglobulin and aspirin is effective at reducing cardiac complications from 25 to 4.7% in the UK. Myocardial, endocardial or pericardial inflammation may occur acutely or many years later and abnormalities of myocardial blood flow may require ongoing medication, interventional catheterization or even cardiac surgery. There are several new drugs that may have important roles to play in managing KD in children and young adults. [References: 93]

Yeung, R. S. (2007). "Lessons learned from an animal model of Kawasaki disease." Clinical & Experimental Rheumatology **25**(1 Suppl 44): S69-71.
Kawasaki disease is the most common cause of multisystem vasculitis in childhood. Kawasaki

disease has been reported throughout the world and affects children of all ethnicity. Coronary artery damage from Kawasaki disease is the leading cause of acquired heart disease in children in the developed world. Diagnostic tests and prognostic markers are lacking, and questions remain unanswered in our understanding of the etiopathogenesis of the disease, thus limiting our ability to improve therapy and coronary outcome. In this article I will review advances made in an animal model of disease, which has helped advance our understanding of the etiology and pathogenesis of this fascinating clinical syndrome. [References: 16]

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Anonymous (2006). "Remdesivir." National Library of Medicine.
Remdesivir is an investigational antiviral drug that is being tested for use against the novel coronavirus disease, COVID-19. Remdesivir is given intravenously because it is poorly absorbed orally, so infants are not likely to absorb clinically important amounts of the drug from milk. In addition, a newborn infants have received intravenous remdesivir therapy for Ebola with no serious adverse drug reactions.[1,2] Given this limited information, it does not appear that mothers receiving remdesivir need to avoid nursing, but until more data are available, remdesivir should be used with careful infant monitoring during breastfeeding. The most common adverse effects reported after intravenous infusion include elevated aminotransferase and bilirubin levels and other liver function tests. Diarrhea, rash, renal impairment and hypotension have also been reported.

Coskun, K. O., et al. (2006). "Pediatric patients with Kawasaki disease and a case report of Kitamura operation." ASAIO Journal **52**(6): e43-e47.
Kawasaki disease (KD), also called mucocutaneous lymph node syndrome, is an acute, self-limiting, small-vessel vasculitis with an unknown cause that affects children between the ages of 6 months and 5 years. It is the most common cause of acquired coronary artery disease in childhood. Acute myocardial infarction and coronary artery aneurysm are major complications.We present a cohort of patients with KD who were followed up and treated in the Heart Center, North Rhine-Westphalia. Included is a review of important relevant items common to cases of KD, such as clinical data and management, including medical management of the acute condition and the diagnosis and management of coronary vasculitis and aneurysms as well as the application of coronary artery bypass grafting (CABG) in those conditions.Between January 2002 and January 2006, we evaluated the findings and characteristics of 18 pediatric patients with a history of KD and their long-term outcome. The acute illness occurred between the ages of 4 months and 14 years of age. Anomalies of the coronary arteries were found in 6 patients ranging in age from 5 months to 10 years. One patient had acute myocardial infarction; another underwent CABG after 5 years from disease onset at the age of 15 years. Kitamura operation was performed successfully. The other patients are still under observation.Coronary artery aneurysms and stenosis requiring surgery are rare in KD; nevertheless, CABG is the standard therapy when myocardial ischemia is detected. Kitamura operation provides good growth potential and long-term graft patency. ©2006Amercian Society of Artificial Internal Organs.

Durall, A. L., et al. (2006). "Infantile Kawasaki disease and peripheral gangrene." Journal of Pediatrics **149**(1): 131-133.
We report a 1-month-old infant with Kawasaki disease and peripheral gangrene. We advocate using the newly published American Heart Association guidelines advising early laboratory and echocardiogram investigations in infants with fever but without other classic manifestations of Kawasaki disease. Initiation of early therapy may prevent this serious complication with its permanent sequelae.

Freeman, A. F. and S. T. Shulman (2006). "Kawasaki disease: summary of the American Heart

Association guidelines." American Family Physician **74**(7): 1141-1148.
Kawasaki disease is an acute vasculitis of childhood that predominantly affects the coronary arteries. The etiology of Kawasaki disease remains unknown, although an infectious agent is strongly suspected based on clinical and epidemiologic features. A genetic predisposition is also likely, based on varying incidences among ethnic groups, with higher rates in Asians. Symptoms include fever, conjunctival injection, erythema of the lips and oral mucosa, rash, and cervical lymphadenopathy. Some children with Kawasaki disease develop coronary artery aneurysms or ectasia, ischemic heart disease, and sudden death. Kawasaki disease is the leading cause of acquired heart disease among children in developed countries. This article provides a summary of the diagnostic and treatment guidelines published by the American Heart Association. [References: 15]

Hu, X. F., et al. (2006). "[Macrophage activation syndrome in 2 cases with Kawasaki disease: clinical analysis and review of literature]." Zhonghua Erke Zazhi **44**(11): 833-835.

Nitsch-Osuch, A., et al. (2006). "A child with Kawasaki disease under general practitioner's supervision. [Polish]." Family Medicine and Primary Care Review **8**(3): 1019-1021.
Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. The disease is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. The most severe complications are those from cardiovascular system. Diagnosis of KD is based on clinical symptoms and results of ultrasound examination of coronary arteries. KD should be considered in all children with unexplained fever lasted longer than 5 days associated with 2 or 3 of the principal features of KD. Treatment of KD in the acute phase is directed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy in individuals who develop coronary aneurysm is aimed at preventing ischemia or infarction. The role of GP is to remember of KD in differential diagnosis of fever of unknown origin in young children. © Copyright by Wydawnictwo Continuo.

Nitsch-Osuch, A., et al. (2006). "Vasculitides in children - A challenge for a general practitioner. [Polish]." Family Medicine and Primary Care Review **8**(3): 1028-1030.
The purpose of this review is to present epidemiology, etiology, diagnosis and treatment of vasculitides and the role of GPs in the early diagnosis of those diseases. The systemic vasculitides (devided into primary and secondary) are heterogenous conditions of unknown etiology characterised by inflammation and necrosis of different sized blood vessels. Some of vasculitides (Wegener's granulomatosis, microscopic polyangitis and Churg Strauss syndrome) are very rare in children while Henoch-Schonlein purpura, Kawasaki disease are more typical for pediatric patients. Diagnosis and treatment of childhood vasculitides have also been discussed. Vasculitides are rare conditions with significant morbidity and mortality whose prognosis has improved with newer diagnostic modalities and treatments. The role of GPs is to recognize paediatric vasculitis and refer a patient to a specialist what provides the proper diagnosis and treatment and implicates the successful therapy and recovery. © Copyright by Wydawnictwo Continuo.

Rigante, D. (2006). "Clinical overview of vasculitic syndromes in the pediatric age." European review for medical and pharmacological sciences **10**(6): 337-345.
Vasculitic syndromes comprise a heterogeneous group of disorders sharing the hystopathologic features of inflammation and necrosis in blood vessels. Their clinical expression depends on site, type and size of the involved vessels and severity of the associated inflammatory symptoms. Classification of vasculitides based on the size of the affected vessels is the most widely used in children. Many different vasculitides with indistinguishable clinical presentation have very different prognosis and treatments. Among the primary systemic non-granulomatous vasculitides

of medium-sized vessels in pediatrics we have to consider Kawasaki disease and among the small-sized ones Henoch-Schönlein purpura, which is the most frequent vasculitis of the pediatric age and is characterized by vascular deposition of IgA-dominant immune complexes. Accurate diagnosis is the mainstay for the definition of the best therapeutical proposal, though therapies available result largely empirical and based on trials with limited numbers of pediatric patients.

Senzaki, H. (2006). "The pathophysiology of coronary artery aneurysms in Kawasaki disease: role of matrix metalloproteinases." Archives of Disease in Childhood **91**(10): 847-851.
Kawasaki disease is an acute inflammatory syndrome that takes the form of systemic vasculitis, and predominantly affects children. Important complications of this disease are coronary artery dilation and aneurysm formation. Recent studies indicate that Kawasaki disease patients have elevated expression, activity, or protein levels of matrix metalloproteinases (MMPs), and suggest that imbalances in MMPs or MMP/tissue inhibitor of MMP (TIMP) play important pathophysiological roles in the development of coronary artery lesions in this disease. However, it remains unclear whether MMP activities at the site of coronary artery lesions are indeed increased. Further studies on the effects of MMP inhibition on coronary outcome are needed to define the roles of MMPs and TIMPs in the formation of coronary artery lesions in Kawasaki disease; findings of such studies may support the use of MMP inhibitors for the prevention of coronary artery complications in patients with this disease. [References: 47]

Tsai, M. H., et al. (2006). "Clinical responses of patients with Kawasaki Disease to different brands of intravenous immunoglobulin." Journal of Pediatrics **148**(1): 38-43.
Objective: To determine whether different brands of intravenous immunoglobulin (IVIG) administered to children with Kawasaki disease (KD) result in different outcomes. Study design: We analyzed children with KD and divided them into 4 groups according to the brand of IVIG. A coronary artery abnormality (CAA) was defined as having a lumen diameter (inner border to inner border) of ≥3 mm in KD cases <5 years old and ≥4 mm in cases ≥5 years old, and giant aneurysm was defined as a lumen diameter ≥8 mm. Patients were considered nonresponsive to IVIG therapy if fever persisted longer than 2 days after completion of treatment and needed retreatment with IVIG. Results: We collected 437 cases, 29 (6.6%) were nonresponsive, 17 (3.9%) had CAA at convalescence, and 3 (0.7%) had giant aneurysm, 2 of whom had development of myocardial infarcts. Patients receiving Brand C IVIG, prepared with β-propiolactone, had higher rates (10%, 9/93, P = .01) of CAA at convalescence and nonresponsiveness (13%, 12/93, P = .001); giant aneurysm occurred in 3/93 (3%) receiving Brand C IVIG and in 0/344 who received the other 3 brands (P = .008). Conclusions: IVIG, prepared with β-propiolactone, was most significantly associated with nonresponsiveness, CAA at convalescence, and giant aneurysm. Physicians should be cautious when using IVIG prepared with β-propiolactone or enzyme digestion to treat KD. Copyright © 2006 Elsevier Inc. All rights reserved.

Yamazaki-Nakashimada, M. A., et al. (2006). "Catastrophic Kawasaki disease or juvenile Polyarteritis nodosa?" Seminars in Arthritis & Rheumatism **35**(6): 349-354.
OBJECTIVE: Juvenile Polyarteritis nodosa (PAN) and Kawasaki Disease (KD) are disseminated vasculitides of unknown cause affecting small- and medium-sized vessels in children. We present an unusually severe case that fulfilled criteria for both KD and PAN. The diagnosis, overlapping clinical features, and treatment options for the 2 diseases are discussed.
METHODS: A 3-year-old girl with systemic vasculitis is presented. We compare our case to 4 other cases reported in the literature which presented with a similar diagnostic dilemma. A review of the medical literature and a qualitative analysis of the diseases were performed, with emphasis on overlapping features, atypical cases, and treatment options.
RESULTS: Many features of KD and PAN are shared; however, there are some clinical features that could help differentiate one from the other. Fever, weight loss, rash, abdominal pain, arthritis, coronary arteritis, peripheral gangrene, anemia, leukocytosis, thrombocytosis, and elevated C-reactive

protein are among many of the features that are shared by both diseases. However, KD also has unique clinical features that include conjunctivitis, changes in the lips and mouth, desquamation of the fingertips, and gallbladder hydrops, whereas renal involvement in KD is rare.
CONCLUSIONS: Occasionally juvenile PAN and KD share clinical manifestations, and when they do, it may be impossible to differentiate between them. Treatment should be directed according to the severity and persistence of these clinical manifestations. [References: 54]

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Burgner, D. and A. Harnden (2005). "Kawasaki disease: what is the epidemiology telling us about the etiology?" International Journal of Infectious Diseases **9**(4): 185-194.
Kawasaki disease (KD) is an important and common inflammatory vasculitis of early childhood with a striking predilection for the coronary arteries. It is the predominant cause of paediatric acquired heart disease in developed countries. Despite 40 years of research, the aetiology of KD remains unknown and consequently there is no diagnostic test and treatment is non-specific and sub-optimal. The consensus is that KD is due to one or more widely distributed infectious agent(s), which evoke an abnormal immunological response in genetically susceptible individuals. The epidemiology of KD has been extensively investigated in many populations and provides much of the supporting evidence for the consensus regarding etiology. These epidemiological data are reviewed here, in the context of the etiopathogenesis. It is suggested that these data provide additional clues regarding the cause of KD and may account for some of the continuing controversies in the field. [References: 129]

Cheng, F. W. T., et al. (2005). "Clinical, virologic and immunologic profiles of a young infant with severe acute respiratory syndrome." Pediatric Infectious Disease Journal **24**(6): 567-568.
The clinical findings, plasma viral load, cytokines and chemokines of a 4-month-old infant with severe acute respiratory syndrome (SARS) were assessed at different phases of the disease. Ribavirin failed to inhibit SARS coronavirus (SARS-CoV) replication. One-step real time reverse transcription-polymerase chain reaction for plasma SARS-CoV RNA quantification was useful for early diagnosis and monitoring viremia.

Christensen, D. D., et al. (2005). "Presentation of atrial septal defect in the pediatric population." Pediatric Cardiology **26**(6): 812-814.
Our recent experience indicates that patients with a hemodynamically significant atrial septal defect secundum (ASD2) do not necessarily present with classic physical and electrocardiographic (ECG) findings. The purpose of the study was to review the records of patients either receiving a catheter device or undergoing surgical repair for the closure of ASD2 to determine their initial physical and ECG findings. Therefore, we did a retrospective review of 47 consecutive patients who had echocardiographic evidence of a hemodynamically significant isolated ASD2 and who underwent ASD2 closure. Of these 47 patients, the presenting complaints were murmur (n = 36), chest pain (n = 6), seizure (n = 1), stroke (n = 1), syncope (n = 1), Kawasaki's disease (n = 1), and cardiomegaly (n = 1). Charts were reviewed for the evaluation of four abnormal physical findings: hyperactive right ventricular impulse, split fixed second heart sound, systolic and diastolic flow murmurs; and three ECG abnormalities: right axis deviation, right atrial enlargement, and evidence of right ventricular hypertrophy. In all, 30% of patients had either one or no typical physical findings, 18% had normal ECG findings, and 7% had no physical or ECG findings. On physical examination and ECG, the abnormalities due to ASD2 may be too subtle to detect. Although it is well known that variations can occur in the clinical signs and symptoms typical of ASD2, dependence on classical physical and or ECG findings may result in the underdiagnosis of a significant number of patients.

Dedeoglu, F. and R. P. Sundel (2005). "Vasculitis in children." Pediatric Clinics of North America **52**(2): 547-575.
Vasculitis is rare in children, and, apart from HSP and perhaps KD, most practicing pediatricians will never encounter a case. Nonetheless, progress in the diagnosis and treatment of these conditions has afforded most children with vasculitis a reasonably good prognosis. Accordingly, it is important to consider vasculitis as a potential cause of unexplained inflammation, perplexing rashes, or strange combinations of symptoms. Although evaluation and management of suspected vasculitis are difficult in the best of situations, they are impossible if the diagnosis is not considered. © 2005 Elsevier Inc. All rights reserved.

Gupta-Malhotra, M. and P. S. Rao (2005). "Current perspectives on Kawasaki disease." Indian Journal of Pediatrics **72**(7): 621-629.
The etiology of Kawasaki disease (KD) remains unknown despite several years of dedicated research in this direction. Recently coronavirus infection and genetic polymorphisms have been implicated. Since first description of the disease there have been few changes in the diagnostic criteria except for newer recommendations of fever of at least 4 instead of 5 days duration. Recently, Echocardiography Criteria and Laboratory Criteria have been added to aid in the diagnosis of incomplete KD where all the historical diagnostic criteria are not present; this is now called the "incomplete form of KD" as opposed to "atypical form of KD". The word "atypical" is reserved for unusual presentations of KD such as those with hemophagocytic syndrome or nerve palsy. The treatment of KD includes infusion of high dose immunoglobulin. Patients non-responsive to immunoglobulin therapy are labeled as having "immunoglobulin resistant KD". The treatment of immunoglobulin resistant KD can be challenging and new therapies that have tried with some success. Late outcomes after 4 decades of treating these patients have recently been published. There has been some concern about increased risk for premature atherosclerosis in patients with childhood KD who had coronary artery abnormalities. [References: 86]

Mekmullica, J., et al. (2005). "Concomitant dengue infection and Kawasaki disease in an infant: A case report and literature review." Journal of the Medical Association of Thailand **88**(3): 436-439.
A previously healthy 11-month-old girl presented with fever and rash for 6 days. Physical examination revealed an irritable infant with a high fever, injected conjunctivae, red cracked lips, posterior auricular lymphadenopathy, hepatomegaly, generalized erythematous maculopapular rash and petechial hemorrhage on trunk, face and extremities. Complete blood count showed atypical lymphocytosis and thrombocytopenia. Dengue infection was initially diagnosed. The persistent fever and clinical manifestations of Kawasaki disease (KD) were observed on day 8 with high erythrocyte sedimentation rate (56 mm/hr). Treatment of KD included intravenous immunoglobulin on day 9 of the illness. Desquamation of the fingers was found on day 15 of the illness. Ectasia of left coronary artery with small aneurysmal dilatation was detected by echocardiography on day 15 of the illness. Hemagglutination-inhibition test and enzyme-linked immunosorbent assay for dengue virus eventually showed a four-fold rising. According to the literature review, this is the second reported case of dengue infection concomitant with KD. The natural course of each disease may be modified and causes some difficulties in diagnosis and management.

Seve, P., et al. (2005). "Adult Kawasaki disease: report of two cases and literature review." Seminars in Arthritis & Rheumatism **34**(6): 785-792.
OBJECTIVES: To describe 2 cases of adult Kawasaki Disease (KD) and to review the medical literature to better define the epidemiological, clinical, laboratory, histopathological, cardiovascular, and therapeutic aspects of adult KD compared with pediatric KD.
METHODS: Report of 2 cases, and review of the literature using a Medline search from 1967 to June 2003.
RESULTS: Including our 2 cases, there are 57 reports of adult KD, 74% among patients aged 18 to 30 years. Nine cases of KD associated with human immunodeficiency virus (HIV) infection were

described, suggesting that an immunocompromised state may predispose to this syndrome. The incidence of specific diagnostic criteria was roughly similar in adults and in children. However, cheilitis, meningitis, and thrombocytosis were observed in a larger percentage of children, while arthralgia, adenopathy, and liver function abnormality were more common in adults. Although adult KD often was diagnosed after the acute phase, when a significant beneficial effect from gammaglobulin infusion could not be expected, this treatment did appear to shorten the course of the disease. Coronary aneurysms were less frequent in adults than in children. Prognosis was more favorable in adults, with less cardiovascular complications and no deaths.
CONCLUSIONS: Adult KD is a rare condition, which may go unrecognized. Other known disease processes with similar clinical presentations such as hypersensitivity drug reaction and toxic shock syndrome must be ruled out. For adult KD, exclusion criteria such as absence of hypotension, visceral impairment, staphylococcal infection, and any drug able to induce a drug hypersensitivity reaction are suggestive of the diagnosis, in the presence of the inclusion criteria, rash, conjunctival effusion, oropharynx changes, extremity changes, or adenopathy. [References: 75]

Tizard, E. J. (2005). "Complications of Kawasaki disease." Current Paediatrics **15**(1): 62-68.
Kawasaki disease (KD) is a systemic vasculitis and the leading cause of acquired heart disease in the developed world. The most severe, frequent complication of KD is the development of coronary artery involvement, although the introduction of treatment with intravenous gammaglobulin has reduced this problem. In those with a history of coronary artery involvement, long-term follow up is recommended. Kawasaki disease can be a widespread vasculitis affecting many systems, and some of the other recognized complications are discussed, including those affecting the skin, nervous system, gastrointestinal tract, musculo-skeletal system, kidneys, lungs, eyes and haematological effects. About 10-30% of children fail to respond to intravenous gammaglobulin and alternative management strategies including the use of steroids are discussed.

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Berdej-Szczot, E., et al. (2004). "Kawasaki disease in a 10-year-old boy as a cause of prolonged fever - Diagnostic problems." Pediatria Polska **79**(11): 944-947.
Kawasaki disease (KD) is generalized vasculitis of unknown etiology. It occurs mainly in children less than 5 years old. Nowadays, KD is a leading cause of acquired heart diseases among children in well-developed countries. There are no specific laboratory tests to diagnose KD. Its diagnosis is based on clinical symptoms. However, in some children, especially in older ones, the course of KD is atypical. We present a 10-year-old boy with atypical KD, treated effectively with immunoglobulin.

Denison, M. R. (2004). "Severe acute respiratory syndrome coronavirus pathogenesis, disease and vaccines: An update." Pediatric Infectious Disease Journal **23**(11 SUPPL.): S207-S214.
Background: A novel coronavirus has recently been identified as the cause of severe acute respiratory syndrome (SARS-CoV). The ability of this family of positive strand RNA viruses to move between species and cause severe disease in humans, with the potential for pandemic spread, has been confirmed. Method(s): An understanding of the disease and its pathogenesis and the genetics of coronavirus infections, as well as strategies to treat or prevent coronavirus infections, are essential. The history of coronavirus vaccines and the occurrence of laboratory-associated SARS-CoV infections underscore the need for stably attenuated strains of SARS-CoV and other coronaviruses. Result(s): Rapid progress has been made in understanding the clinical disease of SARS in adults and children. In adults, systemic infection with clinical and biochemical abnormalities, as well as respiratory infection, may be the rule. SARS is much milder in children younger than 12 years old than it is in adolescents and adults. In children age 12 years and younger, symptoms are generally nonspecific and cold-like. Numerous approaches to

the development of SARS-CoV vaccines have been undertaken, and there is evidence that antibodies to the spike protein may be protective from replication and pathology in animal models. Conclusion(s): The availability of reverse genetic systems has made it possible to engineer and recover coronavirus variants that contain multiple genetically stable mutations that grow well in culture but are attenuated for replication, virulence or both. Such variants will be platforms for the safe growth of SARS-CoV and candidates for live attenuated vaccines. Copyright © 2004 by Lippincott Williams & Wilkins.

Dolezalova, P., et al. (2004). "Incidence of vasculitis in children in the Czech Republic: 2-Year prospective epidemiology survey." Journal of Rheumatology **31**(11): 2295-2299.
Objective. To determine the incidence and presenting features of primary and secondary vasculitides in children across the Czech Republic. Methods. The population of 2.02 million children under 17 years of age was surveyed over 2 years. Cases were identified through monthly questionnaires posted to consultant pediatricians in all hospital pediatric departments in the country. Patients were included in the analysis if they met established inclusion criteria for each diagnosis and had disease onset between 1997 and 1999. Incidence rates were calculated from population rates derived from the 1991 Census. Results. We identified 452 new cases of vasculitis and connective tissue disease. The estimated annual incidence of Henoch-Schonlein purpura (HSP) was 10.2/100,000 children, with a mean age at onset of 7 years. At disease onset palpable purpura was present in all cases; arthritis/arthralgia in 52%; abdominal pain and/or gastrointestinal bleeding in 40%; hematuria/proteinuria in 15%; and genital involvement in 2.8%. Forty-nine percent of all patients with HSP received short term corticosteroids. The estimated annual incidence of Kawasaki disease (KD) was 1.6/100,000 children under 5 years. Thirteen percent of patients with KD had transient dilatation of coronary arteries; 75% received high dose intravenous immunoglobulin. Other primary systemic vasculitides were extremely rare in this population. Secondary vasculitides of connective tissue diseases had an estimated annual incidence of 0.22/100,000 for systemic lupus erythematosus and 0.19/100,000 for dermatomyositis. Conclusion. We determined the incidence of different childhood vasculitides within a hospital based population throughout the Czech Republic. HSP was the most common, with a relatively high proportion of the patients treated with a short course of corticosteroids. A lower incidence than expected of KD raised the suspicion that some cases were not identified. Other childhood vasculitides were rare.

Ebbeson, R. L., et al. (2004). "Kawasaki disease at British Columbia's Children's Hospital." Paediatrics and Child Health **9**(7): 466-470.
OBJECTIVES: To describe the clinical features, diagnosis, treatment and outcome of children with Kawasaki disease (KD) treated at a large tertiary care Canadian paediatric hospital and to try to identify correlations between clinical features and the development of coronary artery abnormalities. METHOD(S): The charts of 176 patients diagnosed with typical, atypical or incomplete KD between 1992 and 2000 at British Columbia's Children's Hospital were reviewed. RESULT(S): The male to female ratio was 1.8:1. The median age was 2.5 years (range two months to 14 years), with 8% nine years or older (42% Caucasian, 43% Asian). Cases occurred steadily throughout the year. One hundred two (58%) patients had typical, 18 (10%) patients had atypical and 56 (32%) patients had incomplete KD. The median time from fever onset to first intravenous immunoglobulin (IVIG) was seven days (range two to 49 days), and treatment began within 10 days of fever onset in 134 (76%) patients. All patients received one or more doses of 2 g/kg IVIG. Forty-two (24%) patients received a second dose for nonresponsiveness, of whom 10 (6%) remained nonresponsive. Eight (5%) patients received intravenous methylprednisolone. Forty-eight (27%) patients developed coronary artery abnormalities, with 10 (6%) echogenic abnormalities, 25 (14%) dilatations and 13 (7%) aneurysms (seven giant). No patient with a normal echocardiogram at four to eight weeks developed an abnormality on subsequent study. Fourteen (8%) patients had persistent abnormalities at last follow-up (median 447 days, range 62 to 3272 days): seven dilations and seven aneurysms (six giant). Five of 13 children (39%)

who developed aneurysms failed to meet diagnostic criteria for typical KD, and three of those five aneurysms were present at less than one year after diagnosis. Four of eight (50%) patients receiving intravenous methylprednisolone for IVIG nonresponsiveness had or developed aneurysms. One patient died. CONCLUSION(S): Some children diagnosed with KD who fail to meet the diagnostic description develop coronary artery abnormalities. There is a need for a more accurate means of diagnosis to more appropriately use IVIG, an expensive and increasingly scarce resource. The role of corticosteroids remains unclear and a randomized controlled clinical trial to determine their role is needed.

Newburger, J. W. and D. R. Fulton (2004). "Kawasaki disease." Current Opinion in Pediatrics **16**(5): 508-514.
PURPOSE OF REVIEW: Kawasaki disease is an acute, self-limited vasculitis of childhood characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15 to 25% of untreated children with the disease and may lead to myocardial infarction, sudden death, or ischemic heart disease.
RECENT FINDINGS: In the United States, Kawasaki disease has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children. The cause of Kawasaki disease remains unknown, but fortunately intravenous immune globulin therapy has proved to be effective at reducing the prevalence of coronary aneurysms in most children treated in the acute phase. Therapy for Kawasaki disease resistant to intravenous immune globulin therapy is an area of research and controversy. The long-term treatment of children with Kawasaki disease is dependent on coronary artery status.
SUMMARY: This review covers key data on the etiology, pathogenesis, treatment, and long-term outcomes of Kawasaki disease, highlighting recent publications. [References: 92]

Rainer, T. H. (2004). "Severe acute respiratory syndrome: Clinical features diagnosis, and management." Current Opinion in Pulmonary Medicine **10**(3): 159-165.
Purpose of review: In November 2003, a new, life-threatening, respiratory illness named severe acute respiratory syndrome (SARS) arose from Guangdong Province in China. The illness spread across the globe, caused many major outbreaks, and had an overall mortality rate of 11%. The purpose of this review is primarily to review the clinical features, diagnosis, and management of SARS, but also to comment briefly on the epidemiology and pathogen. Recent findings: SARS is caused by a novel coronavirus that primarily affects the lower respiratory tract. It starts with an influenza-like illness characterized by nonspecific, systemic symptoms. This is followed by the rapid development of a non-specific bronchopneumonia associated with lower tract respiratory symptoms, or gastrointestinal symptoms. Most patients recover after a week or 2, but some go on to develop acute respiratory distress syndrome. There is no proven treatment, although cocktails of broad-spectrum antibiotics, antiviral, and immunomodulatory therapy have been tried. Secondary spread can be prevented and outbreaks brought under control provided that staff wear personal protective equipment and pay close attention to good personal hygiene, and patients are isolated. The most urgent needs at present are to develop a vaccine, to develop rapid, inexpensive, accurate diagnostic tests that can give results early in the illness and within a few hours of sampling. Other needs are to investigate which therapies have the lowest adverse event/efficacy ratios. Summary: Up-to-date knowledge of SARS should help in early detection, isolation of high-risk patients, to reduce mortality and morbidity, and to prevent a new global epidemic arising. © 2004 Lippincott Williams & Wilkins.

Rozo, J. C., et al. (2004). "Kawasaki disease in the adult: a case report and review of the literature." Texas Heart Institute Journal **31**(2): 160-164.
Kawasaki disease, predominantly a disease of childhood, includes such symptoms as acute vasculitis, mucosal inflammation, rash, cervical adenopathy, and edema. Its most severe forms are associated with coronary artery aneurysms. We report a rare case of this disease in an

asymptomatic adult and review its epidemiology, etiology, diagnosis, treatment, and prognosis. [References: 43]

Shulman, S. T. and A. H. Rowley (2004). "Advances in Kawasaki disease." European Journal of Pediatrics **163**(6): 285-291.
UNLABELLED: Recent studies have increased our understanding of the etiopathogenesis of Kawasaki disease (KD). The inflammatory infiltrate in KD coronary artery aneurysms has been shown to consist of CD8 T lymphocytes, macrophages, and IgA plasma cells, consistent with an immune response to an intracellular pathogen with a mucosal portal of entry. The identification of an oligoclonal IgA response in the vascular wall and the detection of a KD-associated antigen in inflamed KD tissues using a synthetic antibody derived from KD oligoclonal IgA antibodies have provided new approaches to identification of the etiologic agent. Highly effective therapy has evolved for KD, even in the absence of identification of the etiologic agent. The existence of incomplete KD cases remains a significant diagnostic dilemma for the clinician.
CONCLUSION: The development of a diagnostic test, more specific therapy, and ultimate prevention of this potentially fatal illness of childhood are dependent upon continued advances in determining the etiopathogenesis of this fascinating disorder. [References: 61]

Tulloh, R. M. and L. E. Wood (2004). "Coronary artery changes in patients with Kawasaki disease." Acta Paediatrica Supplement **93**(446): 75-79.
Kawasaki disease (KD) is an acute, self-limiting, systemic vasculitis of unknown aetiology, which most commonly occurs in children aged 6 mo to 5 y, with a peak incidence at 9-11 mo. The inflammatory process preferentially involves the coronary arteries, potentially resulting in coronary arteritis, aneurysmal lesions, arterial thrombotic occlusion and sudden death. Kawasaki disease is the most common cause of acquired coronary vessel abnormalities in children. The cause of KD is not known, but evidence is presented for an inflammatory response and a genetic predisposition. The diagnostic tests are not yet defined, but treatment with immunoglobulin and aspirin is effective at reducing the risk of cardiac complications from 25% to 4.7% in the UK. Sequelae may occur, either acutely with myocardial, endocardial or pericardial inflammation, or many years after the original illness. There may be abnormalities of myocardial blood flow as assessed by MRI, radio-nucleide studies or echo Doppler. Such abnormalities of coronary arteries may require ongoing medication, interventional catheterization or even cardiac surgery. In the future, we hope to have more accurate diagnostic tests or prophylaxis against the disease, in addition to improved means of determining the susceptibility to or presence of long-term complications. [References: 32]

Vidal Micó, S., et al. (2004). "Incomplete Kawasaki disease." Revista Espanola de Pediatria **60**(6): 482-486.
Kawasaki disease is an acute vasculitis manifested by fever and signs of mucocutaneous inflammation. Without treatment, coronary artery aneurysms develop in one of every four to five children. This risk is reduced by the administration of high-dose intravenous gammaglobulin in the acute phase of the disease. The diagnosis of Kawasaki disease cannot be made by a laboratory test or pathognomonic clinical finding. In incomplete or atypical Kawasaki disease, patients lack sufficient clinical signs to fulfill the classic criteria for Kawasaki disease but are at risk for the development of coronary aneurysms. Incomplete Kawasaki disease should be considered in children with unexplained fever for at least 5 days that is associated with two or three principal clinical features of the disease and consistent laboratory data such as elevation of inflammatory markers such as CRP and / or ESR.

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Best, B. M., et al. (2003). "Pharmacokinetic and tolerability assessment of a pediatric oral formulation of

pentoxifylline in Kawasaki disease." Current Therapeutic Research - Clinical and Experimental **64**(2): 96-115.
Background: In infants and children, treatment of Kawasaki disease (KD) with high-dose intravenous immunoglobulin (IVIG) and acetylsalicylic acid ([ASA] aspirin) diminishes inflammatory response and reduces the risk for coronary artery abnormalities. However, patients with high serum concentrations of tumor necrosis factor (TNF)-alpha, which is associated with vascular damage, may develop coronary artery lesions even with treatment. The hemorheologic agent pentoxifylline blocks the production of TNF-alpha and may be an appropriate adjunctive therapy to IVIG and ASA. Objective: The objective of this study was to assess the pharmacokinetic characteristics and tolerability of a new oral syrup formulation of pentoxifylline as an adjunct to IVIG and ASA in the treatment of KD in children. Methods: Hospitalized boys and girls aged 6 months to 5 years and who were diagnosed with KD within the first 10 days of illness were eligible. Patients were assigned to 1 of 4 pentoxifylline treatment groups, by dose level (dose levels 1, 2, 3, and 4: 10, 15, 20, and 25 mg/kg daily, respectively, divided into 3 doses). Six plasma samples collected at the time the first dose was administered, and 4 samples collected after administration of the last dose on study day 6, were assessed by high-performance liquid chromatography using noncompartmental and 1-compartment pharmacokinetic analyses for pentoxifylline and its active metabolite (M-1). TNF-alpha levels on days 1 and 6 were assessed using electroimmunoassay. Results: Fourteen boys and 10 girls were enrolled. The mean age, body weight, and illness day at study entry were 34.5 months, 13.8 kg, and 6, respectively. Pentoxifylline exhibited nonlinear kinetic characteristics, with median area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) values of 622, 3428, 8416, and 10,347 ng/mL · h for dose levels 1 to 4, respectively, on study day 1. Pentoxifylline noncompartmental oral clearance and volume of distribution were significantly lower, and dose-normalized AUC0-∞ was significantly higher, for dose level 3 than dose level 1. M-1 parameters were not significantly different between dose levels. No accumulation of pentoxifylline or M-1 was noted. Fifteen of 24 patients (63%) reported mild to moderate adverse events that may or may not have been treatment related. Frequency and severity did not differ significantly between dose levels. Conclusions: In the children in this study, pentoxifylline was well tolerated at the doses studied. No notable differences in clinical outcomes were observed between dose levels, and dose levels 3 and 4 (20 and 25 mg/kg daily, respectively) resulted in similar exposure to both pentoxifylline and M-1. Future efficacy and tolerability studies should use a daily dose of 20 mg/kg of pentoxifylline in acute KD. Copyright © 2003 Excerpta Medica, Inc.

Boralevi, F., et al. (2003). "Kawasaki's disease with eruptive pustular and guttate psoriasis." Annales de Dermatologie et de Venereologie **130**(5): 528-531.
Background. Kawasaki's disease may have numerous atypical forms and these must be recognized in order to avoid delay of treatment. We report a case of psoriasis, first pustular and then guttate, occurring during Kawasaki's disease, and discuss a common pathophysiological mechanism. Case-report. A 3 year-old boy was seen for a febrile exanthema suggestive of Kawasaki disease (bilateral conjunctivitis, red and fissured lips, palmoplantar erythema, scarlet fever-like rash and perineal desquamation) associated with pustular lesions. A biopsy specimen of a pustular area showed histological features consistent with the diagnosis of pustular psoriasis. No coronary abnormality was found. The child was treated with intravenous immunoglobulins (2 g/kg) and oral aspirin (60 mg/kg/d). All the symptoms disappeared and immediate follow-up was marked by the appearance of guttate psoriasis. Discussion. Onset of psoriatic lesions during Kawasaki disease has been reported in 12 cases, either in acute phase or in immediate follow-up. Coronary complications have been found in 4 of 5 cases with acute psoriasis, suggesting a severe prognosis for this association. The hypothesis of a common pathophysiological mechanism is discussed with the intervention of a bacterial toxin acting as a superantigen and resulting in an strong activation of T-cells that leads to keratinocyte activation. The psoriatic lesions could hence be considered as a form of Köbner's phenomenon.

Chien, Y. H., et al. (2003). "Association between levels of TNF-α and TNF-α promoter - 308 A/A polymorphism in children with kawasaki disease." Journal of the Formosan Medical Association **102**(3): 147-150.
Background and Purpose: Tumor necrosis factor-alpha (TNF-α) has been shown to play a central role in the pathogenesis of vasculitis in Kawasaki disease (KD). We investigated the serum levels of TNF-α and soluble TNF receptor 1 (STNFR1) levels, and genetic polymorphisms of the TNF-α promoter gene in children with KD to delineate the genetic basis of KD. Methods: A total of 18 children (12 boys and 6 girls) with KD were studied, 9 of whom had the complication of coronary artery lesion (CAL) within 30 days after the onset of symptoms. Serum levels of TNF-α and STNFR1 were assayed by enzyme-linked immnosorbent assay, and DNA polymorphisms of the 5′ flanking region of TNF-α promoter gene at position -308 [guanine (G) to adenine (A)] and -238 (G to A) were studied by direct nucleotide sequencing. Results: The serum TNF-α level in KD patients was 113 ± 209.9 pg/mL (range, 2.0 to 756.9 pg/mL; median, 24.7 pg/mL; normal, < 10 pg/mL). The serum levels of STNFR1 in KD (4255 ± 2425 pg/mL) were higher than those of the control group (160 ± 116 pg/mL). Allele frequencies of -308A and -238A were 11.1% and 0% in the KD patients, and 0% and 3.1% in the control group. Neither TNF-α promoter polymorphism nor any significant risk factor for CAL was identified in KD patients. One patient, who was homozygous for -308A, showed the highest TNF-α level and elevated STNFR1 level but had no evidence of CAL. Positive correlations were found between serum levels of STNFR1 and C-reactive protein ($r = 0.731$, $p = 0.007$), and between STNFR1 and leukocyte counts at admission ($r = 0.620$, $p = 0.008$). Conclusions: Increased serum levels of TNF-α and STNFR1 were found in KD patients but there was no correlation between these levels. The relationship between the pathogenesis of KD and TNF-α gene promoter -308G to A mutation towards cytokine production remains to be clarified.

Cimaz, R. and F. Falcini (2003). "An update on Kawasaki disease." Autoimmunity Reviews **2**(5): 258-263.
Kawasaki disease (KD) is a febrile systemic vasculitis complicated by coronary and peripheral arterial aneurysms in 20-35% of untreated patients. It is reported as the commonest cause of acquired heart disease in children in developed countries, and may be a risk for adult ischaemic heart disease. Although KD has been reported all over the world, it is overexpressed among Asian populations, especially Japanese. The disease pathogenesis is still unknown and several theories have been proposed, including the possibility of an infection by a toxin-secreting microorganism and of a superantigen-driven process. Despite numerous efforts there is still no diagnostic test available for KD, and the diagnosis is based on clinical criteria after the exclusion of other diseases presenting with high persistent fever. Prompt diagnosis is critical, since the early administration of intravenous immunoglobulins and aspirin reduces the rate of coronary abnormalities to less than 5% of patients. [References: 30]

Genizi, J., et al. (2003). "Kawasaki disease in very young infants: high prevalence of atypical presentation and coronary arteritis." Clinical Pediatrics **42**(3): 263-267.

Hsueh, P. R. and P. C. Yang (2003). "Severe acute respiratory syndrome (SARS) - An emerging infection of the 21st century." Journal of the Formosan Medical Association **102**(12): 825-839.
Severe acute respiratory syndrome (SARS) is an emerging infection caused by a novel coronavirus known as SARS-CoV. The disease has a high propensity to spread to household members and healthcare workers and may be associated with transmission and outbreaks in the community. Severe illness in immunocompromised patients, sophiscated hospital facilities and treatment procedures, particularly those that gene generate aerosols, and lack of adequate isolation and control measures, can amplify transmission and contribute to so-called "super-spreading" events. The presence of non-specific clinical manifestations at presentation and a lack of validated early diagnostic methods and effective management pose great difficulty for frontline physicians in the containment of this disease. The mortality of SARS is in the region of 10 to 15%; the presence of underlying disease, high initial C-reactive protein levels, and

positive SARS-CoV in nasopharyngeal aspirate samples are associated with a higher risk of respiratory failure and mortality. Despite the disapprearance of SARS cases worldwide; the potential evolution of SARS-CoV in animals suggests the disease may re-emerge in the future. Heightened levels of clinical suspicion, rapid case detection and isolation, and contact tracing are essential to effective management of future outbreaks. Further ongoing requirements for successful management include research on the immunopathogenesis of SARS and the development of timely and reliable diagnostic tests, effective antiviral and immunomodulatory agents, and vaccines for the disease.

Kuijpers, T. W., et al. (2003). "Longstanding obliterative panarteritis in Kawasaki disease: lack of cyclosporin A effect." Pediatrics **112**(4): 986-992.
Kawasaki disease is a childhood vasculitis of medium-sized vessels, affecting the coronary arteries in particular. We have treated a therapy-resistant child who met all diagnostic criteria for Kawasaki disease. After the boy was given intravenous immunoglobulins and salicylates, as well as several courses of pulsed methylprednisolone, disease recurred and coronary artery lesions became progressively detectable. Cyclosporin A was started and seemed clinically effective. In contrast to the positive effect on inflammatory parameters, ie, C-reactive protein and white blood cell counts, a novel plasma marker for cytotoxicity (granzyme B) remained elevated. Coronary disease progressed to fatal obstruction and myocardial infarction. Echocardiography, electrocardiograms, and myocardial creatine phosphokinase did not predict impending death. At autopsy an obliterative panarteritis was observed resulting from massive fibrointimal proliferation, affecting the aorta and several large and medium-sized arteries. Immunophenotypic analysis of the inflammatory infiltrates in arteries revealed mainly granzyme-positive cytotoxic T cells and macrophages in the intima and media, as well as nodular aggregates of T cells, B cells, and plasma cells in the adventitia of affected arteries. These findings further endorse the role of specific cellular and humoral immunity in Kawasaki disease. Unremitting coronary arteritis and excessive smooth muscle hyperplasia resulted in coronary occlusion despite the use of cyclosporin A. [References: 37]

Kushner, H. I., et al. (2003). "Rethinking the boundaries of Kawasaki disease: Toward a revised case definition." Perspectives in Biology and Medicine **46**(2): 216-233.
This paper describes the historical evolution of the Kawasaki disease (KD) case definition and its limitations for identification and treatment of children at risk for coronary artery aneurysms (CAA). The dominant view of pathogenesis is that an unknown agent infects infants and children, who then develop the signs of KD. Some of the infected infants and children then develop CAA, and a few die from myocardial infarction. Because the etiologic agent remains unknown, diagnosis of KD relies on observation and recognition of the clinical signs that comprise the KD case definition criteria. This approach has been successful in identifying and treating many children at risk for CAA. Unfortunately, however, it has delayed the effective treatment of children who fail to meet the KD case definition criteria but who, nevertheless, develop CAA. The original case definition was developed before the general acceptance of CAA as sequelae of KD, the availability of the echocardiogram, and effective treatment with intravenous immunoglobulin. Despite an evolution in awareness, detection, and treatment of possible CAA sequela, the case definition has not been altered so as to incorporate this knowledge. Our investigation explores the transformation of the case definition from an epidemiological instrument to a diagnostic tool. We urge the construction of a more sensitive KD case definition that includes signs and laboratory findings associated with CAA.

Martínez-Boné Montero, E., et al. (2003). "Study of the clinical features and course of 10 cases of Kawasaki disease." Acta Pediatrica Espanola **61**(10): 531-535.
Objetive: To report our experience in Kawasaki disease, describing the clinical characteristics, course, treatment and cardiological complications of patients diagnosed in our center. Material and method: Clinical, analytical and cardiological evaluation of 10 cases of Kawasaki disease

diagnosed in our hospital from 1988 to 2000. Results: The mean patient age was 2 years 8 months (range: 4 months to 10 years). The male-to-female ratio was 1.5 to 1. All the patients met 5 of the 6 criteria considered fundamental, with fever, oropharyngeal injuries, exanthema, conjunctival injection and desquamation of hands and feet. Some also presented indurated rash on hands and feet, cervical lymphadenopathy and cracked lips (80%), diffuse oral rash (60%) and perineal desquamation (30%). Diagnosis was delayed in a patient who presented with marked cervical lymphadenopathy. Cardiac symptoms appeared in the acute phase; they were mild and transient in 40% of patients, and one child had a coronary aneurysm which increased in size after an untreated bout of fever. All were treated with acetylsalicylic acid, accompanied by intravenous gammaglobulin in 7. There were no cases of myocardial infarct and no deaths. Conclusion: All the cases were typical, with patients meeting 5 diagnostic criteria. Diagnosis was delayed in those in whom the presentation was unusual. One patient had a relapse, which produced a negative effect on his aneurysm. Treatment was delayed in 80% of cases.

Muise, A., et al. (2003). "Are children with Kawasaki disease and prolonged fever at risk for macrophage activation syndrome?" Pediatrics **112**(6 Pt 1): e495.
Kawasaki disease (KD) patients are known to be at increased risk for coronary artery lesions. We present evidence of another possible complication associated with KD: macrophage activation syndrome (MAS). In this case, a patient with KD and prolonged fever developed MAS. This case is of particular interest because of the late age of onset and recurrent nature of KD as well as the complication of MAS. We also present a review of the literature that supports the inclusion of MAS as an infrequent complication of KD. [References: 16]

Oates-Whitehead, R. M., et al. (2003). "Intravenous immunoglobulin for the treatment of Kawasaki disease in children." Cochrane Database of Systematic Reviews(4): CD004000.
BACKGROUND: Kawasaki disease is the most common cause of acquired heart disease in children in developed countries. The coronary arteries supplying the heart can be damaged in Kawasaki disease. The principal advantage of timely diagnosis is the potential to prevent this complication with early treatment. Intravenous immunoglobulin (IVIG) is widely used for this purpose.
OBJECTIVES: The objective of this review was to evaluate the effectiveness of IVIG in treating, and preventing cardiac consequences, of Kawasaki disease in children.
SEARCH STRATEGY: Electronic searches of the Cochrane Peripheral Vascular Disease Group Specialised Register, CENTRAL, MEDLINE, EMBASE, and CINAHL were performed (last searched April 2003). We also searched references from relevant articles and contacted authors where necessary. In addition we contacted experts in the field for unpublished works.
SELECTION CRITERIA: Randomised controlled trials of intravenous immunoglobulin to treat Kawasaki disease were eligible for inclusion.
DATA COLLECTION AND ANALYSIS: Fifty-nine trials were identified in the initial search. On careful inspection only sixteen of these met all the inclusion criteria. Trials were data extracted and assessed for quality by at least two reviewers. Data were combined for meta-analysis using relative risk ratios for dichotomous data or weighted mean difference for continuous data. A random effects statistical model was used.
MAIN RESULTS: The meta-analysis of IVIG versus placebo, including all children, showed a significant decrease in new coronary artery abnormalities (CAAs) in favour of IVIG, at thirty days RR (95% CI) = 0.74 (0.61 to 0.90). No statistically significant difference was found thereafter. A subgroup analysis excluding children with CAAs at enrollment also found a significant reduction of new CAAs in children receiving IVIG RR (95%) = 0.67 (0.46 to 1.00). There was a trend towards benefit from IVIG at sixty days (p=0.06). Results of dose comparisons showed a decrease in the number of new CAAs with increased dose. The meta-analysis of 400 mg/kg/day for five days versus 2 gm/kg in a single dose showed statistically significant reduction in CAAs at thirty days RR (95%) = 4.47 (1.55 to 12.86). This comparison also showed a significant reduction in duration of fever with the higher dose. There was no statistically significant difference noted between different preparations of IVIG. There was no statistically significant difference of

adverse effects in any group.
REVIEWER'S CONCLUSIONS: Children fulfilling the diagnostic criteria for Kawasaki disease should be treated with IVIG (2 gm/kg single dose) within 10 days of onset of symptoms. [References: 90]

Palazzi, D. L., et al. (2003). "Hemophagocytic syndrome after Kawasaki disease." Pediatric Infectious Disease Journal **22**(7): 663-666.
Hemophagocytic syndrome (HPS) is a rare and life-threatening disease in which a generalized histiocytic proliferation results in hemophagocytosis and up-regulation of inflammatory cytokines. This syndrome has been associated with infections, malignancy, drugs and immunologic triggers such as Kawasaki disease (KD). We describe the clinical and laboratory features of two children with HPS after KD and review the three previously reported pediatric cases of recrudescence of HD leading to HPS. [References: 30]

Parmar, R. C., et al. (2003). "Incomplete Kawasaki disease with recurrent skin peeling: a case report with the review of literature." Journal of Postgraduate Medicine **49**(1): 72-74.
Kawasaki disease (KD) is an acute systemic vasculitis of unknown aetiology that has largely replaced rheumatic heart disease as a cause of acquired heart disease in children of many developed countries. We report a case of incomplete KD in a five-year-old girl. The diagnosis of incomplete KD was made after exclusion of conditions with similar presentation. She was treated with intravenous immunoglobulin following which she made an uneventful recovery but demonstrated thrombocytosis in the second week of convalescence. During the six-month follow up period, she had two episodes of recurrent skin peeling a phenomenon, which is recently reported with KD but not with atypical or incomplete KD. It is important for the treating physicians to become aware of the incomplete KD as prompt diagnosis and early treatment of these patients with intravenous immunoglobulin is vital for the prevention of lethal coronary complications. Physicians need to have a "high index of suspicion" for KD and even, higher for IKD. [References: 14]

Seve, P., et al. (2003). "[Adult Kawasaki disease]." Revue de Medecine Interne **24**(9): 577-584.
PURPOSE: Review of the literature on adult Kawasaki disease.
CURRENT KNOWLEDGE AND KEY POINTS: Kawasaki disease is an acute multisystemic vasculitis affecting predominantly young children. Several studies have suggested that Kawasaki disease is mediated by bacterial superantigens. The diagnosis is established on clinical criteria since no specific laboratory test yet exists for this disorder. The severity of Kawasaki disease relates to the possible occurrence of coronary aneurysms in 20% of childhood cases. Treatment with intravenous immunoglobulins before day 10 is recommended to prevent aneurysm formation. The occurrence of Kawasaki disease is unusual in adults and 52 cases only have been reported in adult patients. Seventy-one per cent of cases occur between 18 and 30 years. The incidence of specific clinical features is quite similar between adults and children. However meningitis and thrombocytosis are more common in children than in adults, while conversely both arthralgias and liver function abnormalities are more common among adults. Coronary aneurysms are less common in the adults with Kawasaki disease. Other diseases with similar clinical presentation such as drug hypersensitivity reaction and the toxic shock syndrome must be ruled out. Kawasaki disease is often diagnosed after the acute phase at the step of desquamation, when it is too late to expect any beneficial effect from immunoglobulins.
FUTURE PROSPECTS AND PROJECTS: Diagnostic criteria of Kawasaki disease have not been validated in an adult population. Criteria of exclusion are necessary to eliminate toxic shock syndrome and drug hypersensitivity syndrome. An international retrospective study to collect data on epidemiologic, clinical, laboratory, and cardiovascular features of adult Kawasaki disease is necessary to validate specific diagnostic criteria and to improve the knowledge on this disease. [References: 72]

Zulian, F., et al. (2003). "Acute surgical abdomen as presenting manifestation of Kawasaki disease."

Journal of Pediatrics **142**(6): 731-735.
Ten children (4.6%) among a cohort of 219 with Kawasaki disease (KD) had their onset with severe abdominal complaints. Incomplete KD presentation at the time of acute abdomen was present in nine of 10 patients. Acute abdominal pain and distension, vomiting, hepatomegaly, and jaundice were the most common symptoms at onset. Hematemesis was present in one; toxic shock syndrome requiring care in the intensive care unit occurred in four. Five patients had laparotomy, three had percutaneous transhepatic biliary drainage, and one had a gastrointestinal endoscopy. Postoperative diagnosis was gallbladder hydrops with cholestasis in five, paralytic ileus in three, appendicular vasculitis in one, and hemorrhagic duodenitis in one. All patients completely recovered, but 50% developed coronary aneurysms despite early intravenous gammaglobulin treatment. Acute surgical abdomen can be the presenting manifestation of KD. In older children with fever, rash, and acute abdominal pain or hematemesis, KD should be considered in the differential diagnosis.

2002 (8)

Bonany, P. J., et al. (2002). "Acute renal failure in typical Kawasaki disease." Pediatric Nephrology **17**(5): 329-331.
Few cases of Kawasaki disease with acute renal failure have been described and only three articles report histological findings. We present an 8-year-old boy with typical Kawasaki disease and acute renal failure who did not require dialysis and had a complete recovery. Pathological findings in percutaneous biopsy included tubulointerstitial nephropathy with mild mesangial expansion, without vessel involvement or deposits in basal membrane. These findings were similar to those previously reported. We also detected apoptotic bodies in tubules. [References: 11]

Burns, J. C. (2002). "Kawasaki disease: the mystery continues." Minerva Pediatrica **54**(4): 287-294.
Kawasaki disease (KD) is an acute vasculitis of infancy and early childhood that continues to baffle researchers and clinicians alike. Although the acute illness resolves spontaneously, permanent damage to the coronary arteries occurs in 20-25% of untreated children. The cause of KD remains unknown and there is no specific laboratory test to identify affected children. Nonetheless, high dose intravenous g-globulin plus aspirin administered within the first 10 days of fever significantly reduces the risk of coronary artery damage by unknown mechanisms. KD thus presents a unique dilemma: the disease may be difficult to recognize, there is no diagnostic laboratory test, there is an extremely effective therapy, and there is a 25% chance of serious cardiovascular damage or death if the therapy is not administered. This review will highlight some of the many unanswered questions about KD. [References: 70]

Jimenez Moya, A. I., et al. (2002). "[Fever and exanthema in the older child]." Anales Espanoles de Pediatria **56**(5): 479-480.

Kitamura, S. (2002). "The role of coronary bypass operation on children with Kawasaki disease." Coronary Artery Disease **13**(8): 437-447.
Background: Kawasaki disease, initially called mucocutaneous lymph node syndrome was reported 35 years ago as a new inflammatory disease in infants and children and is characterized by a variety of symptoms and signs resulted from systemic vasculitis. Although the etiology of the disease remains unknown, its serious coronary complications have been proved to cause ischemic heart disease in children, and are now the most common cause of pediatric coronary disease in the world. The incidence of serious coronary sequelae is fortunately low (2-3% of patients with Kawasaki disease), but once myocardial infarction occurs in children, the mortality is quite high (22% at the first infarction). Development of surgical treatment for the disease was essential in preventing premature death and improving the quality of life of children. Methods and results:

Coronary revascularization surgery was attempted following careful evaluation of characteristic patters of coronary aneurysms and obstructions secondary to Kawasaki disease, although the surgical efficacy was initially questioned because the disease is inflammatory vasculitis in origin. The operation utilizing the pedicled internal thoracic artery has been demonstrated quite successful and now established as a reliable treatment for inflammatory coronary obstructions due to Kawasaki disease (the Kitamura Operation). There is valid evidence for the internal thoracic artery graft being a viable structure, accommodating in length and diameter for the growth of children. Results of the surgery and long-term prognosis are favorable and postoperative quality of life is markedly improved. Conclusions: Coronary bypass operation utilizing the pedicled internal thoracic artery is a safe and reliable surgical modality for coronary artery sequelae in children due to Kawasaki disease, Long-term follow-up results up to 20-years are quite satisfactory.

Okcun, B., et al. (2002). "Utility of dobutamine stress echocardiography in Kawasaki disease: a case report and review of the literature." Turkish Journal of Pediatrics **44**(3): 251-253.
Dobutamine stress echocardiography (DSE) has become widely accepted in the evaluation of adult patients with coronary heart disease. There are new challenges about the use of DSE in the pediatric age group to document ischemia. DSE can demonstrate ischemia noninvasively in Kawasaki disease (KD) patients who are candidates for coronary angiography. We wanted to assess the feasibility and the physiologic responses of DSE in a KD patient with coronary aneurysm. The patient had no ischemia in DSE, which was confirmed by coronary angiography showing no stenosis. The literature about DSE use in KD is reviewed. [References: 8]

Rowley, A. H. (2002). "Incomplete (atypical) Kawasaki disease." Pediatric Infectious Disease Journal **21**(6): 563-565.

Shingadia, D., et al. (2002). "Could a herpesvirus be the cause of Kawasaki disease?" The Lancet Infectious Diseases **2**(5): 310-313.
Kawasaki disease (KD) is an acute vasculitis of early childhood, the cause of which remains unknown. Many lines of evidence suggest an infectious aetiology, which may-in association with host genetic factors-lead to the characteristic clinical presentation of this disease. Accumulating data including animal models and epidemiological and immunological studies, suggest that viruses have an important role in human vasculitic disease. Whereas many infectious agents including viruses have been postulated as possible causes of KD, no single agent has been shown definitely to be associated with this disease and the causative agent remains elusive. We hypothesise that a ubiquitous virus of the gamma herpesvirus family is the likely aetiological agent for KD in genetically susceptible individuals. [References: 50]

Sundel, R. P. (2002). "Update on the treatment of Kawasaki disease in childhood." Current Rheumatology Reports **4**(6): 474-482.
Intravenous immunoglobulin (IVIG) treatment for Kawasaki disease (KD), first discovered almost 20 years ago, dramatically changed the management and prognosis of the condition. Although standard Japanese Ministry of Health criteria suggest that current treatment is more than 95% effective at preventing coronary artery changes, echocardiographic measurements adjusted for body size, imply a far higher incidence of coronary artery dilitation despite prompt therapy. If one also considers data on chronic alterations in endothelial function after KD, then more effective approaches to the management of acute and recurrent KD are needed. A variety of possible adjunct therapies--most notably high-dose corticosteroids--currently are being studied to determine whether better long-term outcomes may be achieved than with IVIG alone. [References: 60]

2001 (6)

Jaeggi, E. T. and S. Suter (2001). "[Clinical presentation, diagnosis and management of inflammatory heart diseases in childhood]." Therapeutische Umschau **58**(2): 87-93.
Inflammatory disorders which may affect the heart muscle, the endocardium, the pericardium and/or the coronary arteries are rare, but potentially devastating diseases. As the incidence of rheumatic heart disease has decreased, children with congenital heart disease now constitute the primary patient population at risk of infective endocarditis. Streptococcus viridans and Staphylococcus aureus are still the most frequently observed organisms. The majority of children with infective endocarditis can be cured today, but good results depend on early diagnosis and accurate treatment. Myocarditis occurs when the heart muscle is involved in an inflammatory process. Causes are numerous, but most common in children are infections with cocksackie viruses. Approximately two-thirds of children with symptomatic acute myocarditis show complete recovery of impaired ventricular function, 10-20% progress of dilatative cardiomyopathy and about 10% die or require heart transplantation. Kawasaki disease is the most prevalent inflammatory coronary artery disease and the leading cause of acquired heart disease in children. The origin of this acute systemic vasculitis remains unknown. Visible coronary arterial abnormalities develop in approximately 20% of children with untreated Kawasaki syndrome. A single dose of gamma-globulin (2 g/kg over 12 h) given within the first 10 days of onset of illness as early as possible, in addition to aspirin has been shown to reduce the duration of fever, which may reflect the severity of ongoing vasculitis, and to reduce the prevalence of coronary artery anomalies. [References: 13]

Kuramochi, Y., et al. (2001). "Feasibility of percutaneous transluminal coronary angioplasty to patients with Kawasaki Disease as an early management strategy." Pediatric Cardiology **22**(3): 183-187.
We successfully performed percutaneous transluminal coronary angioplasty (PTCA) in three infants with Kawasaki disease ages 11 to 29 months. The time from the onset of disease to PTCA ranged from 6 to 21 months. On period reevaluation 12 to 40 months after PTCA, they had no evidence of myocardial ischemia or restenosis. As an early management strategy, PTCA could be a good palliation to control myocardial ischemia associated with Kawasaki disease. From our study and a literature review, we suggest that PTCA may be more effective if it is performed earlier, even in young patients. [References: 13]

Lloyd, A. J., et al. (2001). "Kawasaki disease: is it caused by an infectious agent?" British Journal of Biomedical Science **58**(2): 122-128.
Kawasaki disease (KD) is an acute systemic febrile illness of unknown aetiology, predominantly affecting children under five years of age. Initially described in 1967 by Tomisaku Kawasaki, it is now the most common cause of acquired heart disease in children in the developed world. Although normally self-limiting, KD is associated with a range of complications, the most important of which is the development of life-threatening coronary artery abnormalities. Here, we examine the evidence supporting the concept that KD is caused by an infectious agent. Various infectious agents--including bacterial, viral and Rickettsial organisms--have been implicated as potential causes, as have certain immunological agents such as bacterial toxin-mediated superantigens, allergens such as anionic detergents and house-dust mites, and some chemicals (including heavy metals). Following extensive research, however, no links between any of these individual agents and the disease have been established irrefutably. Despite this, most of the epidemiological and immunological evidence currently available indicates that the causative agent is most likely to be infectious in nature; and additional evidence highlights the likelihood that development of KD is multifactorial in nature, requiring certain genetic and immunological factors, and possibly a vector. [References: 47]

Nasr, I., et al. (2001). "Kawasaki disease: an update." Clinical & Experimental Dermatology **26**(1): 6-12.
Kawasaki disease is one of the commonest vasculitides seen in children. It presents with prolonged fever and a polymorphic exanthem. It is a major cause of acquired heart disease in

western society. Its exact cause is not known, but exposure to a superantigen has been suggested as a possible aetiological factor. Diagnosis of Kawasaki disease still relies on clinical criteria (Table 1) and investigations are done mainly to exclude other diseases and to detect early or established cardiac complications. Coronary complications can be reduced significantly by the use of intravenous immunoglobulin therapy combined with oral aspirin. The serious consequences of Kawasaki disease require a heightened awareness of this condition when dealing with childhood exanthems. [References: 32]

Williams, R. V., et al. (2001). "Pharmacological therapy for patients with Kawasaki disease." Paediatric Drugs **3**(9): 649-660.
Kawasaki disease is a systemic vasculitis of unknown aetiology that has been reported worldwide since its initial description in Japanese children. The most significant sequelae of acute Kawasaki disease are related to the inflammation of small to medium sized arteries and, in particular, the development of coronary artery aneurysms. Because the aetiology is unknown, pharmacological therapy is nonspecific and directed towards modulation of the inflammatory response and inhibition of platelet activation with the aim of preventing coronary artery aneurysms. In the US, the recommended treatment for Kawasaki disease in the acute phase is a single, high dose of intravenous gammaglobulin (2 g/kg) and high dose aspirin (80 to 100 mg/kg/day). Use of this regimen has resulted in a significant decrease in the incidence of coronary artery abnormalities. Although the American Heart Association currently recommends high dose aspirin, moderate doses are used in Japan and the optimal dose of aspirin is not known. There has been renewed interest in the use of corticosteroids in the treatment of acute Kawasaki disease: however, their precise role remains unclear. Newer antiplatelet agents have also shown some promise in the treatment of patients with coronary artery aneurysms. Long term pharmacological therapy consists primarily of anticoagulation in patients with persistent coronary artery abnormalities. In this review, current recommendations for pharmacological therapy in Kawasaki disease are reviewed and some of the controversies in management of this disease, including management of patients who do not respond to initial therapy and the role of corticosteroids in the acute setting, are outlined. [References: 99]

Yalcindag, A. and R. Sundel (2001). "Vasculitis in childhood." Current Opinion in Rheumatology **13**(5): 422-427.
Inadequate understanding of the pathogenesis and etiology of vascular inflammation continues to hinder progress in the diagnosis and treatment of pediatric vasculitis. The greatest amount of work is being done in the most common vasculitides of childhood, including Kawasaki disease and Henoch-Schönlein purpura. Discussion of rarer types of vasculitis, on the other hand, such as antineutrophil cytoplasmic antibody-positive small vessel diseases, is largely restricted to case reports. Most aspects of the care of children with Wegener granulomatosis and microscopic polyangiitis are derived by extrapolating from data about adults. Virtually no data are available concerning ways in which these diseases may be different in children.

2000 (10)

Brenner, J. L., et al. (2000). "Severe Kawasaki disease in infants: two fatal cases." Canadian Journal of Cardiology **16**(8): 1017-1023.
Kawasaki disease is a systemic vasculitis that manifests itself in many ways. Infants may present as atypical cases and commonly experience severe inflammatory changes. The two cases that are presented here highlight unusual severity and pathology. Patient 1 was a three-month-old infant with atypical Kawasaki disease who developed gangrenous lesions, and coronary and extracoronary artery aneurysms. Multiorgan failure ensued with diffuse cardiac and extracardiac aneurysms and thromboses at autopsy. Patient 2 was a five-month-old infant with Kawasaki

disease, cholangitis and peripheral gangrene. Severe coronary artery aneurysms developed and he died following a myocardial infarction, despite multiple doses of intravenous immunoglobulin, acetylsalicylic acid (ASA) and corticosteroids. There is a higher occurrence of atypical disease and more severe vasculitis in infants with Kawasaki disease. Pathological changes are described, including coronary and extracardiac lesions. Patient 1 shows extensive peripheral gangrene and widespread aneurysms, and patient 2 illustrates severe cardiac complications with diffuse organ inflammation. Therapies including intravenous immunoglobulin, ASA, corticosteroids and antithrombotics are reviewed. [References: 32]

Burns, J. C., et al. (2000). "Kawasaki disease: A brief history." Pediatrics **106**(2): E27.
Tomisaku Kawasaki published the first English-language report of 50 patients with Kawasaki disease (KD) in 1974. Since that time, KD has become the leading cause of acquired heart disease among children in North America and Japan. Although an infectious agent is suspected, the cause remains unknown. However, significant progress has been made toward understanding the natural history of the disease and therapeutic interventions have been developed that halt the immune-mediated destruction of the arterial wall. We present a brief history of KD, review progress in research on the disease, and suggest avenues for future study. Kawasaki saw his first case of KD in January 1961 and published his first report in Japanese in 1967. Whether cases existed in Japan before that time is currently under study. The most significant controversy in the 1960s in Japan was whether the rash and fever sign/symptom complex described by Kawasaki was connected to subsequent cardiac complications in a number of cases. Pathologist Noboru Tanaka and pediatrician Takajiro Yamamoto disputed the early assertion of Kawasaki that KD was a self-limited illness with no sequelae. This controversy was resolved in 1970 when the first Japanese nationwide survey of KD documented 10 autopsy cases of sudden cardiac death after KD. By the time of the first English-language publication by Kawasaki in 1974, the link between KD and coronary artery vasculitis was well-established. KD was independently recognized as a new and distinct condition in the early 1970s by pediatricians Marian Melish and Raquel Hicks at the University of Hawaii. In 1973, at the same Hawaiian hospital, pathologist Eunice Larson, in consultation with Benjamin Landing at Los Angeles Children's Hospital, retrospectively diagnosed a 1971 autopsy case as KD. The similarity between KD and infantile periarteritis nodosa (IPN) was apparent to these pathologists, as it had been to Tanaka earlier. What remains unknown is the reason for the simultaneous recognition of this disease around the world in the 1960s and 1970s. There are several possible explanations. KD may have been a new disease that emerged in Japan and emanated to the Western World through Hawaii, where the disease is prevalent among Asian children. Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19th century, but, thus far, cases of IPN have not been discovered in Japan before World War II. Perhaps the factors responsible for KD were introduced into Japan after the World War II and then reemerged in a more virulent form that subsequently spread through the industrialized Western world. It is also possible that improvements in health care and, in particular, the use of antibiotics to treat infections caused by organisms including toxin-producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity. Itsuzo Shigematsu, Hiroshi Yanagawa, and colleagues have conducted 14 nationwide surveys in Japan. These have indicated that: 1) KD occurred initially in nationwide epidemics but now occurs in regional outbreaks; 2) there are approximately 5,000 to 6,000 new cases each year; 3) current estimates of incidence rates are 120 to 150 cases per 100,000 children <5 years old; 4) KD is 1.5 times more common in males and 85% of cases occur in children <5 years old; and 5) the recurrence rate is low (4%). In 1978, David Morens at the Centers for Disease Control and Prevention published a case definition based on Kawasaki's original criteria. The Centers for Disease Control and Prevention developed a computerized database in 1984, and a passive reporting system currently exists in 22 states. Regional investigations and national surveys suggest an annual incidence of 4 to 15 cases per 100 000 children <5 years o [References: 76]

Dohmen, G., et al. (2000). "Coronary artery bypass grafting in adult coronary artery disease due to suspected Kawasaki disease in childhood." Annals of Thoracic Surgery **70**(5): 1704-1706.
Development of coronary artery aneurysms is one typical complication of Kawasaki disease and can cause coronary artery disease even in early childhood. Information about course and outcome in adults is rare. Here, we present a 49-year-old man with serious three-vessel coronary artery disease and giant coronary artery aneurysms following suspected Kawasaki disease. (C) 2000 by The Society of Thoracic Surgeons.

Foster, B. J., et al. (2000). "Kawasaki disease complicated by renal artery stenosis." Archives of Disease in Childhood **83**(3): 253-255.
We report the case of a child who developed severe renovascular hypertension six months after acute Kawasaki disease. The hypertension was well controlled with enalapril, but there was a gradual decrease in function of the affected kidney. The lesion, an ostial stenosis of the right main renal artery, was not amenable to percutaneous balloon angioplasty, so was treated with bypass surgery. Vasculitis is an important cause of renovascular hypertension in children. This case highlights the importance of regular blood pressure monitoring in children with a history of systemic vasculitis.

Fulton, D. R. and J. W. Newburger (2000). "Long-term cardiac sequelae of Kawasaki disease." Current Rheumatology Reports **2**(4): 324-329.
Kawasaki disease is the leading cause of acquired heart disease in childhood. Despite treatment with intravenous gamma globulin, 2% to 4% of patients have coronary abnormalities. Those with giant aneurysms are at risk for stenosis and myocardial ischemia/infarction, and require aggressive anticoagulation with frequent follow-up, including stress testing and coronary angiography. In rare cases, patients will have coronary artery bypass grafting. Those with less severe coronary involvement need antiplatelet therapy and infrequent noninvasive testing. Patients with normal echos after the acute phase are not treated, but the future impact of the disease is not certain particularly in the setting of adult onset coronary artery disease. [References: 48]

Homicz, M. R., et al. (2000). "An atypical presentation of Kawasaki disease resembling a retropharyngeal abscess." International Journal of Pediatric Otorhinolaryngology **54**(1): 45-49.
Kawasaki disease is an acute systemic inflammatory disease, which occurs in children less than 10 years of age. The etiology of the disorder is unknown. Diagnosis is based upon clinician's recognition of a symptom pattern that includes high fevers, oral cavity changes, polymorphous rash, conjunctival injection, and cervical adenopathy. Most feared are the cardiac manifestations of Kawasaki syndrome, which result in an overall mortality rate of 2% in patients. Because of the common presenting symptoms, the otolaryngologist often plays a central role in early diagnosis of the disorder. The following case report describes a patient with Kawasaki disease whose initial presentation mimicked a retropharyngeal abscess. A literature review details the common and atypical early signs and symptoms of Kawasaki disease. [References: 12]

Poon, L. K., et al. (2000). "Facial nerve palsy and Kawasaki disease." Hong Kong Medical Journal **6**(2): 224-226.
We report on a case of facial nerve palsy associated with Kawasaki disease in a 2-year-old boy. Facial nerve palsy is one of the rare neurological manifestations of Kawasaki disease. Twenty-seven other cases that have been reported in the literature are reviewed. There is a high incidence of coronary artery aneurysm (52%) and a female predilection in patients with Kawasaki disease. The facial palsy associated with the disease is self-limiting. Recovery is spontaneous in surviving patients, although the use of intravenous immunoglobulin may be able to hasten the recovery. [References: 11]

Rees, A. H. (2000). "Pediatric autoimmune cardiovascular disease." Journal of the Kentucky Medical Association **98**(7): 289-295.
Pediatric autoimmune cardiovascular disease can cause serious, sometimes life threatening sequelae on the pediatric population. Valvular, myocardial, and pericardial involvement causing morbidity and mortality can occur in association to rheumatic heart disease, systemic lupus erythematosus, and juvenile rheumatoid arthritis. Serious and potentially life threatening coronary artery involvement can occur in patients with childhood polyarteritis nodosa, Takayasu arteritis, and Kawasaki disease. [References: 8]

Suzuki, A., et al. (2000). "Remodeling of coronary artery lesions due to Kawasaki disease: comparison of arteriographic and immunohistochemical findings." Japanese Heart Journal **41**(3): 245-256.
Since the original report of Kawasaki disease in 1967 more than 150,000 cases have been reported in Japan. Although there have been no nationwide epidemics in Japan since 1987, more than 6,000 newly diagnosed cases are reported every year, and the number has been increasing year by year despite the decreasing birth rate. The etiology of the disease is still unknown. High dose intravenous gammaglobulin is currently used during the acute phase in 84% of the patients in Japan with a concomitant decrease in coronary arterial sequelae. However, 7-13% of the patients still have persistent coronary artery aneurysms after the acute stage. The aneurysms are seen mostly in the proximal coronary arteries, and are often associated with aneurysms in the distal coronary artery segments (Figure 1A, 2A). Most of the patients show a decrease in the size of aneurysms soon after the acute phase (Figure 1B). However, the aneurysms may progress to obstructive lesions even after initial regression (Figures 1C, D, 2B). Such obstructive lesions may cause sudden death or myocardial infarction. Long term follow-up of coronary artery lesions has revealed several characteristic features, including progressive localized stenosis (Figure 1D), extensive recanalizations (Figure 2D) and development of collateral arteries. Progressive increases in aneurysm size and the appearance of new aneurysms in the late phase have also been reported. The basic mechanisms of the coronary arterial remodeling in Kawasaki disease have not yet been elucidated. Only recently has immunohistochemical staining in formalin-fixed specimens become feasible. This is a major technical breakthrough since it is almost impossible to obtain fresh frozen specimens of coronary artery lesions of Kawasaki discase. In this paper, we compare immunohistochemical findings in coronary artery lesions with the corresponding coronary angiographic findings, and attempt to make inferences as to the mechanism of remodeling both in early and late phases of the disease based on the expression of vascular growth factors. [References: 22]

Yoskovitch, A., et al. (2000). "Head and neck manifestations of Kawasaki disease." International Journal of Pediatric Otorhinolaryngology **52**(2): 123-129.
Kawasaki disease, also known as acute infantile febrile mucocutaneous lymph node syndrome, is a self-limited vasculitic disease of infants and young children. The cause of the disease remains uncertain. Within the constellation of signs and symptoms, there are numerous otolaryngologic manifestations. The following represents the largest series of patients in the otolaryngology literature, involving 155 confirmed cases of Kawasaki disease as treated at our institution during the last 10 years. The demographic data, clinical pictures of the typical and atypical forms of the illness, as well as the laboratory values, therapy and complications are discussed. Copyright (C) 2000 Elsevier Science Ireland Ltd.

1999 (2)

Chang, J. S., et al. (1999). "Kawasaki disease complicated by peripheral gangrene." Pediatric Cardiology **20**(2): 139-142.
An 8.5-month-old male infant with Kawasaki disease (KD) received high-dose intravenous immunoglobulin (IVIG) therapy on the fifth day after fever onset. However, multiple peripheral

limb ischemias occurred 2 days later. Accordingly, heparin followed by dipyridamole was administered. Aside from a small amputation at the tip of the right middle finger, all other digital ischemias resolved. This presentation demonstrates that early recognition and management of peripheral gangrene in KD may keep its sequela to a minimum. [References: 7]

Pemberton, M. N., et al. (1999). "Recurrent Kawasaki disease." British Dental Journal **186**(6): 270-271.
Kawasaki disease (mucocutaneous lymph node syndrome) is a disease of unknown aetiology characterised by vasculitis which may affect the coronary arteries. Young children are most commonly affected although the disease has been described in adults. We report a case of recurrent Kawasaki disease which presented to an oral medicine clinic, where early recognition prompted appropriate management. [References: 13]

1998 (8)

Barron, K. S. (1998). "Kawasaki disease in children." Current Opinion in Rheumatology **10**(1): 29-37.
Kawasaki disease is an acute systemic vasculitis of childhood. Children are predominantly affected at less than 5 years of age, and coronary artery involvement is responsible for most of the morbidity and mortality of the disease. Since the institution of intravenous immune globulin in the treatment of the disease, outcome has significantly improved. Although multiple infectious agents and toxins have been implicated in the etiology of the disease, none has been identified. Activation of the immune system is known to occur in the acute stage of the disease and plays an important role in the pathogenesis of the disease. [References: 100]

Chung, C. J. and L. Stein (1998). "Kawasaki disease: a review." Radiology **208**(1): 25-33.

Curtis, N. and M. Levin (1998). "Kawasaki disease thirty years on." Current Opinion in Pediatrics **10**(1): 24-33.
This year marks the 30th anniversary of the first description of Kawasaki disease. The disease has emerged as an important cause of acquired heart disease in children. The cause of Kawasaki disease remains unknown and this presents many problems in the diagnosis and management of the disease. This paper reviews recent publications on the pathogenesis, diagnosis, and the short- and long-term management of Kawasaki disease. [References: 138]

Dillon, M. J. (1998). "Childhood vasculitis." Lupus **7**(4): 259-265.
Vasculitis can and does occur in childhood. Apart from the relatively common vasculitides (Henoch-Schonlein purpura, Kawasaki disease and in world wide terms Takayasu disease) there are a number of important but comparatively rare disorders affecting children. These include macroscopic and microscopic polyarteritis, cutaneous polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, primary angiitis of the central nervous system, hypersensitivity angiitis, hypocomplimentaemic urticarial vasculitis, vasculitis associated with various connective tissue disorders and vasculitis associated with conditions such as Behcets syndrome, familial Mediterranean fever and Cogan's syndrome. Distinguishing these conditions from other disorders is often difficult and requires clinical acumen and appropriate investigative procedures. With modern therapeutic agents, it is possible to implement appropriate therapy but in spite of this, there remains a not inconsequential morbidity and mortality. [References: 102]

Kelly, C. J. and J. H. Calhoun (1998). "Ocular manifestations of pediatric disease." Current Opinion in Ophthalmology **9**(6): 111-115.
A review of the ocular manifestations of pediatric disease is in some ways a review of pediatrics itself. A paper this size cannot hope to be comprehensive in scope or encyclopedic in detail. Instead, we have chosen to touch on recent developments in pediatrics that we feel may be of particular interest to the ophthalmologist, as well as certain areas of pediatric ophthalmology that

make it clear that a child's ocular disease takes place in the larger context of the growing child. [References: 12]

Malossi, M. and R. Malossi (1998). "[Compromised tissue perfusion for defective microcirculation in children]." Pediatria Medica e Chirurgica **20**(2): 125-130.
After a brief review of the anatomic and physiological features of the microcirculatory system, the Authors describe a new interpretation of skin edema in acute diffuse infantile glomerulonephritis, in Henoch-Schonlein's purpura, in epidemic parotitis and in Kawasaki's disease. They attribute the cellular swelling typical of elastic oedema of these diseases to respiratory deficiency due to reduced tissue perfusion following insufficient circulation in real capillaries. The ensuring drop in energy is rapidly resolved by use of very small doses of a calcium antagonist, chloropromazine, which also affects hemorheology. The Authors refer to works which regard the microcirculatory hypothesis in encephalic pathology (similar to that arising in subjects who live at high altitudes where oxygen is scarce), in cranial trauma and in psychic depression. The Authors describe the surprising find, following a fortuitous observation, that in certain forms of hepato-splenomegaly--among which a case of splenomegaly with hepato-megaly and initial cirrhosis--three hours after the administration of doses of chloropromazine ranging from 0.5 to 1.0 mg/kg, the liver and spleen considerably reduced in volume, followed by the patients' ensuing excellent general conditions and functionality of their organs. The article then references many other Authors who in the course of time have acknowledged the fact that hypoxia stimulates proliferation, even of osteoblasts. Mention is made of the fact that many medications and therapeutic measures may cause vasoconstriction at microcirculatory system level, similarly to several antineoplastic drugs, X-rays, hyperbaric oxygen treatment, as well as traumas, low environmental temperatures and surgical operations. For this reason, in order to contrast vasoconstriction in many pathological conditions and in certain therapies, the Authors suggest the addition of the use of calcium antagonists to usual therapy. This conclusion is reached in consideration of the fundamental fact that the energy deficiency arising in the hypoperfused tissue areas allow an accumulation of amino acids, mainly deriving from protein disgregation, used with a low consumption of energy to synthesize a great number of simplified proteins. Final reference is made to the concept expressed on hypoxia and simplified structural proliferation in an article published in "Medical Hypotheses" of 1995 referring to neoplastic promotion. [References: 42]

Rowley, A. H. and S. T. Shulman (1998). "Kawasaki syndrome." Clinical Microbiology Reviews **11**(3): 405-414.
Kawasaki syndrome (KS) is an acute, sometimes fatal vasculitis of young children. KS has replaced acute rheumatic fever as the most common cause of acquired heart disease in children in the United States. The illness is manifested by prolonged fever, conjunctival injection, enanthem, exanthem, erythema and swelling of the hands and feet, and cervical adenopathy. These acute features of illness are self-limiting, but coronary artery abnormalities occur in 20% of untreated patients. The etiology of the illness is unknown, but its clinical and epidemiologic features are most consistent with an infectious cause. Common cardiovascular manifestations of the illness include myocarditis, pericardial effusion, and coronary artery aneurysm formation. Treatment with intravenous gamma globulin (IVGG) and aspirin within the first 10 days of illness reduces the prevalence of coronary artery abnormalities from 20% in those treated with aspirin alone to 4%. Patients who develop coronary artery aneurysms, particularly those who develop giant coronary artery aneurysms, may suffer myocardial infarction secondary to thrombosis or stenosis in the abnormal vessel. Additional research to determine the cause of KS is urgently needed to allow for improved diagnosis, more specific therapy, and prevention of the disorder. [References: 108]

Rubin, B. and D. M. Cotton (1998). "Kawasaki disease: a dangerous acute childhood illness." Nurse Practitioner **23**(2): 34, 37-38, 44-38.

Kawasaki disease is an acute febrile illness most commonly seen in children under the age of 5. It is characterized by fever, rash, cervical lymphadenopathy, bilateral nonexudative conjunctivitis, oropharyngeal mucosal changes, and erythema of the hands and feet followed by desquamation. However, a child with Kawasaki disease may not exhibit all of these symptoms. The disease resembles many other childhood illnesses, such as measles and scarlet fever, and misdiagnosis is common. Left untreated, Kawasaki disease has potential life-threatening consequences; 20% to 25% of children develop coronary artery aneurysms as a result. Although no specific laboratory tests exist that identify Kawasaki disease definitively, there are clinical and laboratory findings that guide diagnosis and treatment. Treatment includes the hospitalization of the child and subsequent administration of high doses of aspirin and intravenous immunoglobulin. With recovery, aspirin doses are reduced and the child may be monitored at home with outpatient follow-up. It is imperative that the health care provider be aware of the symptoms of Kawasaki disease in order to make the diagnosis and treat the child before cardiac sequelae ensue. [References: 19]

1997 (7)

Bushara, K., et al. (1997). "Facial palsy in Kawasaki syndrome." Pediatric Neurology **17**(4): 362-364.
Facial nerve palsy, a very rare complication of Kawasaki syndrome, has been reported in only 25 patients. We treated a 12-week-old boy with bilateral coronary artery aneurysms due to Kawasaki syndrome who developed marked unilateral peripheral facial nerve palsy on day 36 of illness. None of the 25 previously reported patients with this complication were treated with immunoglobulin; they required 7 to 90 days to recover. In our patient, treatment with this agent was associated with complete resolution of facial nerve palsy within 36 hours. Review of prior cases demonstrates that children with Kawasaki-associated facial nerve palsy have more than twice the risk for coronary artery aneurysm (52% vs <25%) as that of children who do not develop this neurological complication. Unexplained facial nerve paralysis in young children with a prolonged febrile illness should provoke consideration of Kawasaki syndrome and of echocardiography to exclude coronary artery aneurysms. Although facial palsy appears likely to resolve in all patients that survive the acute phase of Kawasaki syndrome, treatment with intravenous immunoglobulin appears to considerably shorten the time to full recovery and provides an important clue to the mechanisms of neurological injury in this illness. [References: 19]

Cuttica, R. J. (1997). "Vasculitis, Kawasaki disease, and pseudovasculitis." Current Opinion in Rheumatology **9**(5): 448-457.
Vasculitis is the inflammation and necrosis of vessel wall and may be a primary disease or secondary to another condition. At present, there is not an accurate classification; rather, classification depends on the changing nomenclature of these conditions and it is difficult to categorize some syndromes because they involve several vessel sizes. The most interesting type of vasculitis for the pediatrician is Kawasaki disease. New developments in this field are showing a relationship between this disease and superantigens. Some patients are resistant to high doses of intravenous gammaglobulin; in such cases, when some risk factors are present, some authors suggest the use of steroid pulse therapy. Inflammation of vessel walls results in occlusion of the lumen with necrosis; many other diseases have similar findings, such as infective endocarditis, Sneddon's syndrome, and others discussed here that should be included in the differential diagnosis. [References: 52]

Huang, Y. C., et al. (1997). "Unusual manifestations in children with Kawasaki disease." Journal of the Formosan Medical Association **96**(6): 451-456.
Between January 1983 and December 1992, the medical records of 187 patients (116 boys and 71 girls) with Kawasaki disease (KD) who were admitted to the hospital in the acute phase were

retrospectively reviewed. Of these, 175 patients (93.6%) were under 4 years of age. Among the six principal symptoms of KD, the incidence of cervical lymphadenopathy (41.2%) was relatively low. Additionally, we found some unusua featuers including intussusception in a 1-month-old female, transient thrombocytopenia in seven children (3.7) and associated features make KD puzzling and difficult to diagnose. In caring for children with KD, physicians should be alert to the principal symptoms as well as the unusual associated manifestations.

Kuniyuki, S. and M. Asada (1997). "An ulcerated lesion at the BCG vaccination site during the course of Kawasaki disease." Journal of the American Academy of Dermatology **37**(2 Pt 2): 303-304.
We describe a bacillus Calmette-Guerin (BCG) granuloma that occurred during the course of Kawasaki disease. A 12-month-old male infant with Kawasaki disease had an erythematous indurated plaque with prominent necrotic ulceration at the BCG vaccination site on the left upper arm. Histologic study showed a granulomatous reaction consisting of epithelioid histiocytes, lymphoid cells, and Langhans-type giant cells. No evidence of mycobacterial infection was obtained. The lesion healed completely within 2 weeks without administration of antituberculous agents. We believe that the granulomatous reaction occurred as a result of hypersensitivity to proteins in the BCG vaccine, which appeared after the onset of Kawasaki disease. [References: 15]

Mason, W. H. and J. C. Burns (1997). "Clinical presentation of Kawasaki disease." Progress in Pediatric Cardiology **6**(3): 193-201.
In spite of the passage of nearly 30 years since the original description, the etiology of Kawasaki disease (KD) remains enigmatic. As a result the diagnosis of the illness continues to rely on the fulfillment of clinical criteria and the exclusion of other illnesses with similar symptoms and signs. The principal diagnostic criteria include fever of 5 days duration and presence of at least four of the five following findings: changes in extremities, polymorphous exanthem, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical adenopathy. In the presence of fever and coronary artery changes fewer than four of the other clinical criteria are required to establish the diagnosis. The illnesses most often confused with KD include scarlet fever, measles, other viral exanthems, and allergic reactions to drugs or other antigens. Variations in the clinical presentation of KD are common and practitioners should maintain a high index of suspicion for KD, especially in persistently febrile infants less than 1 year of age.

Ravi, K. V. and J. R. Brooks (1997). "Peritonsillar abscess - An unusual presentation of Kawasaki disease." Journal of Laryngology and Otology **111**(1): 73-74.
Kawasaki disease (KD) is a paediatric illness characterised by prolonged high fever, mucocutaneous lesions and lymphadenopathy. It is potentially fatal as coronary arteritis occurs in up to a third of affected children. We present a seven-year-old child who was admitted to hospital with neck pain and fever. Despite intravenous antibiotic therapy and a quinsy right tonsillectomy on the sixth day after admission, the patient's symptoms persisted. With the appearance of further signs and symptoms the diagnosis of KD was made two days after operation. The patient's symptoms resolved with aspirin and intravenous gammaglobulin therapy. A literature review of the various aspects of KD is presented.

Resnick, S. D. (1997). "New aspects of exanthematous diseases of childhood." Dermatologic Clinics **15**(2): 257-266.
The childhood exanthems include a spectrum of common and uncommon disorders caused by a variety of pathogens. In this article, timely issues relating to immunization for measles and varicella are discussed. Recently reported exanthematous illnesses, including papular-purpuric gloves and socks syndrome, unilateral laterothoracic exanthem, and eruptive pseudo-angiomatosis, are described. The current research and debate about bacterial toxins as the cause of Kawasaki syndrome are presented. [References: 95]

1996 (7)

Burns, J. C., et al. (1996). "Sequelae of Kawasaki disease in adolescents and young adults." Journal of the American College of Cardiology **28**(1): 253-257.
Kawasaki disease is an acute vasculitis of unknown etiology that predominantly affects children <5 years of age. Structural damage to the coronary arteries after the acute, self-limited illness is detected by echocardiography in approximately 25% of untreated patients. The long-term effects of the acute coronary arteritis are unknown. To define the spectrum of clinical disease in young adults that can be attributed to Kawasaki disease in childhood, we performed a retrospective survey of cases reported in the English and Japanese published data of adult coronary artery disease attributed to antecedent Kawasaki disease. The mean age at presentation with cardiac sequelae was 24.7 +/- 8.4 years (range 12 to 39) for the 74 patients identified with presumed late sequelae of Kawasaki disease. Symptoms at the time of presentation with cardiac sequelae included chest pain/myocardial infarction (60.8%), arrhythmia (10.8%) and sudden death (16.2%). These symptoms were precipitated by exercise in 82% of patients. One-third of the patients in whom a chest radiograph was taken had ring calcification. Angiographic findings included coronary artery occlusion (66.1%). Extensive development of collateral vessels was reported in 44.1% of patients. Autopsy findings included coronary artery aneurysms (100%) and coronary artery occlusion (72.2%). The acute vasculitis of Kawasaki disease can result in coronary artery damage and rheologic changes predisposing to thrombus formation or progressive atherosclerotic changes that may remain clinically silent for many years. Coronary artery aneurysms and calcification on chest radiography were unusual features in this group of patients. A history of antecedent Kawasaki disease should be sought in all young adults who present with acute myocardial infarction or sudden death. [References: 76]

Chung, C. J., et al. (1996). "Kawasaki disease presenting as focal colitis." Pediatric Radiology **26**(7): 455-457.
Kawasaki disease (mucocutaneous lymph node syndrome) typically presents with fever, rash, lymphadenitis, and mucositis. The colon is rarely involved and, to date, colitis has not been described as the presenting symptom. We report the imaging findings of a child with Kawasaki disease who presented with fever and focal left colitis.

Davies, H. D., et al. (1996). "Simultaneous presentation of Kawasaki disease and toxic shock syndrome in an adolescent male." Pediatric Infectious Disease Journal **15**(12): 1136-1138.

Desgripes, A., et al. (1996). "Acute episode of cholestasis as the first manifestation of Kawasaki disease." Archives de Pediatrie **3**(7): 694-696.
Background. - Hepatic dysfunction with mild obstructive jaundice occurs occasionally in Kawasaki disease. Acute episode of cholestasis as a presenting symptom has never been reported. Case report. - A 14 year-old-boy was admitted with fever and cholestasis. He subsequently developed the classical manifestations of Kawasaki disease. No signs of liver cell injury or hepatic failure were present. Bacteriological cultures and seroimmunologic markers for viral infection remained negative. There was no ultrasonic abnormality of bile ducts. The child was given intravenous gamma globulins and salicylate. The outcome was favourable without any cardiovascular complications. Conclusion. - A persistent febrile cholestasis of unknown etiology should evoke the diagnosis of Kawasaki disease.

Dimakakos, P., et al. (1996). "A case of relapsing Kawasaki disease and review of the literature." Vasa **25**(4): 317-326.
A review of the literature was carried out on the occasion of one case of Kawasaki disease in a small infant aged 3 months which relapsed 17 years later. Kawasaki disease is of unknown aetiology and mainly affects children under 5 years of age. It is manifested as a necrotizing

vasculitis with aneurysms of the coronary arteries and the proximal medium size arteries. One hundred and fifteen thousand cases have been reported up to the present date, an incidence of 6-11/100,000 children. The evidence of coronary aneurysms range from 20-30%, while peripheral aneurysms are rare. Eighteen cases of peripheral ischemia have been reported in the international literature. The diagnosis is clinical and treatment remains symptomatic (anti-inflammatory and anticoagulant). Thrombolytic and anticoagulant management is applied in acute heart attack, and surgical bypass in chronic ischemia. Reversion of the aneurysms is observed in 60% of the cases, while relapse of the disease is possible years or decades later. Death is due to thrombosis of the coronary or rupture of the coronary or distal aneurysm. For this reason, regular fellow-up of the patients is recommended, according to the guidelines for long-term management of patients with Kawasaki disease. [References: 71]

Leung, D. Y. (1996). "Kawasaki syndrome: immunomodulatory benefit and potential toxin neutralization by intravenous immune globulin." Clinical & Experimental Immunology **104 Suppl 1**: 49-54.
Kawasaki Syndrome (KS) is an acute multi-system vasculitis of infancy and early childhood associated with the development of coronary artery abnormalities. The prevalence of cardiovascular abnormalities can be significantly reduced by treating patients during the first 10 days of illness with high-dose intravenous immune globulin (IVIG). Despite the widely held belief that KS is caused by an infectious agent, the aetiology of this illness remains controversial. Recent immunological and microbiological studies suggest a potential role for staphylococcal and streptococcal toxins (superantigens) in the pathogenesis of KS. Confirmation of these findings could result in more effective diagnostic and therapeutic approaches for the treatment of this common cause of acquired heart disease in children. [References: 41]

Nappo, A., et al. (1996). "[Youthful sudden cardiac death and the Kawasaki syndrome. An anatomopathological case report]." Minerva Cardioangiologica **44**(3): 127-132.
In 1967 Kawasaki studied 50 cases with the same features as mucocutaneous lymph node syndrome, further reported throughout Japan with the eponym of Kawasaki's disease. It is frequent in Japan and in USA, whereas in Europe it is sporadic and often misinterpreted. It presents as an acute fever, attended by irritation of the skin and oral mucosa, with swelling of cervical lymph nodes, easily misdiagnosed as scarlet fever, Stevens Johnson syndrome, or infantile exanthema or allergy. After the acute phase, Kawasaki's disease becomes chronic and sudden death is possible even if many years have elapsed. In the chronic phase, coronaritis, coronary aneurysms, marked stenosis and/or occlusive thrombosis are often present. Cardiac Lesions were classified from stage I to IV according to the duration of illness at death. The present work deals with the case of a 17 year old man, dying from undiagnosed coronary artery chronic Kawasaki disease. The patient had been hospitalized for Wolff-Parkinson-white syndrome; ten months after discharge he died suddenly, while performing gymnastics at school. Occluding thrombosis of cylindrical aneurysm of both coronary arteries, from undiagnosed Kawasaki arteritis, was found and the young boy succumbed to hyperacute infarction. The heart was fixed in buffered formalin 10% and embedded in paraffin. Histological examination of the cardiac conduction system has been carried out on serial sections, with the technique usually adopted by one of the present authors (L. Rossi). Hema-toxylin-eosin (H-E) and trichromic (Hei-denhein-azan) stainings have routinely employed. [References: 14]

1995 (5)

Alva-Espinosa, C., et al. (1995). "[Kawasaki disease: the echocardiographic diagnosis of coronary aneurysms. A report of 2 cases]." Archivos del Instituto de Cardiologia de Mexico **65**(1): 75-77.
We report two infants with Kawasaki disease and coronary aneurysms diagnosed by echocardiography. First case, a one year old male with abnormalities of left coronary artery, developed a myocardial infarction and died three weeks later. Second case a two months old

male with aneurysm in the right coronary artery who doing well three months after the diagnosis was made. Echocardiography is the primary tool for evaluation and follow up of coronary abnormalities. [References: 8]

Applegate, B. L. (1995). "Kawasaki syndrome. An important consideration in the febrile child." Postgraduate Medicine **97**(2): 121-126.
Many aspects of Kawasaki syndrome remain a mystery. The cause of the disease has eluded researchers, and its pathophysiology is a subject of much debate. However, the diagnostic features have been identified: A significant fever for at least 5 days, bilateral nonexudative conjunctivitis, erythema of the palms and soles, a polymorphic diffuse rash, cervical lymphadenopathy, and injection of the mouth and oropharynx. The recently instituted treatment protocol of high-dose aspirin with gamma globulin (Gamastan, Gammar) helps patients recover more quickly and with fewer potentially life-threatening sequelae than does aspirin alone. [References: 7]

Kawasaki, T. (1995). "General review and problems in Kawasaki disease." Japanese Heart Journal **36**(1): 1-12.
This paper discusses the brief history of Kawasaki disease, its main clinical features, diagnosis, main laboratory findings, cardiovascular complications in brief, treatment, epidemiology mainly in Japan, a summary of the pathology and concludes with five major problems which must be solved. [References: 28]

Leung, D. Y., et al. (1995). "Superantigens in Kawasaki syndrome." Clinical Immunology & Immunopathology **77**(2): 119-126.
Kawasaki syndrome (KS) is an acute multisystem vasculitis of infancy and early childhood associated with the development of myocarditis and coronary artery abnormalities. Despite the widely held belief that KS is caused by an infectious agent, there remains considerable controversy over its etiology. Recent immunologic and microbiologic studies suggest a potential role for staphylococcal and streptococcal toxins (superantigens) in the pathogenesis of KS. Confirmation of these findings could result in more effective diagnostic and therapeutic approaches to this common cause of acquired heart disease in children. [References: 48]

Takahashi, N., et al. (1995). "Occlusion of the right coronary artery as sequelae of Kawasaki disease: The clinical features of 9 cases." Cardiology **86**(3): 207-210.
Among the 302 children with Kawasaki disease (KD) who were evaluated by angiography from 1973 through 1992, 9 (3.0%) had either an occlusion (OC) or segmental stenosis (SS) of the right coronary artery. The interval from the onset of KD to the recognition of OC or SS ranged from 0.5 to 7.7 years (median 4.0 years). Left coronary arterial lesions were also present in 8 of 9 patients. In spite of severe sequelae, children or young adolescents with cardiovascular system-related symptoms were unexpectedly rare, Asymptomatic patients, however, are also at risk of developing myocardial infarction since they have been shown to have a high rate of abnormalities on myocardial scintigraphy. A close observation and careful follow-up are thus considered to be indispensable.

1994 (6)

Gidding, S. S. and S. T. Shulman (1994). "Diagnosis and management of children with Kawasaki disease." Heart Disease & Stroke **3**(4): 210-215.
Significant progress has been made in understanding the epidemiology, natural history, and management of Kawasaki disease since 1967. The introduction of intravenous gamma globulin therapy as well as more vigilant care has reduced the mortality rate to well below 1%. Major goals for future research are to identify the etiology and pathogenesis of Kawasaki disease and

the associated coronary artery disease and to develop more precise diagnostic techniques and therapy. [References: 13]

Kato, H., et al. (1994). "[Kawasaki vasculitis]." Nippon Rinsho - Japanese Journal of Clinical Medicine **52**(8): 2095-2102.
Kawasaki disease is an acute febrile illness recognized most often in children under 4 years of age. It is characterized by mucosal inflammation, indurative edema of the hands and feet, skin rash and cervical lymphadenopathy. This is an acute systemic vasculitis syndrome of unknown etiology which has been recognized not only in Japan but all over the world. This article reports on the clinical spectrum of Kawasaki disease, analysis of coronary artery and other lesions, and long-term cardiovascular problems including premature atherosclerosis. The etiology and pathogenesis of this disease are still unknown. Current hypotheses and leading studies on the etiology and the pathogenesis of Kawasaki disease are also reviewed. [References: 31]

Pongratz, G., et al. (1994). "Myocardial infarction in an adult resulting from coronary ancurysms previously documented in childhood after an acute episode of kawasaki's disease." European Heart Journal **15**(7): 1002-1004.
Coronary aneurysms resulting from a previous episode of Kawasaki's disease are considered an important cause of myocardial infarction in children. A case of a 19-year-old man presenting with an acute myocardial infarction associated with coronary aneurysms is described. These coronary lesions were previously evaluated angiographically and echocardiographically at the age of 13 years, 5 months after the acute episode of a Kawasaki's disease. © 1994 The European Society of Cardiology.

Schaller, J. G. (1994). "Aggressive treatment in childhood rheumatic diseases." Clinical and Experimental Rheumatology **12**(SUPPL. 10): S97-S105.
Much remains to be learned about the optimal therapy for children with rheumatic diseases. Current therapies remain inexact and are aimed at either the inflammatory or the immune responses of patients. There have been a few advances, for example in the treatment of children with dermatomyositis, lupus and, in particular, Kawasaki disease. Progress in the treatment of juvenile rheumatoid arthritis (JRA) and the spondylarthropathies has lagged behind, however, although methotrexate does appear to be promising in the short-term treatment of JRA. Another urgent problem which remains to be resolved is the identification of those children who will have poor outcomes and who warrant early, aggressive treatment. A number of interesting alternative therapies for adults have been proposed, but their applicability to children remains an open question. Further investigation of combined therapies with various drugs also warrants exploration.

Senzaki, H., et al. (1994). "Acute heart failure and acute renal failure in Kawasaki disease." Pediatrics International **36**(4): 443-447.
Acute renal failure and acute heart failure are rare in Kawasaki disease. We experienced two patients with Kawasaki disease who presented acute renal failure and acute heart failure. These two patients gave us an important insight into the understanding of water balance and fluid therapy in Kawasaki disease. One patient showed acute prerenal failure due to fluid exudation from the intravascular to the extravascular space, and subsequent acute heart failure. The other patient showed acute heart failure caused by fluid infusion for the treatment of dehydration. It is suggested that acute renal failure could be caused by a fluid shift from the intravascular to the extravascular space in Kawasaki disease. It is also demonstrated that the reserve of cardiac function could be decreased in patients with Kawasaki disease due to myocarditis even with normal echocardiography and chest X-rays. 1994 Japan Pediatric Society

Yamamoto, L. G. and J. E. Martin (1994). "Kawasaki syndrome in the ED." American Journal of Emergency Medicine **12**(2): 178-182.

In a retrospective case review of inpatient and emergency department (ED) records during a 55-month period, 155 hospitalizations for Kawasaki syndrome (KS) were identified, of which 44 were seen in the ED. In 16 cases, KS was already suspected by their private physicians and confirmed in the ED by a KS specialist. In the remaining 28, patients presented initially to the ED. In 18 of these 28 (64%), KS was identified or suspected in the ED. In the other 10, the diagnosis was delayed. In four instances, patients were hospitalized for other reasons. In all cases in which the diagnosis of KS was not made in the ED, viral infections or sepsis were suspected. One child presented to the ED in respiratory arrest and severe bradycardia. [References: 22]

1993 (8)

Blakeley, S. L. and P. R. Cohen (1993). "Kawasaki syndrome: a case report." Cutis **52**(2): 117-120.
A four-year-old black boy with Kawasaki syndrome is reported. The child was treated with intravenous gamma globulin and aspirin. He had no disease-associated adverse sequelae. The clinical findings, diagnostic criteria, and treatment of Kawasaki syndrome are reviewed. [References: 17]

Dajani, A. S., et al. (1993). "Diagnosis and therapy of Kawasaki disease in children." Circulation **87**(5): 1776-1780.

Ducos, M. H., et al. (1993). "[Cutaneous manifestations of Kawasaki disease. Apropos of 30 cases]." Annales de Dermatologie et de Venereologie **120**(9): 589-597.
A series of 30 cases of Kawasaki disease has been studied retrospectively over a period of 11 years. The aim was to reassess the diagnostic value of the dermatological manifestations. A modification of the extremities was observed in 28 patients (23 had early inflammatory lesions, 25 had late desquamation). Exanthema was constant, polymorphous and most often urticaria-like. Vesicles, pustules or purpura were noted during the course of the eruption in 7 patients. A perineal eruption was observed in 17 cases and was found of good diagnostic value even though not pathognomonic. Cheilitis was the most frequent of buccopharyngeal modifications (93 p. 100). Conjunctival hyperemia was noted in 26 patients. Eight children had cardiovascular complications. Among these cases, the modification of the extremities seemed to be more pronounced and stomatitis and arthritis were apparently more frequent. Most of all, the inflammatory syndrome was significantly more severe as concerns CRP and polymorphonuclear leukocytes counts. Dermatological examination often rules out other diagnoses, such as measles, scarlet fever and staphylococcal toxic shock syndrome. However, a complete etiological workup remains mandatory. [References: 59]

Elamin, A. (1993). "Kawasaki disease in a Sudanese family." Annals of Tropical Paediatrics **13**(3): 263-268.
Kawasaki disease (mucocutaneous lymph node syndrome) is an acute inflammatory multisystem disease of children. The acute phase of the disease is characterized by high grade fever, conjunctivitis, exanthematous skin rash and non-suppurative lymph node enlargement. The subacute phase follows with the manifestations of arthritis, myocarditis and thrombocytosis. The disease is self-limiting in most children but is associated with coronary artery aneurysms in 15-20% of cases. The aetiology is unknown, but results of epidemiological studies suggest that an unidentified infectious agent might be the causative factor. Since the first description of the disease by the Japanese doctor, Tomisaku Kawasaki, in 1967 and his report for the English literature in 1974, thousands of cases have been reported worldwide. The highest prevalence is found in Japan and among the Japanese in Hawaii, followed by the United States. Although the disease was first reported in Africa in 1979, to date only four cases have been reported there. The following account reviews the literature and describes the manifestations of Kawasaki disease as seen in two siblings in Khartoum, Sudan. [References: 43]

Shaukat, N., et al. (1993). "Myocardial infarction in a young adult due to Kawasaki disease. A case report and review of the late cardiological sequelae of Kawasaki disease." International Journal of Cardiology **39**(3): 222-226.
Although Kawasaki disease is generally self-limiting, 15-25% of children with Kawasaki disease may develop significant cardiovascular sequelae, presentation may occur acutely or late (death has been reported up to 14 years after the acute illness). The most common late complication is the persistence of coronary artery aneurysms, these may produce myocardial ischaemia and even myocardial infarction, valvular dysfunction has also been reported. However the occurrence of late abnormalities of myocardial function is controversial. We describe a 24-year-old man who presented with myocardial infarction as a result of coronary artery aneurysms caused by Kawasaki disease, he gave no recent or childhood history of prodromal illness compatible with Kawasaki disease. The diagnosis was confirmed at post mortem. [References: 14]

Shreve, B. (1993). "Kawasaki disease: early treatment/positive results--one family's story." Pediatric Nursing **19**(6): 607-610.
Kawasaki disease is appearing with increasing frequency in the U.S. A childhood disease of unknown etiology, it is characterized by an acute self-limiting inflammation of the systemic vascular system affecting multiple organs. This article presents a single case of a 13-month old Caucasian male patient diagnosed and treated early for Kawasaki disease. Also included are the incidence of the disease, the clinical manifestations, a review of current literature, the treatment provided, and the nursing implications. [References: 26]

Smith, P. K. and P. N. Goldwater (1993). "Kawasaki disease in Adelaide: a review." Journal of Paediatrics & Child Health **29**(2): 126-131.
The role of Kawasaki disease (KD) as a contributor to early childhood cardiac morbidity in Adelaide was investigated by a review of hospital admission and case-note data from January 1979 to June 1990. There were 57 episodes in 55 patients. The epidemiological data in this South Australian series are similar to that seen in other Australian and New Zealand centres and correlate better with the clinical data from North America than from Japan. The average age of admission was 3.2 years (median 2.7 years) with 38 and 85% of cases being less than 2 and 5 years respectively. The male to female ratio was 1.5. The incidence of KD in the 0-5 year age group was 3.9 cases per 100,000 children. This series represents a minimum number of cases for this period and illustrates an association of aneurysm-risk with prolonged fever; improved defervescence with the combination of intravenous gamma-globulin (IVGG) and aspirin compared with aspirin alone; and a more severe disease process in the very young. The series supports the efficacy of single dose IVGG therapy. Antibiotics were given prior to diagnosis of KD in 79% of patients, often causing diagnostic confusion with possible drug reactions. The pathogenic mechanisms of KD are reviewed and a new hypothesis is proposed that incorporate mechanisms of vessel pathology resulting from release of endothelin and recognized mediators of endothelial damage including tumour necrosis factor-alpha and interleukin-1 beta. [References: 45]

Sundel, R. P., et al. (1993). "Gamma globulin re-treatment in Kawasaki disease." The Journal of Pediatrics **123**(4): 657-659.
We retrospectively reviewed the effects of intravenous γ-globulin (IVGG) re-treatment of 13 children with Kawasaki disease and persistent or recrudescent fever. Fever and mucocutaneous inflammation resolved within 48 hours in nine patients; fever abated in two other children after a third course of IVGG. We conclude that IVGG re-treatment of Kawasaki disease appears to be safe and may improve the clinical course.

Fiano Valverde, M. C., et al. (1992). "[Atypical Kawasaki disease: presentation of a case and review of the literature]." Anales Espanoles de Pediatria **36**(3): 235-238.

Kazi, A., et al. (1992). "Uvulitis and supraglottitis: Early manifestations of Kawasaki disease." The Journal of Pediatrics **120**(4 PART 1): 564-567.
Two children with Kawasaki disease initially had upper respiratory tract manifestations. The first was admitted with a diagnosis of uvulitis; in the second the clinical picture was chracterized by supraglottic involvement, confirmed by direct laryngoscopic examination. © 1992 Mosby-Year Book, Inc.

1991 (5)

Barron, K. S. (1991). "Kawasaki disease. Epidemiology, late prognosis, and therapy." Rheumatic Diseases Clinics of North America **17**(4): 907-919.
Kawasaki disease is an immunologically mediated diffuse vasculitis of childhood of unknown etiology. While most of the clinical features--including diffuse mucosal inflammation, indurative edema, rash, and lymphadenopathy--are self-limiting, coronary artery aneurysms and the possibility of thrombotic occlusion occurs in up to 20% of children. The epidemiologic and clinical features of this disease suggest an infectious etiology; however, a specific organism has not been consistently identified. An abnormal immune response to this as yet to be defined organism plays a critical role in the progression of this disease. The morbidity and mortality of this disease are related primarily to the potential cardiovascular complications. The natural history of the coronary artery aneurysms is that most lesions regress with time. Factors leading to a higher probability of regression include age less than 1 year, female sex, fusiform aneurysm, and maximum diameter less than 4 mm. Current recommendations for therapy include aspirin and IVIG. The range of dosages regimens for each medication are discussed in the text. [References: 71]

Kadar, K., et al. (1991). "[Coronary artery anomalies studied by Doppler echocardiography in infancy and childhood--possibilities and limitations]." Orvosi Hetilap **132**(29): 1581-1586.
We investigated infants with Kawasaki disease, congenital coronary artery fistulas and anomalous origin of the left coronary artery from the pulmonary trunc (Bland-White-Garland syndrome) by 2-dimensional and Doppler echocardiography. We describe the systematic approach for visualizing in detail coronary anatomy by two-dimensional echocardiography. Our results suggest that this echocardiographic technique is useful for detecting coronary anomalies and has a great rolbefore angiocardiography especially in sick babies. We recommend performing 2-dimensional echocardiography in the acute and chronic stage of Kawasaki disease for evaluating coronary arterial aneurysms. [References: 26]

Leung, D. Y. (1991). "The potential role of cytokine-mediated vascular endothelial activation in the pathogenesis of Kawasaki disease." Acta Paediatrica Japonica **33**(6): 739-744.
Kawasaki disease (KD) is an acute febrile illness of infancy and early childhood characterized by diffuse vasculitis. Although the disease is generally self-limited, up to 30% of untreated patients with KD may develop coronary artery (CA) abnormalities. The acute phase of KD is characterized by marked activation of the immune system leading to increased cytokine production by immune effector cells, the induction of activation antigens on their vascular endothelium and the generation of lytic antibodies directed against vascular endothelial cells (EC) stimulated with cytokines. Treatment with intravenous gammaglobulin (IVGG) usually rapidly reduces acute clinical symptoms and prevents CA abnormalities. Immunologically, successful IVGG treatment is associated with decreased lymphocyte activation, reduced cytokine secretion and the loss of cytokine induced expression of leukocyte adhesion molecules on vascular endothelium. The association between improvement of clinical symptoms with the reduction of cytokine secretion, and reversal of EC activation supports a role for immune mediated injury to cytokine induced EC

antigens in the pathogenesis of this disorder. [References: 38]

Tomiyama, J., et al. (1991). "Acute febrile mucocutaneous lymph node syndrome (Kawasaki disease) in adults: case report and review of the literature." Japanese Journal of Medicine **30**(3): 285-289.
A 25-year-old female meeting all six criteria for Kawasaki disease is reported. A total of 22 reported cases of adult Kawasaki disease, including the present case, are reviewed. In adult Kawasaki disease, arthralgia, gastrointestinal complications and hepatic dysfunction are seen more frequently than in childhood cases. Cardiac complications are rarely seen in adult Kawasaki disease. Two cases have been positive for anti-nuclear antibody (ANA). The present patient had increased levels of serum IgE and was positive for ANA, suggesting involvement of an immune mechanism. Adult Kawasaki disease is rare but appears to be on the increase; internists treating adults must be aware of this disease. [References: 25]

Zsadanyi, J., et al. (1991). "[Fatal outcome of Kawasaki syndrome in a 4-week-old infant]." Orvosi Hetilap **132**(38): 2101-2103.
A male infant at 4 weeks of age with features of Kawasaki disease is described who died at the end of the second week of his illness in consequence of serious pneumonia. The diagnosis was confirmed by laboratory tests and post mortem histological examinations. The latter showed systemic vasculitis without any changes of coronary arteries. [References: 16]

1990 (6)

Cuttica, R. J. (1990). "Kawasaki disease and vasculopathies." Current Opinion in Rheumatology **2**(5): 809-816.

Gallagher, P. G. (1990). "Facial nerve paralysis and Kawasaki disease." Reviews of Infectious Diseases **12**(3): 403-405.
A case of facial nerve paralysis in a patient with Kawasaki disease is described, and 17 cases in the literature are reviewed. A female predominance and a high rate of cardiovascular involvement were noted in patients with facial nerve paralysis and Kawasaki disease. The paralysis was self-limited, resolving without treatment in all surviving patients. [References: 13]

Nakashima, L. and D. L. Edwards (1990). "Treatment of Kawasaki disease." Clinical Pharmacy **9**(10): 755-762.
The epidemiology, etiology, diagnosis, and treatment of Kawasaki disease are reviewed. Kawasaki disease, or mucocutaneous lymph node syndrome, is an acute, usually self-limiting, multiple-organ-system disease of childhood that occurs both epidemically and endemically worldwide. The etiology of the disease is unknown but may involve an infectious agent. To be diagnosed, a patient must be febrile for at least five days and show four of five additional clinical features: bilateral conjunctivitis, changes in the oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. The most important complications are cardiac; patients may develop aneurysms or thrombosis of the coronary arteries or myocarditis. Other complications include arthritis, conjunctivitis, and hydrops of the gallbladder. Aspirin, intravenous immune globulin, corticosteroids, and antithrombotic agents have been investigated for use in the treatment of Kawasaki disease with varying results. Current recommendations suggest therapy with aspirin 80-100 mg/kg/day every six hours for the first 14 days after diagnosis and intravenous immune globulin 400 mg/kg/day for the first four days. The dose of aspirin should then be reduced and continued for six to eight weeks if no coronary artery abnormalities are present. Treatment guidelines for Kawasaki disease are being refined. Current evidence supports early use of aspirin and intravenous immune globulin to prevent cardiac complications.

Rothfield, R. E., et al. (1990). "Peritonsillar abscess in Kawasaki disease." International Journal of

Pediatric Otorhinolaryngology **20**(1): 73-79.
Mucocutaneous lymph node syndrome, Kawasaki disease, is a potentially fatal pediatric disease characterized by prolonged high fever, conjunctivitis, stomatitis. myocarditis, aseptic meningitis and coronary artery vasculitis. We present peritonsillar abscess as a previously unreported otolaryngologic symptom and presentation of Kawasaki disease. A previously healthy 7-year-old boy required hospitalization for a peritonsillar abscess. Despite adequate surgical drainage and appropriate intravenous antibiotics, the patients' systemic symptoms persisted. After the week of hospitalization, the child was transferred to the intensive care unit with acute myocarditis, heart failure and severe arthritis. The diagnosis of Kawasaki disease was confirmed with echocardiographic evidence of coronary artery aneurysms and the development of the characteristic hand and foot desquamation. The patient's symptoms resolved with salicylates and intravenous gamma globulin therapy. He was discharged in good condition after 3 weeks of hospitalization. This is the first report of Kawasaki syndrome presenting with peritonsillar abscess. Although we discuss a unique presentation of this disease. Kawasaki syndrome often exhibits other otolaryngologic findings early in its course. A literature review of the clinical characteristics, pathogenesis and therapy of this disease is presented. [References: 9]

Takagi, K., et al. (1990). "[Meningoencephalitis in Kawasaki disease]." No to Hattatsu [Brain & Development] **22**(5): 429-435.
Kawasaki disease (KD) is a syndrome characterized by various degrees of vasculitis in small-and medium-sized arteries. We discussed the characteristic manifestations and prognosis of 5 KD patients (male 3, female 2) with meningoencephalitis in the acute stage. The incidence was 3.7% (5 of 138 patients) in our institute. The age of onset was between 3 months and 15 months. The clinical manifestations included disturbance of consciousness and seizures; disturbance of consciousness developed in all patients in the early acute stage. The duration was between 2 and 11 days; seizures developed as status convulsions in two. Electroencephalograms (EEG) demonstrated certain abnormalities in 2 of 4 patients studied. Computed-tomographic scanning (CT scan) revealed fluid collection in the frontal extracerebral space, and monocyte-predominant pleocytosis was observed in the cerebrospinal fluid (CSF) in all 5 patients studied. The age of onset in the 5 KD patients was significantly earlier than that in non-complicated cases (n = 138, P less than 0.01). Blood hemoglobin (P less than 0.05) and hematocrit (P less than 0.05), serum total protein (P less than 0.01), and serum albumin levels (P less than 0.01) were also significantly lower. Moreover the period until CRP values turned negative was significantly longer (P less than 0.05) and erythrocyte sedimentation rate was significantly lower (P less than 0.01) in these 5 patients. It was considered that meningoencephalitis in KD may develop in cases having more severe and prolonged inflammatory changes; the clinical findings revealed a serious form of KD. We suggest that this might because by vasculitis of small arteries, arterioles, capillaries, and venules, which consists of infiltration of lymphocytes and large mononuclear cells, and edema. There was no neurological sequela in 4 of the 5 patients. However, one patient was found to have hearing difficulty 3 years after the onset. Therefore, the prognosis of meningoencephalitis in KD was considered to be generally favorable. [References: 20]

Zanchetta, S., et al. (1990). "[Kawasaki disease: between mystery and reality. A clinical contribution]." Pediatria Medica e Chirurgica **12**(3): 243-250.
Kawasaki disease was described by T. Kawasaki in Japan in 1967 and since then numerous cases have been reported from all over the world. The Authors reports a review of the literature on the main epidemiologic, clinical, etiopathogenetic aspects of the Kawasaki disease, pointing up the present therapeutical trends and the importance of a correct follow-up. A case is reported of children with a particularly complete M.K.: she presented fever, mucosal hyperemia, lymph node swelling, cutaneous rash and desquamation of the fingers of hands and feet. Furthermore leukocytes platelets, alpha 2 globulins and ESR were raised. [References: 80]

1989 (5)

Allal, J., et al. (1989). "[Value of echocardiography in the diagnosis of a complicated form of Kawasaki's disease]." Archives des Maladies du Coeur et des Vaisseaux **82**(8): 1443-1449.
Kawasaki disease affects children under 4 years of age and is characterized by fever, mucocutaneous rash and cervical lymph node enlargement. It is often complicated by coronary vasculitis and/or pericarditis, myocarditis and endocarditis. Echocardiography is indispensable to diagnose and follow up these complications. A study of the literature and of 4 personal patients showed that it is also useful for the early detection of coronary aneurysm and simple dilatation of the coronary arteries. The sensitivity and specificity of echocardiography in recognizing these complications are such that coronary angiography is exceptionally required. In the search for a cause of prolonged fever in children, the sensitivity of echocardiography makes it possible to diagnose an atypical form of Kawasaki disease. [References: 30]

Choi, Y. S. and B. Sharma (1989). "Gallbladder hydrops in mucocutaneous lymph node syndrome." Southern Medical Journal **82**(3): 397-398.
A 36-month-old boy had acute gallbladder hydrops in association with mucocutaneous lymph node syndrome. A review of 46 other cases of this association has shown that patients having MLNS with gallbladder hydrops are older than those without gallbladder hydrops. The diagnosis is suggested by abdominal symptoms and abnormal results of liver function tests. The diagnosis is confirmed by ultrasonography, which shows the gallbladder to be twice the normal size. Cardiac complications may be increased. Treatment is largely supportive, but cholecystostomy is the procedure of choice in cases requiring operative intervention. [References: 27]

Leung, D. Y. (1989). "The immunologic effects of IVIG in Kawasaki disease." International Reviews of Immunology **5**(2): 197-202.
Kawasaki disease (KD) is an acute febrile illness of early childhood that is associated with the development of coronary artery aneurysms in 15-25% of the cases. The acute phase of KD is characterized by a deficiency of suppressor T cells, marked activation of the immune system and increased secretion of cytokines by immune effector cells. Evidence that this immune activation contributes to the vascular endothelial cell damage in KD is suggested by the observation that patients in the acute phase of KD have circulating antibodies lytic for vascular endothelial cells activated with gamma interferon, IL-1 or tumor necrosis factor. In contrast, sera from these patients do not lyse unstimulated endothelial cells. High dose intravenous gammaglobulin (IVGG) treatment is effective in preventing the occurrence of coronary artery abnormalities in KD. Patients treated with IVGG have a significant increase in T suppressor cells, a decrease in circulating activated T helper cells, and a decrease in spontaneous IgG and IgM synthesis. These observations suggest that IVGG reduces the vasculitis in KD by suppressing the marked immune activation associated with this disease. [References: 24]

Rauch, A. M. (1989). "Kawasaki syndrome: issues in etiology and treatment." Advances in Pediatric Infectious Diseases **4**: 163-182.
To date several infectious agents have been proposed to cause KS, but none of these agents have been consistently demonstrated in KS. Epidemiologic studies suggest that host factors, including age, race, and sex, play an important role in KS. One hypothesis is that primary infection or activation of a latently infecting agent may play a role in KS; the other factors may be related to KS by activating such an agent. The 13 to 30 days between rug or carpet cleaning and onset of KS may represent an incubation or induction period for an infectious agent. The presence of certain epidemiologic risk factors and infectious agents in some outbreaks and not in others is puzzling (Table 4). Nevertheless, there are precedents for intermittently occurring epidemiologic risk factors, as with hepatitis, in which enteral and parenteral transmission can occur with the associated risk factors for each mode of transmission. The mechanisms by which the intermittently associated epidemiologic risk factors of antecedent illness and exposure to

recently shampooed or spot-cleaned rugs or carpets relate to KS remain unknown. Similarly, how living near a body of water relates to KS awaits further clarification. The cause of KS remains a fascinating and controversial question, and the answer continues to grow in importance with the increasing health impact of this disease. As more data accumulate, high-dose IVIG therapy appears to brighten the outlook for KS patients as we await identification of the cause of this disease and more definitive treatment. Because we have just begun to use this therapy in KS, it is most important that any adverse effects that may occur be brought to the attention of the medical community. One question regarding KS will remain unanswered for years, that is, long-term sequelae of the disease in both treated and untreated patients. There have been a few anecdotal reports of onset of exertional angina in children several years after onset of KS. Histopathologic studies of coronary vessels of five KS patients who died of causes unrelated to KS and who apparently had completely recovered from the illness revealed abnormalities of the coronary vessels, primarily changes in the intima and internal elastic lamina. This has led to speculation that patients with a history of KS may have some coronary artery lesions not serious enough to be clinically detectable or to become an immediate cause of death but which may lead to juvenile arteriosclerosis.(ABSTRACT TRUNCATED AT 400 WORDS) [References: 91]

Shulman, S. T. (1989). "IVGG therapy in Kawasaki disease: mechanism(s) of action." Clinical Immunology & Immunopathology **53**(2 Pt 2): S141-146.
Kawasaki disease (mucocutaneous lymph node syndrome) has emerged as a major pediatric disorder throughout the developed world, including the United States where it is now a leading cause of acquired heart disease in children. Coronary artery abnormalities, including ectasia, aneurysms, stenosis, and thrombosis, that may result in myocardial ischemia and/or infarction, develop in approximately 20-25% of patients as a consequence of coronary arteritis. Although epidemiologic and clinical findings strongly suggest an infectious etiology, the etiology of Kawasaki disease remains unknown. Marked immune activation is present in the acute state of Kawasaki disease. Investigators in Japan and a U.S. multicenter investigative group have demonstrated in controlled studies that administration of IVGG early in the course of Kawasaki disease is associated with (i) a striking anti-inflammatory effect, and (ii) a marked reduction in the development of coronary abnormalities, as assessed by echocardiography and/or angiography. The mechanism(s) by which IVGG produces these dramatic effects is unclear. Possible mechanisms include (i) Fc receptor blockade, (ii) a direct anti-etiologic agent (neutralization) effect, (iii) an anti-toxic effect, (iv) an immunomodulating effect possibly mediated either by anti-idiotypic antibodies or by induction of suppressor T cells, and (v) down-regulation of cytokine production by activated immune cells. Clarification of the mechanism of action of IVGG in Kawasaki disease should provide insights into the pathogenesis and/or the etiology of this fascinating disorder. [References: 23]

1988 (1)

Kalamkarian, A. A., et al. (1988). "[Clinical cases of the mucocutaneous syndrome (Kawasaki syndrome)]." Vestnik Dermatologii i Venerologii(11): 64-66.

1987 (7)

Bligard, C. A. (1987). "Kawasaki disease and its diagnosis." Pediatric Dermatology **4**(2): 75-84.
Mucocutaneous lymph node syndrome, or Kawasaki disease, is a febrile, exanthematous disease of children that has potentially fatal complications. The most important complication is the development of aneurysms in the coronary arteries, which may thrombose or occasionally, rupture and cause severe morbidity or death. Criteria for the diagnosis of Kawasaki disease have been developed that may help the clinician make the diagnosis and prevent complications. The

major criteria include fever, skin eruption, ocular changes, oral changes, changes in the extremities, and lymphadenopathy. Prognosis may be evaluated by the clinical picture and cardiac work-up with echocardiogram. [References: 86]

Hansson, G. K. (1987). "Pathogenetic mechanisms of arteritis in Kawasaki disease--a critical analysis." Progress in Clinical & Biological Research **250**: 383-394.

Hattori, T., et al. (1987). "Facial palsy in Kawasaki disease. Report of two cases and a review." European Journal of Pediatrics **146**(6): 601-602.
A case of facial palsy was reported initially in 1974 by Murayama as one of the neurological manifestations in Kawasaki disease. Thereafter, an additional nine case have been documented in Japan. This facial palsy, in the revised "Diagnostic Guideline of Kawasaki Disease" released in 1984, has been added recently as one of the neurological signs and symptoms of Kawasaki disease. This is a report on two cases of Kawasaki disease showing facial palsy with indurative oedema during their clinical course, and also a clinical review of the ten previously reported cases of facial palsy complicating Kawasaki disease. [References: 10]

Hedoui, M. M., et al. (1987). "[Kawasaki syndrome in Tunisia. Apropos of 2 new cases]." Tunisie Medicale **65**(5): 343-347.

Landing, B. H. and E. J. Larson (1987). "Pathological features of Kawasaki disease (mucocutaneous lymph node syndrome)." American Journal of Cardiovascular Pathology **1**(2): 218-229.
Kawasaki disease (mucocutaneous lymph node syndrome) (MCLS) is an apparently infectious disease, an etiological agent of which has not been established, with peak age incidence at about 1 year, but with progressively fewer cases occurring into the fourth decade. Early clinical features include fever, rash, conjunctival injection, dry reddened lips, oropharyngeal reddening, enlarged cervical nodes, and swelling and redness of hands and feet. Peeling of skin of fingers and toes, arthralgia, and marked thrombocytosis are frequent 1-2 weeks after onset. Myocarditis, cardiac valvulitis, and lymphocytic or mixed interstitial infiltration of pancreas, renal, splenic, and hepatic hilar regions are seen in the early phase, but arteritis, typically of extraparenchymal arteries, is the most important aspect of MCLS, hence the term infantile periarteritis nodosa, formerly applied to fatal cases of MCLS. Thrombosis of coronary artery aneurysms is the most common cause of death (rate about 0.5%). The peak time of death is 3-4 weeks from onset, but death from coronary occlusion has been seen as late as 14 years after the acute phase. Aneurysmal rupture with hemopericardium or retroperitoneal hemorrhage is rare, as are late brachial, iliac, or other arterial aneurysms. Pathological features of MCLS in the early and later stages are described and illustrated, and the epidemiologic, etiologic, forensic, and other aspects of the disease are discussed. [References: 46]

Medicus, L. (1987). "Kawasaki disease: what is this puzzling childhood illness?" Heart & Lung **16**(1): 55-60.

Suddleson, E. A., et al. (1987). "Hydrops of the gallbladder associated with Kawasaki syndrome." Journal of Pediatric Surgery **22**(10): 956-959.
Hydrops of the gallbladder is recognized as a major component of the abdominal crisis occurring in children with Kawasaki syndrome. Sixteen patients with hydrops of the gallbladder secondary to Kawasaki syndrome have been diagnosed and treated at the Childrens Hospital of Los Angeles. One patient was treated by cholecystectomy and 15 nonoperatively without untoward sequelae. Nonoperative management with serial ultrasonic evaluation and close clinical monitoring is a safe method of treatment for this entity. Pathologic and clinical data are presented and discussed. Review of diagnosis and treatment of 41 reported cases of hydrops of the gallbladder in Kawasaki syndrome from the English language literature is also presented. [References: 12]

1985 (2)

Kato, H. and M. Morimatsu (1985). "[Kawasaki disease and infantile polyarteritis]." Nippon Rinsho - Japanese Journal of Clinical Medicine **43**(10): 2108-2116.

Pitruzzella, E., et al. (1985). "[Kawasaki's syndrome in Italy. Review of the literature and personal contribution]." Pediatria Medica e Chirurgica **7**(6): 869-877.
Clinical outcome, lab examinations, therapy and aetiological theories of Kawasaki disease are discussed. All cases diagnosed in Italy since 1977 to 1984 have been collected (64 patients). This review shows that the disease affected mainly children from 3 months of age to 4 year, with a male to female ratio of 1.5:1 and the outcome was quite always benign, a part from a single case that went to death, with an overall mortality of 1 out of 64. Two cases observed from the AA are extensively described. The outcome was benign and one case showed high level of IgE. We stress that even if the Kawasaki disease is occasionally seen in our country, the physician must know the major features not to oversee the diagnosis. [References: 56]

1984 (1)

Kubryk, N. and M. Borde (1984). "[Kawasaki syndrome. Apropos of a case]." Semaine des Hopitaux **60**(8): 583-587.
We report the case of a twelve-year old boy with a disease fitting the diagnostic criteria for Kawasaki disease as defined by the Japanese research committee on this mucocutaneous lymph node syndrome. Although Kawasaki disease has been reported throughout the world, it is more prevalent in Japan. Etiology is unknown. An immunologic mechanism is likely. Main manifestations are an acute febrile mucocutaneous syndrome with enlargement of cervical lymph nodes. Cardiovascular involvement is responsible for death in 1 to 2% of cases and makes prolonged follow-up requisite. Some authors believe Kawasaki disease and infantile periarteritis nodosum to be the same condition. Acetylsalicylic acid seems to prevent cardiovascular complications. [References: 25]

1983 (3)

Campelli, A., et al. (1983). "[Kawasaki disease: a new pediatric nosological entity]." Pediatria Medica e Chirurgica **5**(1-2): 119-131.
Kawasaki disease (KD) is a new, well characterized pediatric syndrome. In this work the last epidemiologic, diagnostic and clinical data are pointed. Especially the heart-disease and its monitoring and therapy are studied. Our casuistry (5 cases in 4 years) is also presented. The international literature and our clinical experience suggest that KD is more spread than we think and therefore in needs to be studied carefully by the pediatricians. [References: 78]

Kato, H., et al. (1983). "[Kawasaki disease and polyarteritis of infants]." Ryumachi **23**(5): 376-381.

Zernov, N. G., et al. (1983). "[Kawasaki disease (mucocutaneous lymph node syndrome in children)]." Pediatriia(4): 71-73.

1982 (2)

Melish, M. E. (1982). "Kawasaki syndrome (the mucocutaneous lymph node syndrome)." Annual Review of Medicine **33**: 569-585.

Kawasaki Syndrome is a newly recognized clinical entity characterized by multisystem involvement. It has an acute onset and a triphasic clinical course. Although essentially a self-limited disease, permanent vascular damage, especially involving the coronary arteries, may result. Pathologically the disease is characterized by widespread vasculitis. There is a monomodal age distribution with peak occurrence during the first 2 years of life; few affected over the age of 8 years. Males outnumber females 1.5:1, persons of Japanese extraction are overrepresented compared with other races, and Caucasians are underrepresented. Community-wide epidemics occur in diverse locations but there is no evidence for direct person-to-person transmission. Etiology remains unknown. Therapy remains supportive and should be directed at careful clinical evaluation for cardiovascular abnormalities and antiplatelet aggregation therapy. [References: 116]

Taylor, M. H. and D. S. Peterson (1982). "Kawasaki's disease." Journal of the American Dental Association **104**(1): 44-47.

1980 (1)

Wingen, A. M. and E. Kleihauer (1980). "[Kawasaki syndrome--a new disease?]." Klinische Padiatrie **192**(3): 173-178.
Kawasaki recognized in 1967 the acute febrile mucocutaneous lymph node syndrome (MCLS) as a well defined entity among a variety of hitherto unidentified atypical exanthems. The etiology is uncertain. There are close relations to infantile polyarteritis nodosa (IPN) which is probably the severe variant of Kawasaki's disease. Histologically it is a generalized necrotizing vasculitis, most probably caused by circulating immune complexes. The disease is supposed to be initiated by various infections in patients with certain predispositions. Considerations about etiology and pathogenesis as well as relations to IPN are mainly discussed theoretically. Therefore it is recommended to investigate the Kawasaki syndrome following a devised protocol. [References: 81]

1979 (1)

South, A. M., et al. (1979). "ACE2, COVID-19, and ACE Inhibitor and ARB Use during the Pandemic: The Pediatric Perspective." Hypertension(pagination).
Potential but unconfirmed risk factors for coronavirus disease 2019 in adults and children may include hypertension, cardiovascular disease, and chronic kidney disease, as well as the medications commonly prescribed for these conditions, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Coronavirus binding to angiotensin-converting enzyme 2, a crucial component of the renin-angiotensin-aldosterone system, underlies much of this concern. Children are uniquely impacted by the coronavirus but the reasons are unclear. This review will highlight the relationship of coronavirus disease 2019 with hypertension, use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and lifetime risk of cardiovascular disease from the pediatric perspective. We briefly summarize the renin-angiotensin-aldosterone system and comprehensively review the literature pertaining to the angiotensin-converting enzyme 2/angiotensin-(1-7) pathway in children and the clinical evidence for how angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers affect this important pathway. Given the importance of the angiotensin-converting enzyme 2/angiotensin-(1-7) pathway and the potential differences between adults and children, it is crucial that children are included in coronavirus-related research, as this may shed light on potential mechanisms for why children are at decreased risk of severe coronavirus disease 2019.

Title Page

Running Title: Intravenous Immunoglobulin of COVID-19

Effectiveness of Intravenous Immunoglobulin for Children with Severe COVID-19: A Rapid Review

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Abstract

Background: Intravenous immunoglobulin (IVIG) is usually used as supportive therapy, but the treatment of COVID-19 by IVIG is controversial. This rapid review aims to explore the clinical effectiveness and safety of IVIG in the treatment of children with severe COVID-19.

Methods: We systematically searched the literature on the use of IVIG in patients with COVID-19, Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS), including both adults and children. We assessed the risk of bias and quality of evidence and reported the main findings descriptively.

Results: A total of 1519 articles were identified by initial literature search, and finally six studies, included one randomized controlled trial (RCT), four case series and one case report involving 198 patients. One case series showed the survival of COVID-19 patients with acute respiratory distress syndrome (ARDS) was not improved by IVIG. One case report showed high-dose IVIG could improve the outcome of COVID-19 adults. Three observational studies showed inconsistent results of the effect of IVIG on SARS patients. One RCT showed that IVIG did not reduce mortality or the incidence of nosocomial infection in adults with severe SARS. The quality of evidence was between low and very low.

Conclusions: The existing evidence is insufficient to support the efficacy or safety of IVIG in the treatment of COVID-19.

Keywords: COVID-19; children; intravenous immunoglobulin; rapid review.

Background

Coronavirus disease 2019 (COVID-19), first reported in China on December, 2019, is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 belongs to the family of coronaviruses, which are enveloped viruses that can cause illnesses ranging from common cold to severe diseases such as SARS and MERS (2,3). The COVID-19 epidemic massively influences the public health and people's daily lives, and the disease was declared a pandemic on 11 March 2020 (4). All populations are susceptible to infection and there is a research shows children are as likely to be infected as adults (5). On February 11, 2020, there were 44672 confirmed cases in mainland China, of whom 416 were under the age of 10 years and 549 between the ages of 10 to 19 years (6). The main symptoms in children are fever and cough, and the disease is on average less severe in children than adults (7). However, severe cases have been reported also in children (8). So far, there has been no specific treatment for COVID-19, antiviral therapy and vaccination are currently under development (9,10).

IVIG is prepared from the plasma of healthy humans and usually used as supportive therapy. Its main component is immunoglobulin (Ig) G, which has dual therapeutic effects of immune-modulation effects and immune substitution (11). IVIG is one of the alternative treatments for children with agammaglobulinemia, and an effective treatment of Kawasaki disease (12,13). IVIG was used to treat SARS patients during the SARS outbreak in 2003 (14,15), but there is no convincing evidence of its effectiveness.

According to recent reports, about 33% of patients with severe COVID-19 received IVIG in China (16). Some published guidelines of COVID-19 have indicated that IVIG could be used to treat children with severe or critical disease (17).

The purpose of this study is to perform a comprehensive rapid review to explore whether it is beneficial to treat children with severe COVID-19 with IVIG and provide supporting evidence support for COVID-19 guidelines. Because of the urgent situation, the review was not registered (18).

Methods

Search strategy

We carried out a comprehensive search in the following electronic databases: the Cochrane library, MEDLINE (via PubMed), EMBASE, Web of Science, China Biology Medicine disc (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Data, by using the terms "COVID-19", "SARS-CoV-2", "Novel coronavirus", "2019-novel coronavirus", "2019-nCoV", "SARS", "MERS", "IVIG", "intravenous immunoglobulin" and their derivatives. The search covered the time from each database's inception to March 31, 2020. The search strategies are determined by multiple pre-searches and will be discussed with the clinicians about the appellation of disease and IVIG. We also searched the World Health Organization Clinical Trials Registry Platform, ISRCTN Registry, ClinicalTrials, Google Scholar, three preprint services, including medRxiv (https://www.medrxiv.org/), bioRxiv (https://www.biorxiv.org/) and SSRN

(https://www.ssrn.com/index.cfm/en/) and references of included studies. The details of the search strategy can be found in the ***Supplementary Material 1***.

Inclusion and exclusion criteria

We included RCTs that compared IVIG treatment (standard intravenous immunoglobulin preparations, excluding IgM-enriched immunoglobulin, hyperimmune immunoglobulin and specific immunoglobulin from convalecent plasma) with a control group (placebo or no treatment with IVIG), and cohort studies, cross-sectional studies, case-control studies, case series and cases report that can distinguish the corresponding outcomes caused by IVIG. The inclusion of COVID-19 adult patients and patients with SARS or MERS helps to provide indirect evidence, if studies on COVID-19 in children are scarce. Studies with all patients diagnosed with COVID-19, SARS or MERS were included, without restrictions on age, race, gender, or geographical location or setting. The primary outcomes were the risk of death and severity of the disease. Secondary outcomes included the incidence of nosocomial infection, the duration of hospitalization, clinical symptoms, absorption of lung lesions, improvement in abnormal biochemical indicators, and adverse effects. We excluded duplicates, conference abstracts, comments and letters, studies published in languages other than English or Chinese, and studies where we could not access the full text.

Study selection

After eliminating duplicates by EndNote software and manual check, two reviewers (J Zhang and Y Yang) independently reviewed the titles and abstracts of records retrieved

from the search and selected all potentially relevant studies according to the pre-defined inclusion and exclusion criteria. After this, the same reviewers screened the full texts and made the final selection. A pilot search was conducted before the full screening of the literature to ensure that each researcher understood the screening criteria and process. Disagreements about selection of studies were resolved by consulting a third party (N Yang). The process of study selection was documented using a PRISMA flow diagram (19).

Data extraction

Two reviewers (J Zhang and Y Yang) independently extracted the following data from included trials using a standardized extraction sheet: 1) basic information (year of publication, first author and affiliation, journal, funding, conflict of interest); 2) study details (type of study, sample size, research purpose, research population characteristics, interventions; and 3) outcome data. A pre-test was conducted before formal extraction to ensure that each researcher agreed with the extraction criteria and process. Disagreements were solved through discussion with a third researcher (N Yang).

Risk of bias assessment

Two reviewers (J Zhang and Y Ma) assessed the quality of the included studies independently. We used the Cochrane bias risk assessment tool (Risk of bias) to assess the randomized controlled trials and clinical controlled trials (20), the criteria recommended by the National Institute of Health and Clinical Optimization (NICE) for case series to assess the risk of bias (21), the Joanna Briggs Institute'(JBI) case report

quality appraisal tool for case reports(22) Newcastle-Ottawa Quality Assessment Scale (NOS) for the quality of cohort studies and case-control studies (23), and Agency for Healthcare Research and Quality (AHRQ) tool for cross-sectional studies (24).

Data synthesis

For dichotomous outcomes we calculated the risk ratio (RR) and the corresponding 95% confidence interval (CI) and *P* value. For continuous outcomes, we calculated the mean difference (MD) and its corresponding 95% CI when means and standard deviations (SD) were reported. If sufficient data were available, we considered examined the robustness of meta-analyses in a sensitivity analysis.When effect sizes could not be pooled, we reported the study effectives narratively.

Quality of the evidence assessment

The quality of the body of evidence was graded using the GRADE method (25,26). Evidence from randomized trials could be downgraded by the following five factors: risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias. The quality of evidence for each outcome was graded as high, medium, low, or very low. The results of the grading were presented in "GRADE evidence profile" (27-30).

Results

We identified 1519 articles in the initial literature search (*Figure 1*). After removing duplicates, we screened the titles and abstracts of 1405 records. Thirty-one articles were retrieved for full-text reviewing. Finally, one RCT, four case series and one case report involving a total of 198 patients were included for rapid review (31-36).

The studies were published between 2004 and 2020, and all studies were from China (*Table 1 and Table 3*). We found one case series on IVIG in COVID-19 adults with ARDS, one case report in COVID-19 adults, one randomized controlled trial of 44 adults with severe SARS, which included 25 adults with acute lung injury (ALI) and 19 adults with ARDS), one case series involving children with SARS, and two case series also involving adults with SARS. The outcomes of the studies were the duration of fever, total peripheral blood WBC, time of the lung lesions subsided obviously, adverse effects, WBC counts, platelet counts, serum globulin, the incidence of nosocomial infection, the risk of death, survival probability and the progression of disease cascade. In all studies IVIG was used before or in combination with other drugs and treatment (such as antibiotics, glucocorticoids, antivirals, oxygen therapy). The IVIG dose and duration of use differed across studies.

Risk of bias for included studies

We found a high risk of bias in random sequencing, allocation concealment and blinding in the only included RCT. All case series had a moderate risk (score 4 to 5 out of 8), one case report meeting 8 of the 8 items of the JBI quality appraisal tool (*Table 1*).

Quality of the evidence

The quality of evidence for all outcomes assessed in the only included RCT was graded low (*Table 2*), primarily due to serious risk of bias and imprecision. As we included four case series, we judged that reporting a 'GRADE evidence profile' would not be meaningful. Overall, the quality of evidence was very low for most outcomes and cannot thus provide a reliable indication of any likely effect across outcomes.

COVID-19

A case series of 109 adults with COVID-19 reported that most patients used antibiotics and antiviral treatment, and over half of the patients were given glucocorticoid therapy and IVIG. The survival probability of patients with ARDS could not be improved by antiviral, glucocorticoid, or immunoglobulin treatment. The risk of death was not associated with the use of IVIG in the patients with ARDS (31).A case report of three adults with COVID-19 reported that a high dose IVIG (25 g/d for 5 days) administered at the appropriate point could successfully block the progression of disease cascade (result of the clinical symptoms, laboratory inspection indicators and chest CT scan), and finally improve the outcome of COVID 19 (32).

SARS

The incidence of nosocomial infection and the risk of death

The randomized controlled trial of 44 adults with severe SARS found no significant difference in the risk of death (18.1% vs. 23.8%) or the incidence of nosocomial infection (65.2% vs. 52.4%) between adults treated either with IVIG or with conventional treatment. And there was no significant difference in the incidence of nosocomial infection between ALI (50.0% vs. 38.5%) and ARDS (81.8% vs. 75.0%) patients (36).

Laboratory inspection

One case series reported the patients with SARS who did not receive steroids for severe hemocytopenia had increased WBC counts and platelet counts after undergoing IVIG (34). Another case series reported the children with persistent fever who were given

IVIG had significantly improved total peripheral blood WBC after undergoing IVIG (33). The included RCT showed the serum globulin increased slightly in the IVIG group, but decreased in the conventional treatment group, the difference was not significant (36).

The duration of fever

One case series included ten children with persistent fever who were given IVIG. The body temperature ranged between 38.4℃ and 40℃ at baseline and the duration of fever was 1 to 4 days after IVIG (33).

Imaging testing

One case series reported that chest radiographs in children who were given IVIG showed more patchy focal asymmetric infiltrative shadows, more rapid time of the lung lesions subsided obviously than in a randomly selected, age- and sex-matched control group of 20 children without IVIG (33).

Adverse effects

One case series reported no adverse effects associated with IVIG , when IVIG was used in the patients who had high fever or other obvious poisoning symptoms, who were in the early stage of the disease, who were treated with glucocorticoids, or whose white blood cell counts below 3.0×10^9 /L (35).

Discussion

We only found limited evidence about the use of IVIG to treat children or adults with severe COVID-19. Since SARS and COVID-19 belong to the same family of viruses,

we used IVIG treatment of SARS as indirect evidence, even though the quality of the included studies was generally low. The results were also inconsistent, and no benefit was found in the only identified randomized controlled trial.

An earlier systematic review of treatment effects with SARS concluded that although four studies suggested an improvement in the patients' condition after IVIG treatment, more controlled trials are needed to provide evidence of the potential benefits on IVIG against SARS. The results of the review are roughly in line with our findings, more high-quality evidence about the benefits and disadvantages of IVIG for COVID-19 and SARS are needed (37).

There was no apparent benefit from IVIG, despite it being used to treat other respiratory infections. A meta-analysis of seven RCTs in children aged less than three years with respiratory syncytial virus infection found no evidence of differences between children treated with immunoglobulin or with placebo in the risk of death (RR=0.87, 95% CI: 0.14,5.27) or serious adverse events (RR=1.08, 95% CI: 0.65,1.79), or in the duration of hospitalization (MD=-0.70, 95% CI: -1.83,0.42) (38). SARS belongs to the category of systemic inflammatory response syndromes (SIRS), and severe SARS often manifests as ALI, ARDS and progresses to severe sepsis (39,40). The course of COVID-19 may also be similar. A meta-analysis of nine RCTs showed that IVIG did not reduce the mortality (OR=0.95, 95% CI: 0.80,1.13), length of hospital stay (MD=-4.08, 95% CI: -6.47,-1.69]), or the risk of death or major disability before two years of age (RR=0.98,95% CI: 0.88,1.09]) in infants with suspected or confirmed

infection, compared with placebo or no intervention (41).

IVIG is prepared from pools of plasma obtained from several thousand healthy blood donors. Unlike convalescent plasma from patients with COVID-19, IVIG does not contain SARS-Cov-2 neutralizing antibody (42,43). The review showed that there was no evidence that IVIG has an effect on anti-MERS-CoV, or that IVIG would cause kidney failure or thrombosis in patients with MERS (44). IVIG could increase the risk of vaccination delay. A study by National Advisory Committee on Immunization and the American Advisory Committee on Immunization showed a delay of five months of varicella vaccine in patients who received IVIG and varicella immune globulin (VZIG) (45). IVIG may increase the risk of infections transmitted by transfusion (42). Some adverse effects, such as thrombosis, aseptic meningitis, hemolysis, and renal failure, are mainly associated with the use of high-dose IVIG (46).

The condition, dose and duration of IVIG were inconsistent between studies, the efficacy, and the associated adverse effects remain unclear. The first severe case of COVID-19 in children in China took IVIG with a dose of 400 mg/kg for a duration of five days (8). The recommended dosage of IVIG for children with severe COVID-19 was also inconsistent in different guidelines, including 1.0g/kg/d for 2 days, or 400mg/kg/d for 5 days, 0.2g/kg/d for 3~5 days, or 1~2g/kg for 2~3 days (47-49). Therefore, it is particularly important and urgent to study the benefits and disadvantages of IVIG treatment in children with COVID-19. It is promising that a trial addressing efficacy and safety of IVIG therapy in patients with severe or critical COVID-19

disease has been registered on (50). Randomized, double-blinded, large sample, multicenter clinical trials on children are urgently needed for getting scientific evidence to support clinical decision-making.

Strength and limitations

This is the first systematic review of IVIG treatment for children with COVID-19. There are several limitations in this systematic review. First, the use of glucocorticoids or a combination of a variety of broad-spectrum antibiotics before IVIG may lead to changes in the microecology of the body, affect the immune regulation function, and thus also affect the effect of IVIG. Second, the total sample size of this study was insufficient to make strong conclusions, and the quality of the methodology was generally low which affect the certainty of the results. Finally, we may have missed some studies as we only included studies published in Chinese and English.

Conclusion

There is no direct evidence for IVIG in children with COVID-19, current evidence is insufficient to assess the effectiveness and safety of IVIG for children with severe COVID-19. Therefore, we cannot suggest use of IVIG for the treatment of COVID-19 in children. More clinical studies to address this topic are needed.

Author Contributions

(I) Conception and design: Y Chen, and E Liu; (II) Administrative support: K Yang and Z Fu; (III) Provision of study materials or patients: J Zhang, Y Yang; (IV) Collection

and assembly of data: Y Yang and N Yang; (V) Data analysis and interpretation: Y Ma and J Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material 1-Search strategy

EMBASE

#1 'middle east respiratory syndrome coronavirus'/exp
#2 'severe acute respiratory syndrome'/exp
#3 'sars coronavirus'/exp
#4 'COVID-19':ab,ti
#5 'SARS-COV-2':ab,ti
#6 'novel coronavirus':ab,ti
#7 '2019-novel coronavirus':ab,ti
#8 'coronavirus disease-19':ab,ti
#9 'coronavirus disease 2019':ab,ti
#10 'COVID 19':ab,ti
#11 'novel cov':ab,ti
#12 '2019-ncov':ab,ti
#13 '2019-cov':ab,ti
#14 'wuhan-cov':ab,ti
#15 'wuhan coronavirus':ab,ti
#16 'wuhan seafood market pneumonia virus':ab,ti
#17 'middle east respiratory syndrome':ab,ti
#18 'middle east respiratory syndrome coronavirus':ab,ti
#19 'mers':ab,ti
#20 'mers-cov':ab,ti
#21 'severe acute respiratory syndrome':ab,ti
#22 'sars':ab,ti
#23 'sars-cov':ab,ti
#24 'sars-related':ab,ti
#25 'sars-associated':ab,ti
#26 #1-#25 / OR
#27 'Immunoglobulins'/exp
#28 'Intravenous Immunoglobulin*':ab,ti
#29 'Intravenous IG':ab,ti
#30 'immune globulin*':ab,ti
#31 'IVIG':ab,ti
#32 'IV Immunoglobulin*':ab,ti
#33 'Intravenous Antibodies':ab,ti
#34 'gamma globulin*':ab,ti
#35 'gamma-globulin*':ab,ti
#36 'Flebogamma DIF':ab,ti
#37 'Gamunex':ab,ti
#38 'Globulin-N':ab,ti
#39 'Globulin N':ab,ti
#40 'Intraglobin':ab,ti
#41 'Gammagard':ab,ti

#42 'Gamimune':ab,ti
#43 'Gamimmune':ab,ti
#44 'Privigen':ab,ti
#45 'Sandoglobulin':ab,ti
#46 'Venoglobulin':ab,ti
#47 'Iveegam':ab,ti
#48 'Endobulin':ab,ti
#49 'Gammonativ':ab,ti
#50 27-49/OR
#51 #26 AND #50

PubMed

#1 "COVID-19" [Supplementary Concept]
#2 "Severe Acute Respiratory Syndrome Coronavirus 2" [Supplementary Concept]
#3 "Middle East Respiratory Syndrome Coronavirus" [Mesh]
#4 "Severe Acute Respiratory Syndrome" [Mesh]
#5 "SARS Virus" [Mesh]
#6 "COVID-19" [Title/Abstract]
#7 "SARS-COV-2" [Title/Abstract]
#8 "Novel coronavirus" [Title/Abstract]
#9 “2019-novel coronavirus” [Title/Abstract]
#10 “coronavirus disease-19” [Title/Abstract]
#11 “coronavirus disease 2019” [Title/Abstract]
#12 “COVID 19” [Title/Abstract]
#13 “Novel CoV” [Title/Abstract]
#14 “2019-nCoV” [Title/Abstract]
#15 “2019-CoV” [Title/Abstract]
#16 “Wuhan-Cov” [Title/Abstract]
#17 “Wuhan Coronavirus” [Title/Abstract]
#18 “Wuhan seafood market pneumonia virus” [Title/Abstract]
#19 “Middle East Respiratory Syndrome” [Title/Abstract]
#20 “MERS" [Title/Abstract]
#21 “MERS-CoV" [Title/Abstract]
#22 "Severe Acute Respiratory Syndrome" [Title/Abstract]
#23 "SARS" [Title/Abstract]
#24 "SARS-CoV" [Title/Abstract]
#25 "SARS-Related" [Title/Abstract]
#26 "SARS-Associated" [Title/Abstract]
#27 #1-#26/ OR
#28 "Immunoglobulins, Intravenous" [Mesh]
#29 "gamma-Globulins" [Mesh]
#30 "Intravenous Immunoglobulin*" [Title/Abstract]

#31 "Intravenous IG" [Title/Abstract]
#32 "immune globulin*" [Title/Abstract]
#33 IVIG [Title/Abstract]
#34 "IV Immunoglobulin*" [Title/Abstract]
#35 "Intravenous Antibodies" [Title/Abstract]
#36 "gamma globulin*" [Title/Abstract]
#37 "gamma-globulin*" [Title/Abstract]
#38 "Flebogamma DIF" [Title/Abstract]
#39 Gamunex [Title/Abstract]
#40 "Globulin-N" [Title/Abstract]
#41 "Globulin N" [Title/Abstract]
#42 Intraglobin [Title/Abstract]
#43 Gammagard [Title/Abstract]
#44 Gamimune [Title/Abstract]
#45 Gamimmune [Title/Abstract]
#46 Privigen [Title/Abstract]
#47 Sandoglobulin [Title/Abstract]
#48 Venoglobulin [Title/Abstract]
#49 Iveegam [Title/Abstract]
#50 Endobulin [Title/Abstract]
#51 Gammonativ [Title/Abstract]
#52 28-#51/ OR
#53 #27 AND #52

Cochrane library

#1 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees
#2 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees
#3 MeSH descriptor: [SARS Virus] explode all trees
#4 "COVID-19":ti,ab,kw
#5 "SARS-COV-2":ti,ab,kw
#6 "Novel coronavirus":ti,ab,kw
#7 "2019-novel coronavirus":ti,ab,kw
#8 "Novel CoV":ti,ab,kw
#9 "2019-nCoV":ti,ab,kw
#10 "2019-CoV":ti,ab,kw
#11 "coronavirus disease-19":ti,ab,kw
#12 "coronavirus disease 2019":ti,ab,kw
#13 "COVID 19":ti,ab,kw
#14 "Wuhan-Cov":ti,ab,kw
#15 "Wuhan Coronavirus":ti,ab,kw
#16 "Wuhan seafood market pneumonia virus":ti,ab,kw
#17 "Middle East Respiratory Syndrome":ti,ab,kw

#18 "MERS":ti,ab,kw
#19 "MERS-CoV":ti,ab,kw
#20 "Severe Acute Respiratory Syndrome":ti,ab,kw
#21 "SARS":ti,ab,kw
#22 "SARS-CoV":ti,ab,kw
#23 "SARS-Related":ti,ab,kw
#24 "SARS-Associated":ti,ab,kw
#25 #1-#24/ OR
#26 MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees
#27 MeSH descriptor: [gamma-Globulins] explode all trees
#28 "Intravenous Immunoglobulin*" :ti,ab,kw
#29 "Intravenous IG":ti,ab,kw
#30 "immune globulin*":ti,ab,kw
#31 "IVIG":ti,ab,kw
#32 "IV Immunoglobulin*":ti,ab,kw
#33 "Intravenous Antibodies":ti,ab,kw
#34 "gamma globulin*":ti,ab,kw
#35 "gamma-globulin*":ti,ab,kw
#36 "Flebogamma DIF":ti,ab,kw
#37 "Gamunex":ti,ab,kw
#38 "Globulin-N":ti,ab,kw
#39 "Globulin N":ti,ab,kw
#40 "Intraglobin":ti,ab,kw
#41 "Gammagard":ti,ab,kw
#42 "Gamimune":ti,ab,kw
#43 "Gamimmune":ti,ab,kw
#44 "Privigen":ti,ab,kw
#45 "Sandoglobulin":ti,ab,kw
#46 "Venoglobulin":ti,ab,kw
#47 "Iveegam":ti,ab,kw
#48 "Endobulin":ti,ab,kw
#49 "Gammonativ":ti,ab,kw
#50 26-#49/ OR
#51 #25 AND #50

Web of Science

#1 TOPIC: "COVID-19"
#2 TOPIC: "SARS-COV-2"
#3 TOPIC: "Novel coronavirus"
#4 TOPIC: "2019-novel coronavirus"
#5 TOPIC: "coronavirus disease-19" [Title/Abstract]
#6 TOPIC: "coronavirus disease 2019" [Title/Abstract]
#7 TOPIC: "COVID 19" [Title/Abstract]

#8 TOPIC: "Novel CoV"
#9 TOPIC: "2019-nCoV"
#10 TOPIC: "2019-CoV"
#11 TOPIC: "Wuhan-Cov"
#12 TOPIC: "Wuhan Coronavirus"
#13 TOPIC: " Wuhan seafood market pneumonia virus"
#14 TOPIC: " Middle East Respiratory Syndrome"
#15 TOPIC: " MERS"
#16 TOPIC: " MERS-CoV"
#17 TOPIC: "Severe Acute Respiratory Syndrome"
#18 TOPIC: "SARS"
#19 TOPIC: "SARS-CoV"
#20 TOPIC: "SARS-Related"
#21 TOPIC: "SARS-Associated"
#22 #1-#21 /OR
#23 TOPIC: "Intravenous Immunoglobulin*"
#24 TOPIC: "Intravenous IG"
#25 TOPIC: "immune globulin*"
#26 TOPIC: "IVIG"
#27 TOPIC: "IV Immunoglobulin*"
#28 TOPIC: "Intravenous Antibodies"
#29 TOPIC: "gamma globulin*"
#30 TOPIC: "gamma-globulin*"
#31 TOPIC: "Flebogamma DIF"
#32 TOPIC: "Gamune"
#33 TOPIC: "Globulin-N"
#34 TOPIC: "Globulin N"
#35 TOPIC: "Intraglobin"
#36 TOPIC: "Gammagard"
#37 TOPIC: "Gamimune"
#38 TOPIC: "Gamimmune"
#39 TOPIC: "Privigen"
#40 TOPIC: "Sandoglobulin"
#41 TOPIC: "Venoglobulin"
#42 TOPIC: "Iveegam"
#43 TOPIC: "Endobulin"
#44 TOPIC: "Gammonativ"
#45 #23-#44 /OR
#46 #22 AND #45

CBM

#1 "新型冠状病毒"[常用字段:智能]

#2 "COVID-19"[常用字段:智能]

#3 "COVID 19"[常用字段:智能]

#4 "2019-nCoV"[常用字段:智能]

#5 "2019-CoV"[常用字段:智能]

#6 "SARS-CoV-2"[常用字段:智能]

#7 "武汉冠状病毒"[常用字段:智能]

#8 "中东呼吸综合征冠状病毒"[不加权:扩展]

#9 "中东呼吸综合征"[常用字段:智能]

#10 "MERS"[常用字段:智能]

#11 "MERS-CoV"[常用字段:智能]

#12 "严重急性呼吸综合征"[不加权:扩展]

#13 "SARS 病毒"[不加权:扩展]

#14 "严重急性呼吸综合征"[常用字段:智能]

#15 "SARS"[常用字段:智能]

#16 #1-#15/ OR

#17 丙种球蛋白[常用字段:智能]

#18 静脉丙球[常用字段:智能]

#19 免疫球蛋白[常用字段:智能]

#20 IVIG[常用字段:智能]

#21 "免疫球蛋白类"[不加权:扩展]

#22 #17-#21/ OR

#23 #16 AND #22

万方

#1 新型冠状病毒[主题]

#2 COVID-19[主题]

#3 COVID 19[主题]

#4 2019-nCoV[主题]

#5 2019-CoV[主题]

#6 SARS-CoV-2[主题]

#7 武汉冠状病毒[主题]

#8 中东呼吸综合征[主题]

#9 MERS[主题]

#10 MERS-CoV[主题]

#11 严重急性呼吸综合征[主题]

#12 SARS[主题]

#13 #1-#12/ OR

#14 丙种球蛋白[主题]

#15 静脉丙球[主题]

#16 IVIG[主题]

#17 免疫球蛋白[主题]

#18 #14-#17/OR

#19 #13 AND #18

CNKI

#1 "新型冠状病毒"[主题]

#2 "COVID-19"[主题]

#3 "COVID 19"[主题]

#4 "2019-nCoV"[主题]

#5 "2019-CoV"[主题]

#6 "SARS-CoV-2"[主题]

#7 "武汉冠状病毒"[主题]

#8 "中东呼吸综合征"[主题]

#9 "MERS"[主题]

#10 "MERS-CoV"[主题]

#11 "严重急性呼吸综合征"[主题]

#12 "SARS"[主题]

#13 #1-#12/ OR

#14 "丙种球蛋白"[主题]

#15 "静脉丙球"[主题]

#16 "免疫球蛋白"[主题]

#17 "IVIG"[主题]

#18 #13-#17/ OR

#19 #13 AND #18

Supplementary Material 2.

Table 1 Basic characteristics of the included studies

Author	Study Location	Study design	Number (M/F)	Disease	Age(range or mean±SD)	Intervention		Outcome	Risk of bias[#]
						Other treatment[*]	IVIG		
Zeng 2003 (33)	Guangzhou	Case series	5/5	SARS	7.3±5.1	Antibiotics, oxygen inhalation, symptomatic , Comprehensive treatment, etc.	200-400mg/kg/d for 3 days	Ⅰ, Ⅱ, Ⅲ	4/8
Wu 2003 (35)	Guangzhou	Case series	66	SARS	16~62	Antibiotics, glucocorticoids, interferons, antivirals and oxygen therapy.	5~10 g/d for 3 to 6 days	Ⅳ	4/8
Jann-Tay 2004 (34)	Taiwan	Case series	22	SARS	24~87	Methylprednisolone	1g/kg/d for 2 days	Ⅴ, Ⅵ	5/8
Wu 2005* (36)	Guangzhou	RCT	15/29	SARS	Mean:42/43	Antibiotics, glucocorticoids	2.5mg/d for 2 days~10mg/d for 13 days	Ⅶ, Ⅷ, Ⅸ	NA
Liu 2020 (31)	Wuhan	Case series	29/24	COVID-19	Mean:55	Antibiotics, glucocorticoids, interferons, antivirals and oxygen therapy.	NR	Ⅹ	5/8
Cao 2020 (32)	Wuhan	Case report	3	COVID-19	34~56	NR	25 g/d for 5 days	XI	NA

* Prior to IVIG treatment, the patient received other treatment.

[#] Risk of bias in case series.

Outcome: Ⅰ: The duration of fever; Ⅱ: Total peripheral blood WBC (10^9/L); Ⅲ: Time of the lung lesions subsided obviously; Ⅳ: Adverse effects; Ⅴ: WBC counts (10^9/L); Ⅵ: Platelet counts (10^9/L); Ⅶ: Serum globulin (g/L); Ⅷ: The incidence of nosocomial infection; Ⅸ: The risk of death;Ⅹ: Survival probability; XI: The progression of disease cascade;

NR: Not Report; NA: Not Applicable.

Table 2 GRADE evidence profile

№ of studies	Sample size	Certainty assessment					Effect Value (95% CI)	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Serum globulin								
RCT (31)	44	serious [1]	-	serious [2]	-	none	-	⊕⊕◯◯ LOW
Nosocomial infection rate								
RCT (31)	44	serious [1]	serious [3]	not serious	not serious	none	OR 1.25 (0.47 to 3.31)	⊕⊕◯◯ LOW
the risk of death								
RCT (31)	44	not serious	not serious	not serious	not serious	not serious	-	⊕⊕◯◯ LOW

CI: Confidence Interval; **OR:** Odds Ratio;

Explanations

1.Unclear risk of bias in allocation concealment, random sequence generation and blinding.

2.Using other drugs (such as interferon, hormone, etc.) before intervention

3.The value of square I above 50%.

Table 3 The characteristics of excluded studies

No.	Title	Country	Journal	Year	Study type	Cause
1	Five cases of infant hematuria caused by human immunoglubulin.	China	Chinese Journal of Rural Medicine and Pharmacy	2005	Case report	Intramuscular injection of IVIG
2	SARS: Systematic review of treatment effects	US	PLoS Medicine	2006	Review	review
3	A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China	China	Chinese medical journal	2003	Case series	without the outcomes of efficacy and safety of IVIG
4	Comparison of clinical course of patients with severe acute respiratory syndrome among the multiple generations of nosocomial transmission	China	Chinese Medical Journal	2004	Case series	without the outcomes of efficacy and safety of IVIG
5	Evaluation of the efficacy and safety of corticosteroid in the treatment of severe SARS in Guangdong province with multi-factor regression analysis	China	Chinese Critical Care Medicine	2008	regression analysis	without the outcomes of efficacy and safety of IVIG
6	The therapeutic effect of high flow nasal cannula oxygen therapy for the first imported case of Middle East respiratory syndrome to China	China	Chinese Critical Care Medicine	2015	Case report	without the outcomes of efficacy and safety of IVIG
7	Clinical analysis of pediatric SARS cases in Beijing	China	Chinese Journal of Pediatrics	2003	Case series	without the outcomes of efficacy and safety of IVIG
8	Clinical analysis of the first patient with imported Middle East respiratory syndrome in China	China	Chinese Critical Care Medicine	2015	Case report	without the outcomes of efficacy and safety of IVIG
9	Clinical characteristice and therapy of severe acute respiratory syndrom	China	Chinese Famous Doctor Forum	2004	Case series	full-text unavailable
10	Multivariable Analysis of Factors Affecting Clinical Course in Patients with SARS	China	Journal of Sun Yat-sen University(Medical Sciences)	2004	regression analysis	without the outcomes of efficacy and safety of IVIG
11	Clinical analysis of 136 cases of severe acute respiratory syndrome	China	Chinese Journal of Respiratory and Critical Care Medicine	2003	Case series	without the outcomes of efficacy and safety of IVIG

12	Evaluation of the efficacy and safety of corticosteroid in the treatment of severe SARS in Guangdong province with multi-factor regression analysis	China	Chinese Critical Care Medicine	2008	regression analysis	without the outcomes of efficacy and safety of IVIG
13	Study of the clinical diagnosis and treatment of the severe acute respiratory syndromes	China	Jiangsu Medical Journal	2003	Case report	without the outcomes of efficacy and safety of IVIG
14	Can immunoglobulin, thymosin, and interferon protect against SARS?	China	Hohhot TechnologyJounal	2003	Science & Technology Daily	review
15	The search for therapeutic options for Middle East Respiratory Syndrome (MERS)	Saudi Arabia	Journal of Infection and Public Health	2016	Editorial	review
16	Clinical findings, treatment and prognosis in patients with severe acute respiratory syndrome (SARS)	China	Journal of the Chinese Medical Association	2005	Editorial	review
17	Intravenous immunoglobulin G is remarkably beneficial in chronic immune dysschwannian/dysneuronal polyneuropathy, diabetes-2 neuropathy, and potentially in severe acute respiratory syndrome	United States	Acta Myologica	2003	Review	full-text unavailable
18	Severe acute respiratory syndrome: Public health response and clinical practice update for an emerging disease	United States	Current Opinion in Pediatrics	2004	Review	IVIG not mentioned
19	Treatment of severe acute respiratory syndrome	Hong Kong	European Journal of Clinical Microbiology and Infectious Diseases	2005	Review	IVIG not mentioned
20	Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review	Saudi Arabia	Journal of Infection and Public Health	2018	Review	review
21	Management of hospital-acquired severe acute respiratory syndrome with different disease spectrum	China	Journal of the Chinese Medical Association: JCMA	2003	Case report	without the outcomes of efficacy and safety of IVIG

22	Neurological manifestations in severe acute respiratory syndrome	China	Acta Neurologica Taiwanica	2005	Review	review
23	Diagnosis and treatment of severe acute respiratory syndrome in children	China	Journal of Applied Clinical Pediatrics	2003	Medical advice	review
24	Experience of INF-2 for treating severe acute respiratory distress syndrome	China	Journal of Modern Medicine & Health	2004	Case series	without the outcomes of efficacy and safety of IVIG
25	Study of Severe Acute Respiratory Syndrome in Shantou	China	Journal of Shantou University Medical College	2003	Case report	without the outcomes of efficacy and safety of IVIG

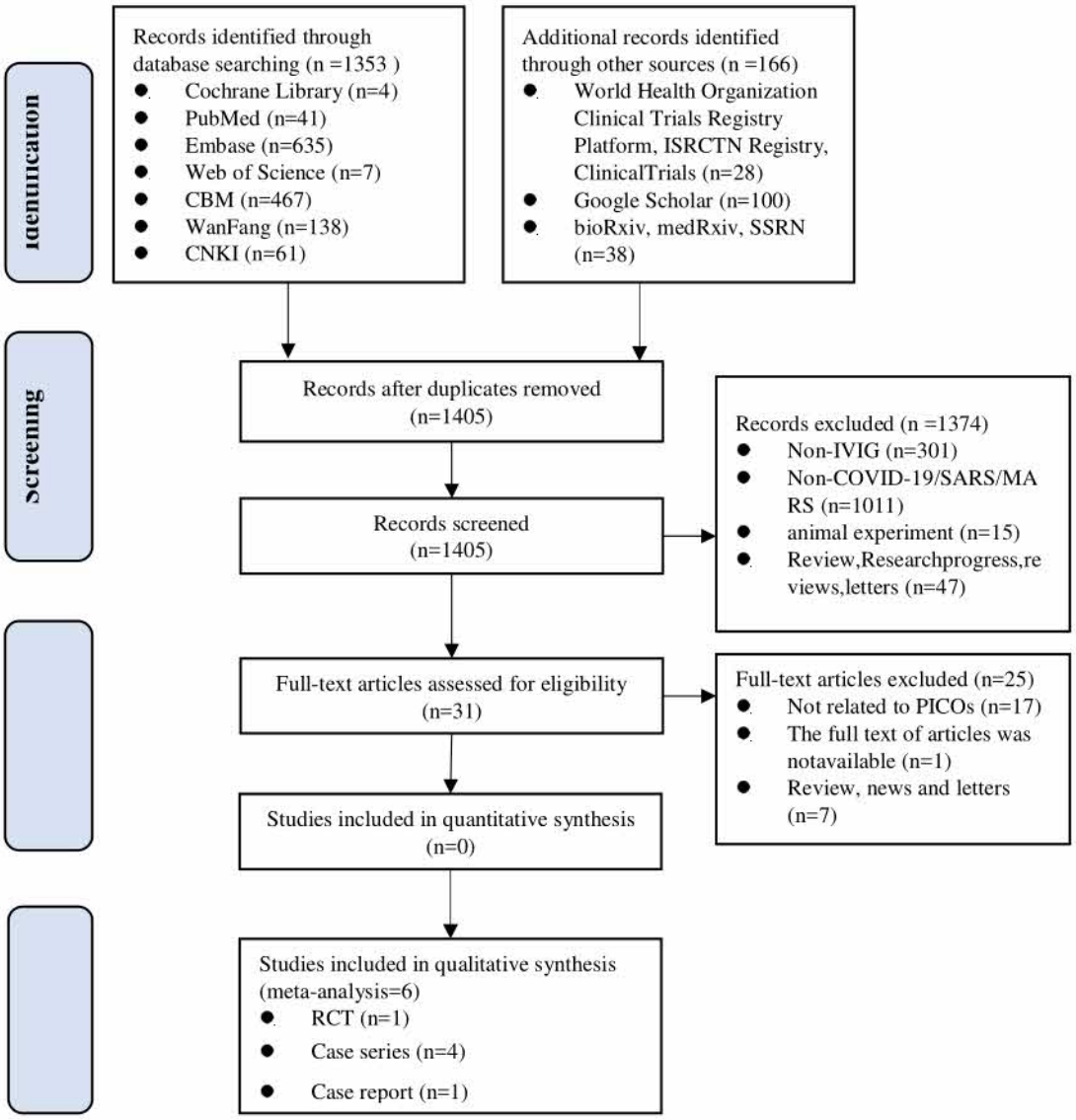

Figure 1 The flow chart of the literature search

Key Words for Literature Review # 3 for Steve Grube, MD 18 May 2020

Steve, this is the search task list and key words used for the 3rd search.

Task list search 3:

- Pediatric cytocine or cell-mediated or auto-antibody mediated pathology associated with SARS CoV-19 or Kawasaki disease
- Pediatric pathology associated with laboratory evidence of inflammation with or without or Kawasaki disease
- Pediatric SARS CoV-2 infection in children verified by RT-PCR, Serology or antigen test
- SARS CoV-2 in children with "blue toes"
- Pediatric SARS CoV-2 and dialysis
- Pediatric SARS CoV-2 or Kawasaki-like disease pathology
- Pediatric SARS CoV-2 **symptomology and pathology**
- Pediatric diagnosis of Kawasaki or Kawasaki-like disease and SARS CoV-2
- Differences between Pediatric and adult symptoms and/or diagnosis with SARS CoV-2 or multisystem inflammation or Kawasaki-like disease
- Pediatric **autoimmune disease** and SARS CoV-2 or Kawasaki-like disease
- Pediatric **treatment** of SARS CoV-2 or Kawasaki-like disease with immune modifiers
- Use of IVIg in treatment of SARS CoV-2 or Kawasaki-like disease in children
- Use of steroids in treatment of SARS CoV-2 or Kawasaki-like disease in children
- Efficacy of treating children with hospitalized SARS CoV-2 or Kawasaki-like disease
- International reports of pediatric SARS CoV-2 or Kawasaki-like disease
- International reports of treating pediatric SARS CoV-2 or Kawasaki-like disease
- Reports of the "Index" first case of pediatric COVID-19
- associated hospitalization and/or multisystem organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic pathology) associated with SARS CoV-19

Search Strategy: Pathology

Database	Strategy	Run Date
Medline (OVID) 1946-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dt) AND (pa.fs OR patho*) OR *mucocutaneous lymph node syndrome/pa OR ((kawasaki syndrome OR kawasaki disease).ti and (pa.fs OR pathology.ti)) AND (review.pt) AND Pediatric* OR paediatric* OR child* OR infant* OR adolescent*	05/18/2020
Embase (OVID) 1988-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR	05/18/2020

	2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dc) AND exp pathology/ OR *mucocutaneous lymph node syndrome/ AND exp pathology/ AND Pediatric* OR paediatric* OR child* OR infant* OR adolescent*	
Scopus	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus") AND TITLE-ABS(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*) AND INDEXTERMS(Pathology)	05/18/2020

Search Strategy: Symptoms

Database	Strategy	Run Date
Medline (OVID) 1946-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dt) AND exp "Signs and Symptoms"/ OR (*mucocutaneous lymph node syndrome/ OR (kawasaki syndrome OR kawasaki disease).ti) and exp "Signs and Symptoms"/ AND (review.pt) AND Pediatric* OR paediatric* OR child* OR infant* OR adolescent*	05/18/2020
Embase (OVID) 1988-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dc) AND exp "Signs and Symptoms"/ OR *mucocutaneous lymph node syndrome/ AND exp "Signs and Symptoms"/ AND	05/18/2020

	(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	
Scopus	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus" OR "mucocutaneous lymph node syndrome" OR "kawasaki syndrome" OR "kawasaki disease") AND TITLE-ABS(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*) AND INDEXTERMS(Symptoms)	05/18/2020

Search Strategy: Diagnostics

Database	Strategy	Run Date
Medline (OVID) 1946-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dt) AND (di.fs OR diagnostic*) OR (*mucocutaneous lymph node syndrome/ OR (kawasaki syndrome OR kawasaki disease).ti) AND (di.fs OR diagnostic*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Embase (OVID) 1988-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*)) AND (di.fs OR diagnostic*) OR *mucocutaneous lymph node syndrome/ AND (di.fs OR diagnostic*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Scopus	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus" OR "mucocutaneous lymph node syndrome" OR	05/18/2020

	"kawasaki syndrome" OR "kawasaki disease") AND TITLE-ABS(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*) AND INDEXTERMS(diagnos*)	

Search Strategy: Epidemiology

	Strategy	Run Date
Medline (OVID) 1946-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dt) AND (ep.fs OR epidemiolog*) OR (*mucocutaneous lymph node syndrome/ OR (kawasaki syndrome OR kawasaki disease).ti) AND (ep.fs OR epidemiolog*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Embase (OVID) 1988-	((novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*)) AND (ep.fs OR epidemiolog*) OR *mucocutaneous lymph node syndrome/ AND (ep.fs OR epidemiolog*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Scopus	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus" OR "mucocutaneous lymph node syndrome" OR "kawasaki syndrome" OR "kawasaki disease") AND TITLE-ABS(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*) AND INDEXTERMS(epidemiolog*)	05/18/2020

Key Words for Literature Review # 3 for Steve Grube, MD 18 May 2020

Search Strategy: Treatment

	Strategy	Run Date
Medline (OVID) 1946-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND (201912* OR 2020*).dt) AND (th.fs OR treatment* OR therap*) OR (*mucocutaneous lymph node syndrome/ OR (kawasaki syndrome OR kawasaki disease).ti) AND (th.fs OR treatment* OR therap*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Embase (OVID) 1988-	((novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*)) AND (ep.fs OR epidemiolog*) OR *mucocutaneous lymph node syndrome/ AND (ep.fs OR epidemiolog*) AND (Pediatric* OR paediatric* OR child* OR infant* OR adolescent*).ti,ab.	05/18/2020
Scopus	TITLE-ABS("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus" OR "mucocutaneous lymph node syndrome" OR "kawasaki syndrome" OR "kawasaki disease") AND TITLE-ABS(Pediatric* OR paediatric* OR child* OR infant* OR adolescent*) AND INDEXTERMS(diagnos*)	05/18/2020

Notes: Duplicates were identified using the Endnote automated "find duplicates" function with preference set to match on title, author and year, and removed from your Endnote library. There will likely be additional duplicates found that Endnote was unable to detect.

There are 100+ articles for your review in this document. Both search 1 & 2 were very broad to capture as many articles as possible.

This search result used a different search engine and criteria from the first list I sent. This search produced articles without active URL links to the original article.

If an article you wish to review beyond what is provided and does not have an active URL link, then we will have to request it from the CDC Library. If you prefer, I can do that because the procedure takes time. So, rather than go over all 100+ articles without links, perhaps you can identify the ones that are most helpful, and I'll try to get those for you.

And finally, the first two document search lists were purposefully broad. If you find gaps that you want to fill, then I can refine the search for missing data.

I will begin working on the "CFIUS-like" supply chain today.

From CDC Science Reviews and "drill down" CDC Library Searches

Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy Lodigiani *et al.* Thrombosis Research (Apr 23, 2020). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177070/pdf/main.pdf
Conclusions: The high number of arterial and, in particular, venous thromboembolic events diagnosed within 24 h of admission and the high rate of positive VTE imaging tests among the few COVID-19 patients tested suggest that there is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory COVID-19 patients.

Obesity could shift severe COVID-19 disease to younger ages. Kass *et al.* Lancet (April 29, 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31024-2/fulltext
Key findings:
• Among COVID-19 patients, the median body mass index (BMI) was 29.3 kg/m² (overweight):
• 25% of patients had a BMI < 26.0 kg/m² (overweight)
• 25% had a BMI > 34.7 kg/m² (severely obese).
• Younger individuals admitted to the ICU were more likely to be obese (BMI > 30 kg/m2) (Figure). No difference was observed by sex (p=0.9).
Methods: A cross-sectional study to assess the correlation between BMI and age in 265 COVID-19 patients admitted to the ICU in hospitals in six US states. 58% of these patients were male. Least squares univariate and multivariate linear regression analyses were conducted. *Limitations*: Cross-sectional design.
Implications: Among severe COVID-19 cases admitted to the ICU, those who were younger were more likely to be obese and therefore at greater risk of severe illness and death. Further examination of the relationship between obesity and severity of COVID-19 in younger patients is needed.

Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020; (published online April 6.) DOI:10.1001/jama.2020.5394
Demographic and clinical data were collected, including data on clinical management, respiratory failure, and patient mortality. Data were recorded by the coordinator center on an

electronic worksheet during telephone calls by the staff of the COVID-19 Lombardy ICU Network. 1,591 patients were included in the study. For more information go to: https://jamanetwork.com/journals/jama/fullarticle/2764365

Hyperinflammatory shock in children during COVID-19 pandemic. Riphagen *et al.* Lancet (May 7, 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31094-1/fulltext

Key findings:
• Among 8 children with pediatric multisystem inflammatory syndrome (PMIS) aged 4-14 years, none tested positive for SARS-CoV-2 while in the hospital, but 2 tested positive for SARS-CoV-2 via RT-PCR following discharge; all eventually were antibody positive, indicating previous infection.
• Cases presented with persistent fever, rash, conjunctivitis, swelling, gastrointestinal symptoms, severe drop in blood pressure requiring treatment, and other clinical signs indicative of systemic inflammation.
• Respiratory system involvement was minimal.
• Cardiovascular complications dominated: • 7 had abnormalities of the heart vessels that put patients at risk of stroke or heart attack and required mechanical ventilation for cardiovascular stabilization.
• 1 died of a stroke.
• All were treated with immunoglobulin to reduce inflammation, antibiotics, and aspirin to limit risk of cardiovascular abnormalities.

Methods: During a 10-day period in April 2020, 8 pediatric cases presented to a UK hospital with PMIS. Authors describe clinical presentation of these cases. *Limitations*: Small case series; limited generalizability.

Implications: This is the first published report describing cases of PMIS among children with COVID-19. Patients with potential PMIS should be monitored to ensure early detection and prompt treatment.

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Cavalli *et al.* Lancet Rheumatology (May 7, 2020).
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext
Key findings:
• Patients who received a high dose of anakinra (an interleukin-1 receptor blocker) were more likely than those who received standard treatment to: • Have improved respiratory function (72% vs. 50%, respectively).
• Survive (90% vs. 56%, respectively; p=0.009) (Figure 1).
• C-reactive protein levels (a marker of hyperinflammation) decreased over time among patients who received anakinra, but not among those who received standard treatment (Figure 2).
• No difference in adverse events occurred between patients who did and did not receive anakinra treatment.

Autoimmune hemolytic anemia associated with Covid-19 infection. Lazarian *et al.* British Journal of Hematology (May 6, 2020).
https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.16794

Key findings:
• The median time from first symptom to onset of autoimmune hemolytic anemia (AIHA, the abnormal breakdown of red blood cells by autoantibody attack) was 9 days (range 4 to 13 days).
• At diagnosis, the median hemoglobin level was 70 g/L (range 38-108 g/L). All patients had positive anti-erythrocyte (red blood cell) antibodies and positive direct antiglobulin test results, which indicate that red blood cells circulating in the bloodstream were covered with antibodies.
• Four patients had lymphoid malignancies (leukemia or lymphoma), one had monoclonal gammopathy (presence of an abnormal protein in the blood) of undetermined significance, and one had prostate cancer.
• Five patients received corticosteroid treatment, while the other two received blood cell infusions. All patients were alive and had at least partly recovered at the end of follow-up.

Methods: A case report of seven patients (four male and three female) from six French and Belgian hospitals who developed AIHA during COVID-19 infection. The median age was 62 years (range 61-89 years). All patients had positive oropharyngeal RT-PCR results for SARS-CoV-2 and typical chest CT images. To treat the infection, three patients received hydroxychloroquine and one patient received lopinavir and ritonavir. *Limitations*: Small number of cases.

Implications: Viral infections are known to trigger autoimmune conditions that deplete red blood cells. AIHA among patients with COVID-19 warrants further investigation.

Severe acute respiratory syndrome coronavirus 2 detection in the female lower genital tract. Cui *et al.* Journal of Obstetrics and Gynecology (May 4, 2020). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7196539/pdf/main.pdf

Key findings:
• Among 35 female COVID-19 patients (median age 64 years, interquartile range 56 to 69 years), SARS-CoV-2 RNA was not detected in samples of vaginal fluid or cervical exfoliated cells, but was detected from one patient's anal swab.

Methods: A case report of 35 female COVID-19 patients from China, of whom 27 tested positive for SARS-CoV-2 RNA by RT-PCR. Three types of samples (vaginal fluid, cervical exfoliated cells, and anal swabs) were obtained and tested for SARS-CoV-2. *Limitations*: Small sample size; few women included of childbearing age.

Implications: The digestive tract may be a possible transmission route for SARS-CoV-2, while the lower female genital tract is likely not a transmission route; however larger studies are needed.

A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. Cao B *et al.* NEJM (May 7, 2020). https://www.nejm.org/doi/full/10.1056/NEJMoa2001282

Key findings:
• In an intent-to-treat analysis of patients with severe illness who initiated treatment a median of 13 days after illness onset, those who received lopinavir-ritonavir (vs. standard of care

alone) experienced no significant differences in clinical improvement (Figure 1) or reductions in viral load over time (Figure 2).

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Hung I *et al.* The Lancet (May 8, 2020).

Key findings: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext

• In an intent-to-treat analysis of patients with mild-to-moderate illness who initiated treatment soon after illness, those patients who received interferon beta-1b, lopinavir-ritonavir, and ribavirin vs. standard of care alone achieved an undetectable SARS-CoV-2 RNA viral load sooner (7 vs. 12 days, $p<0.001$) (Figure 1), had a shorter hospital stay (9 vs. 15 days, $p<0.003$), and resolved symptoms more quickly (4 vs. 8 days, $p<0.001$) (Figure 2).
• Side effects of treatment did not differ between the groups and no serious side effects or deaths occurred during the study.

Cuadrado-Payán, *et al*. **SARS-CoV-2 and influenza virus co-infection**. Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31052-7/fulltext

Clinical presentation of 4 cases of SARS-CoV-2 and influenza co-infection; one patient did not undergo treatment or suffer complications while the other 3 required mechanical ventilation.

Special Topic: April 23, 2020, Edition 3 – COVID 19 and Potential Seasonality
http://intranet.cdc.gov/library/covid19/042320_ed3_covidupdate.html
Observational data regarding SARS-CoV-2 infections that compare incidence in tropical (wet vs. dry) with temperate (i.e., warm vs. cold) global regions are at present biased and inadequate to inform seasonality estimation. Evidence from statistical models and experimental studies of SARS-CoV-2 and other coronaviruses suggest that temperature and humidity could affect SARS-CoV-2 transmission so that if they were major factors cases may progressively decrease in the U.S. as heat and humidity increase in summer months. If SARS-CoV-2 elicits at least short-duration immunity, a seasonal pattern of infections is likely to emerge after the current infection wave, with winter seasonal peaks. Predicting seasonality of SARS-CoV-2 based on the available evidence is impossible at this time. Additional experimental evidence and seasonal experience is needed to assess the interplaying roles of temperature, humidity, and other environmental factors, including ultraviolet radiation, on transmissibility of viable SARS-CoV-2.

John B. Moore, Carl H. June. Science 01 May 2020, Vol. 368, Issue 6490, pp. 473-474.
"Cytokine release syndrome in severe COVID-19"
https://science.sciencemag.org/content/368/6490/473 In December 2019, a new strain of coronavirus, severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), was recognized to have emerged in Wuhan, China. Along with SARS-CoV and Middle East respiratory syndrome–coronavirus (MERS-CoV), SARS-CoV-2 is the third coronavirus to cause severe respiratory illness in humans, called coronavirus disease 2019 (COVID-19). This was recognized as a pandemic by the World Health Organization (WHO) in March 2020 and has had considerable global economic and health impacts. Although the situation is rapidly evolving, severe disease manifested by fever and pneumonia, leading to acute respiratory distress syndrome (ARDS), has been described in up to 20% of COVID-19 cases. This is reminiscent of cytokine release syndrome (CRS)–induced ARDS and secondary

hemophagocytic lymphohistiocytosis (sHLH) observed in patients with SARS-CoV and MERS-CoV as well as in leukemia patients receiving engineered T cell therapy. Given this experience, urgently needed therapeutics based on suppressing CRS, such as tocilizumab, have entered clinical trials to treat COVID-19. **Steve G., A graphic illustrating pathways leading to cytokine release syndrome and a slide deck for this article are also available.**

Bioinformation. 2020; 16(3): 219–222. Published online 2020 Mar 31.
doi: 10.6026/97320630016219
PMCID: PMC7147500, PMID: 32308263. Francesco Chiappelli,[1,*] Allen Khakshooy,[2] and Gillian Greenberg ***CoViD-19 Immunopathology and Immunotherapy.***
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147500/

New evidence on the T-cell immuno-pathology in patient's with Corona Virus Disease 2019 (CoViD-19) was reported by Diao et al. in MedRxiv (doi: 10.1101/2020.02.18.20024364) [1]. It reports observations on 522 patients with confirmed CoViD-19 symptomatology, compared to 40 control subjects. In brief, notable T cytopoenia was recorded by flow cytometry in the CD4+ and the CD8+ populations, which were significantly yet inversely correlated with remarkably increased serum levels of the pro-inflammatory cytokines IL-6, IL-10 and TNF-a. Flow cytometry established a progressive increase in the expression of programmed cell death marker-1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) as patients (n=14) deteriorated from prodromal to symptomatic CoViD-19 requiring intensive care. Here, we interpret these observations of Diao et al from our current understanding of T cell immunophysiology and immunopathology following an immune challenge in the form of sustained viral infection, as is the case in CoViD-19, with emphasis on exhausted T cells (Tex). Recent clinical trials to rescue Tex show promising outcomes. The relevance of these interventions for the prevention and treatment of CoViD-19 is discussed. Taken together, the data of Diao et al could proffer the first glimpse of immunopathology and possible immunotherapy for patients with CoViD-19.

Keywords: Corona Virus Disease 2019 (CoViD-19), T cell exhaustion (Tex) markers, programmed cell death marker 1 (CD279 - PD-1), T cell immunoglobulin and mucin domain-3 (CD366 - Tim-3), cytokine storm, clinical trials.

"**Conducting Clinical Trials During the COVID-19 Pandemic**." Collier, EK; Hsiao, JL; Shi, VY. Journal of dermatological treatment, 28 April 2020, pp. 1-8.
https://www.ncbi.nlm.nih.gov/pubmed/32343162
Description: The COVID-19 pandemic has greatly impacted dermatology clinical trial operations due to mandated governmental and institutional shutdowns and newly implemented restrictions. During this unprecedented time, measures should be taken to maintain research conduct compliance while also ensuring the safety of trial staff and participants. Herein, we underscore the challenges facing dermatology trials during the COVID-19 pandemic, and offer strategies to maintain compliant and safe conduct.

Impact of COVID-19 on the Cardiovascular System: A Review. PMID: 32397558
May 14, 2020
Matsushita, Kensuke; Marchandot, Benjamin; Jesel, Laurence; Ohlmann, Patrick; Morel, Olivier
J Clin Med

The recent outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has been declared a public health emergency of international concern. COVID-19 may present as acute respiratory distress syndrome in severe cases, and patients with pre-existing cardiovascular comorbidities are reported to be the most vulnerable. Notably, acute myocardial injury, determined by elevated high-sensitivity troponin levels, is commonly observed in severe cases, and is strongly associated with mortality. Therefore, understanding the effects of COVID-19 on the cardiovascular system is essential for providing comprehensive medical care for critically ill patients. In this review, we summarize the rapidly evolving data and highlight the cardiovascular considerations related to COVID-19.
https://www.mdpi.com/2077-0383/9/5/1407
Keywords: COVID-19; cardiovascular disease; myocardial injury

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Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom.PMID32402996 Thomas W, Varley J ... Besser M; Thromb. Res.2020 Letter to the Editors-in-Chief.

This article reports the results of an observational study examining the thrombotic omplications of patients admitted with COVID-19 to Addenbrooke's Hospital ICU, a tertiary centre in Cambridge, United Kingdom. This study had full approval from the Trust research and development department. Patient consent was not required for this observational study. The composite endpoint was PE, DVT (including line associated) and arterial thrombosis (myocardial infarction, stroke, or peripheral artery embolism). The index date was date of ICU admission and the censor date was the 14.4.20, discharge from hospital, death, transfer to Royal Papworth Hospital (which runs the regional ECMO service) or thrombosis; whatever was soonest. Patients were investigated for PE based on clinical suspicion (e.g. unexplained hypotension or hypoxia felt disproportionate to the pneumonia) with CT pulmonary angiogram (CTPA), line associated thrombosis due to local symptoms and arterial ischaemia based on clinical symptoms or troponin and electrocardiogram abnormalities suggestive of myocardial ischaemia. Only patients with radiologically confirmed thrombosis have been included (in the case of myocardial infarction by coronary angiography).

Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis Thrombosis Research, 2020; F.A. Klok, M.J.H.A. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman

This article reports a high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 admitted to the intensive care units (ICUs) of three Dutch hospitals. In answering questions raised regarding our study, we updated our database and repeated all analyses.

J. Helms, C. Tacquard, F. Severac, I. Leonard-Lorant, M. Ohana, et al.*High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study* Intensive Care Med. (2020), 10.1007/s00134-020-06062-x

Results

150 COVID-19 patients were included (122 men, median age 63 [53; 71] years, SAPSII 49 [37; 64] points). Sixty-four clinically relevant thrombotic complications were diagnosed in 150 patients, mainly pulmonary embolisms (16.7%). 28/29 patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting. Three thrombotic occlusions (in 2 patients) of centrifugal pump occurred in 12 patients (8%) supported by ECMO. Most patients

(> 95%) had elevated D-dimer and fibrinogen. No patient developed disseminated intravascular coagulation. Von Willebrand (vWF) activity, vWF antigen and FVIII were considerably increased, and 50/57 tested patients (87.7%) had positive lupus anticoagulant. Comparison with non-COVID-19 ARDS patients ($n = 145$) confirmed that COVID-19 ARDS patients ($n = 77$) developed significantly more thrombotic complications, mainly pulmonary embolisms (11.7 vs. 2.1%, $p < 0.008$). Coagulation parameters significantly differed between the two groups.

Conclusion

Despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. Higher anticoagulation targets than in usual critically ill patients should therefore probably be suggested.

Naira M Mustafa, Laila A Selim, Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis; Journal of Clinical Virology, Volume 128July 2020Article 104395.
Download PDF
We performed a systematic review and meta-analysis to analyze the disease characterization in pediatric age group including the possibility of vertical transmission to the neonates.
Methods
Articles published up to 2nd April 2020 in PubMed and google Scholar were considered for this study.
Findings
The most frequently reported symptoms were cough 49% (95% CI: 42 – 55%) and fever 47% (95% CI: 41- 53%). Lymphopenia and increased Procalcitonin were recorded in (21%, 95% CI: 12 – 30%) and (28%, 95% CI: 18 – 37%) respectively. No sex difference for COVID-19 was found in pediatric age group (p = 0.7). Case fatality rate was 0%. Four out of 58 neonates (6.8%) born to COVID-19 confirmed mothers tested positive for the disease.
Conclusion
The disease trajectory in Pediatric patients has good prognosis compared to adults. Intensive care unit and death are rare. Vertical transmission and virus shedding in breast milk are yet to be established.

SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and Other Drugs for the Treatment of the New Coronavirus; Michele Costanzo1,2, Maria Anna Rachele De Giglio3 and Giovanni Nicola Roviello. ***Current Medicinal Chemistry,* 2020*, Vol. 27, No. 00.***
http://www.eurekaselect.com/181009/article

Abstract: Here we report on the most recent updates on experimental drugs successfully employed in the treatment of the disease caused by SARS-CoV-2 coronavirus, also referred to as COVID-19 (COronaVIrus Disease 19). In particular, several cases of recovered patients have been reported after being treated with lopinavir/ritonavir (which is widely used to treat human immunodeficiency virus (HIV) infection) in combination with the anti-flu drug oseltamivir. In addition, remdesivir, which has been previously administered to Ebola virus patients, has also proven effective in the U.S. against coronavirus, while antimalarial chloroquine and hydroxychloroquine, favipiravir and co-administered darunavir and umifenovir (in patient therapies) were also recently recorded as having anti-SARS-CoV-2 effects. Since the recoveries/deaths ratio in the last weeks significantly increased, especially in China, it is

clear that the experimental antiviral therapy, together with the availability of intensive care unit beds in hospitals and rigorous government control measures, all play an important role in dealing with this virus. This also stresses the urgent need for the scientific community to devote its efforts to the development of other more specific antiviral strategies.

Keywords SARS-CoV-2, Coronavirus, COVID-19, antiviral drugs, hydroxychloroquine, remdesivir, favipiravir, lopinavir, ritonavir.

Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020 May 4:102567. doi: 10.1016/j.autrev.2020.102567. [Epub ahead of print]; Jamilloux Y[1], Henry T[2], Belot A[3], Viel S[4], Fauter M[5], El Jammal T[6], Walzer T[2], François B[7], Sève P[6]. https://www.ncbi.nlm.nih.gov/pubmed/32376392

Abstract. The coronavirus disease-19 pandemic (COVID-19), which appeared in China in December 2019 and rapidly spread throughout the world, has forced clinicians and scientists to take up extraordinary challenges. This unprecedented situation led to the inception of numerous fundamental research protocols and many clinical trials. It quickly became apparent that although COVID-19, in the vast majority of cases, was a benign disease, it could also develop a severe form with sometimes fatal outcomes. Cytokines are central to the pathophysiology of COVID-19; while some of them are beneficial (type-I interferon, interleukin-7), others appear detrimental (interleukin-1β, -6, and TNF-α) particularly in the context of the so-called cytokine storm. Yet another characteristic of the disease has emerged: concomitant immunodeficiency, notably involving impaired type-I interferon response, and lymphopenia. This review provides an overview of current knowledge on COVID-19 immunopathology. We discuss the defective type-I IFN response, the theoretical role of IL-7 to restore lymphocyte repertoire, as well as we mention the two patterns observed in severe COVID-19 (i.e. interleukin-1β-driven macrophage activation syndrome vs. interleukin-6-driven immune dysregulation). Next, reviewing current evidence drawn from clinical trials, we examine a number of cytokine and anti-cytokine therapies, including interleukin-1, -6, and TNF inhibitors, as well as less targeted therapies, such as corticosteroids, chloroquine, or JAK inhibitors.

Images from this publication. **See all images (2)**

Asymptomatic Seroconversion of Immunoglobulins to SARS-CoV-2 in a Pediatric Dialysis Unit. Hains DS, Schwaderer AL, Carroll AE, Starr MC, Wilson AC, Amanat F, Krammer F. JAMA. 2020 May 14. doi: 10.1001/jama.2020.8438. [Epub ahead of print] No abstract available. PMID: 32407440

This study found a high prevalence of subclinical seroconversion in individuals interacting in a pediatric dialysis unit. To our knowledge, no other studies of seroconversion in health care settings exist. The 1 symptomatic, PCR-positive patient may have been the source of spread, but other health care environment or community transmission cannot be ruled out. The prevalence of subclinical seroconversion in the health care workers suggests that more health care workers may be antibody-positive than would otherwise be expected. Information on seroprevalence can allow strategically staffing the care of SARS-CoV-2–positive or patients suspected to be positive with seroconverted nurses and physicians. This study has limitations including a small sample size, short follow-up, lack of large-scale sensitivity/specificity of ELISA, .lag of antibody positivity from PCR positivity, and the setting of a single pediatric dialysis unit

Replication in additional sites is needed to define the broad applicability of these findings, as is longer-term follow up to determine the persistence of the antibody response to SARS-CoV-2.
https://jamanetwork.com/journals/jama/fullarticle/2766215

May 14, 2020 (Added to PubMed)
SARS-CoV-2/COVID-19: Viral Genomics, Epidemiology, Vaccines, and Therapeutic Interventions.
Uddin, Mohammed; Mustafa, Farah, Senok, Abiola C,
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32397688

Findings: The COVID-19 pandemic is due to infection caused by the novel SARS-CoV-2 virus that impacts the lower respiratory tract. The spectrum of symptoms ranges from asymptomatic infections to mild respiratory symptoms to the lethal form of COVID-19 which is associated with severe pneumonia, acute respiratory distress, and fatality. To address this global crisis, up-to-date information on viral genomics and transcriptomics is crucial for understanding the origins and global dispersion of the virus, providing insights into viral pathogenicity, transmission, and epidemiology, and enabling strategies for therapeutic interventions, drug discovery, and vaccine development. Therefore, this review provides a comprehensive overview of COVID-19 epidemiology, genomic etiology, findings from recent transcriptomic map analysis, viral-human protein interactions, molecular diagnostics, and the current status of vaccine and novel therapeutic intervention development. Moreover, we provide an extensive list of resources that will help the scientific community access numerous types of databases related to SARS-CoV-2 OMICs and approaches to therapeutics related to COVID-19 treatment.

Emergence of genomic diversity and recurrent mutations in SARS-CoV-2. van Dorp, Lucy; Acman, Mislav; Richard, et. all; PMID: 32387564;
https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32387564

Results. Our results are in line with previous estimates and point to all sequences sharing a common ancestor towards the end of 2019, supporting this as the period when SARS-CoV-2 jumped into its human host. Due to extensive transmission, the genetic diversity of the virus in several countries recapitulates a large fraction of its worldwide genetic diversity. We identify regions of the SARS-CoV-2 genome that have remained largely invariant to date, and others that have already accumulated diversity. By focusing on mutations which have emerged independently multiple times (homoplasies), we identify 198 filtered recurrent mutations in the SARS-CoV-2 genome. Nearly 80% of the recurrent mutations produced non-synonymous changes at the protein level, suggesting possible ongoing adaptation of SARS-CoV-2. Three sites in Orf1ab in the regions encoding Nsp6, Nsp11, Nsp13, and one in the Spike protein are characterised by a particularly large number of recurrent mutations (>15 events) which may signpost convergent evolution and are of particular interest in the context of adaptation of SARS-CoV-2 to the human host. We additionally provide an interactive user-friendly web-application to query the alignment of the 7666 SARS-CoV-2 genomes.

Keywords: #betacoronaviridae, #homoplasies, #mutation, #phylogenetics

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Understanding SARS-CoV-2: Genetic Diversity, Transmission and Cure in Human. Bajaj, Abhay; Purohit, Hemant J
Indian J Microbiol; https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32317810.
Or Full Access: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7169643/

Abstract: As the SARS-CoV-2 virus race around the world across the different population, there needs to be a consolidated effort to understand the divergence of demographically distributed strains. The emerging trends in SARS-CoV-2 genome data show specific mutation and genetic diversity, which could provide the basis to develop a cocktail of vaccine and may also be used to develop the region-specific diagnostic tool, thus decreasing the chances of testing failures in fields. Since the transmission of SARS-CoV-2 is subject to the extent of human interaction, the insights from the correlation of genetic diversity with epidemiological parameter would give paramount information to tackle this transmission. Previously, studies have also correlated the epidemiological data with gut microbiome and its role in immunomodulation for maintaining health status, and such information could be generated from recovered individuals from different demographic regions. It will help in designing a probiotic-based diet for modulation of the gut microbiome, and that could be another plausible prophylactic treatment option. The genomics data suggest that a specific variant of SARS-CoV-2 gets enriched with the specific demographic region. Overall, demographic data suggests that host influences mutation and expression of the virus. Hence, the experiences from the clinical intervention for that region should be considered in control and treatment strategies. Figures are helpful.

Keywords: #drug development, #genetic diversity, #gut microbiome, #phylogeny, #sars-cov-2 genome

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Hyperinflammatory shock in children during COVID-19 pandemic. Riphagen *et al.* Lancet (May 7, 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31094-1/fulltext

Key findings:

• Among 8 children with pediatric multisystem inflammatory syndrome (PMIS) aged 4-14 years, none tested positive for SARS-CoV-2 while in the hospital, but 2 tested positive for SARS-CoV-2 via RT-PCR following discharge; all eventually were antibody positive, indicating previous infection.
• Cases presented with persistent fever, rash, conjunctivitis, swelling, gastrointestinal symptoms, severe drop in blood pressure requiring treatment, and other clinical signs indicative of systemic inflammation.
• Respiratory system involvement was minimal.
• Cardiovascular complications dominated: • 7 had abnormalities of the heart vessels that put patients at risk of stroke or heart attack and required mechanical ventilation for cardiovascular stabilization.
• 1 died of a stroke.
• All were treated with immunoglobulin to reduce inflammation, antibiotics, and aspirin to limit risk of cardiovascular abnormalities.

Implications: This is the first published report describing cases of PMIS among children with COVID-19. Patients with potential PMIS should be monitored to ensure early detection and prompt treatment.

Toward a clinically based classification of disease severity for paediatric COVID-19
Danilo Buonsenso, Niccolò Parri, Cristina De Rose, Piero Valentini on behalf of the Gemelli-pediatric COVID-19 team DOI: https://doi.org/10.1016/S1473-3099(20)30396-0, The Lancet Infectious Diseases, Published: May 15, 2020. **The PDF is attached.**

From the CDC Library Search -- Pediatric Inflammatory Disease related to SARS CoV-2

2020 (102)

Allergy, N. I. o., et al. (2020). **Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC**). ClinicalTrials, https://ClinicalTrials.gov/show/NCT04378777 .

Ammirati, E. and J. P. Kaski (2020). "**Resident inflammatory cells in the myocardium of children: On the way to set histologic reference standards to differentiate normal myocardium from myocarditis.**" International journal of cardiology **303**: 64-65. https://www.sciencedirect.com/science/article/pii/S0167527319350417

Ashton, J. J., et al. (2020). **"Challenges in chronic paediatric disease during the COVID-19 pandemic: diagnosis and management of inflammatory bowel disease in children."** Archives of disease in childhood.

Awad, S., et al. (2020). "Viral Surveillance of Children with Acute Respiratory Infection in Two Main Hospitals in Northern Jordan, Irbid, during Winter of 2016." Journal of Pediatric Infectious Diseases **15**(1): 001-010. Acute lower respiratory infection (ALRI) is a major cause of morbidity and mortality worldwide. Data regarding the etiology of acute respiratory infection (ARI) is scarce in developing countries. The aim of this study was to identify the viral etiology of ARI/ALRI in hospitalized children and factors associated with increased length of stay (LoS) and severe disease presentation in Northern Jordan. This was a prospective viral surveillance study using real-time reverse transcriptase-polymerase chain reaction in children younger than 5 years admitted with ARI to two main hospitals in Northern Jordan during the winter of 2016. Nasopharyngeal swabs were obtained and tested for respiratory syncytial virus (RSV) and other viruses. Demographic and clinical characteristics of RSV-positive patients were compared with those of RSV-negative patients. There were 479 patients hospitalized with ARI. Their mean age (standard deviation) was 10.4 (11.6) months. 53.9% tested positive for at least one virus, with RSV being the most commonly detected virus (34%). Compared with RSV-negative patients, RSV-positive patients were younger, more likely to have chronic lung disease, and more likely to present with cough, rhinorrhea, difficulty in breathing, retraction, flaring, grunting, wheezing, and a higher respiratory rate. Prematurity, presence of a chronic illness, oxygen saturation 90%, and atelectasis and consolidation on chest X-rays were significantly associated with an increased mean LoS. Patients with a history of prematurity had higher risk of severe disease (odds ratio = 2.6; 95% confidence interval: 1.5, 4.7; p = 0.001). Compared with patients 6 months old and younger, patients aged 6.1 to 12 months were less likely to have severe disease. Human metapneumovirus (HMPV)-positive ALRI was associated with increased odds of severe disease. Viruses are recognized as etiological agent of ARI/ALRI-associated morbidity in developing countries that need more attention and implementation of targeted strategies for prevention and detection. HMPV can be a cause of severe ALRI. Copyright © 2020 by Georg Thieme Verlag KG, Stuttgart New York.

Balasubramanian, S., et al. (2020). **"Hyper-inflammatory Syndrome in a Child With COVID-19 Treated Successfully with Intravenous Immunoglobulin and Tocilizumab."** Indian Pediatrics **10**: 10.

Barton Forbes, M., et al. (2020). **"COVID- 19 Infection in Children: Estimating Pediatric Morbidity and Mortality."** 2020.2005.2005.20091751.
BACKGROUND: Estimates of pediatric morbidity and mortality from COVID-19 are vital for planning

optimal use of human and material resources throughout this pandemic. METHODS: Government websites from countries with minimum 1000 cases in adults and children on April 13, 2020 were searched to find the number of cases confirmed in children, the age range, and the number leading to hospitalization, intensive care unit (ICU) admission or death. A systematic literature search was performed April 13, 2020 to find additional data from cases series. RESULTS: Data on pediatric cases were available from government websites for 23 of the 70 countries with minimum 1000 cases by April 13, 2020. Of 424 978 cases in these 23 countries, 8113 (1.9%) occurred in children. Nine publications provided data from 4251 cases in 4 additional countries. Combining data from the websites and the publications, 330 of 2361 cases required admission (14%). The ICU admission rate was 2.2 % of confirmed cases (44 of 2031) and 7.2% of admitted children (23 of 318). Death was reported for 15 cases. CONCLUSION: Children accounted for 1.9% of confirmed cases. The true incidence of pediatric infection and disease will only be known once testing is expanded to individuals with less severe or no symptoms. Admission rates vary from 0.3 to 10% of confirmed cases (presumably varying with the threshold for testing) with about 7% of admitted children requiring ICU care. Death is rare in middle and high income countries.Competing Interest StatementThe authors have declared no competing interest.Funding StatementFunding Source: No external funding for this manuscript.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesExtracted data and meta-data for all bibliographic records screened is available on request.

Benucci, M., et al. (2020). **"Médicaments rhumatologiques pour le traitement de l'infection par le COVID-19."** Revue du Rhumatisme (Edition Francaise) **87**(3): 150-152.

Berg, E. A., et al. (2020). "COVID-19 - A Guide to Rapid Implementation of Telehealth Services: A Playbook for the Pediatric Gastroenterologist." Journal of pediatric gastroenterology and nutrition.

Calgary, U. o. (2020). Clinical Characteristics and Outcomes of Pediatric COVID-19. ClinicalTrials.

Cao, Q., et al. (2020). "SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics." Journal of Formosan Medical Association **119**(3): 670-673.

Carmona-Gutierrez, D., et al. (2020). "Digesting the crisis: autophagy and coronaviruses." Microbial Cell **7**(5): 119-128.
Autophagy is a catabolic pathway with multifaceted roles in cellular homeostasis. This process is also involved in the antiviral response at multiple levels, including the direct elimination of intruding viruses (virophagy), the presentation of viral antigens, the fitness of immune cells, and the inhibition of excessive inflammatory reactions. In line with its central role in immunity, viruses have evolved mechanisms to interfere with or to evade the autophagic process, and in some cases, even to harness autophagy or constituents of the autophagic machinery for their replication. Given the devastating consequences of the current COVID-19 pandemic, the question arises whether manipulating autophagy might be an expedient approach to fight the novel coronavirus SARS-CoV-2. In this piece, we provide a short overview of the evidence linking autophagy to coronaviruses and discuss whether such links may provide actionable targets for therapeutic interventions.

Chang, T. H., et al. (2020). "Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis." Journal of Formosan Medical Association **16**: 16.
BACKGROUND/PURPOSE: Current studies on pediatric coronavirus disease 2019 (COVID-19) are rare. The clinical characteristics and spectrum are still unknown. Facing this unknown and emerging pathogen,

we aimed to collect current evidence about COVID-19 in children. METHODS: We performed a systematic review in PubMed and Embase to find relevant case series. Because some reports were published in Chinese journals, the journals and publications of the Chinese Medical Association related to COVID-19 were completely reviewed. A random effects model was used to pool clinical data in the meta-analysis. RESULTS: Nine case series were included. In the pooled data, most of patients (75%) had a household contact history. The disease severity was mainly mild to moderate (98%). Only 2 children (2%) received intensive care. Fever occurred in 59% of the patients, while cough in 46%. Gastrointestinal symptoms (12%) were uncommon. There are 26% children are asymptomatic. The most common radiographic finding was ground glass opacities (48%). Currently, there is no evidence of vertical transmission to neonates born to mothers with COVID-19. Compared with the most relevant virus, SARS-CoV, SARS-CoV-2 causes less severe disease. CONCLUSION: COVID-19 has distinct features in children. The disease severity is mild. Current diagnosis is based mainly on typical ground glass opacities on chest CT, epidemiological suspicion and contact tracing.

Channappanavar, R. and S. Perlman (2020). "Evaluation of Activation and Inflammatory Activity of Myeloid Cells During Pathogenic Human Coronavirus Infection." Methods in Molecular Biology **2099**: 195-204.
Innate immune cells play a vital role in mounting an effective host response to a variety of pathogen challenges. Myeloid cells such as neutrophils and monocyte-macrophages are major innate leukocytes that orchestrate protective immunity to viral lung infections. However, a dysregulated cytokine response can promote excessive infiltration and robust pro-inflammatory activity of neutrophils and monocyte-macrophages, leading to fatal disease. Following virus infection, the beneficial or deleterious role of infiltrating neutrophils and monocyte-macrophages is determined largely by their ability to secrete inflammatory cytokines and chemokines. A majority of studies use the total number of infiltrating cells and their activation status as measures to demonstrate their role during an infection. Consequently, the ability of neutrophils and Inflammatory Monocyte Macrophages (IMMs) to secrete inflammatory cytokines and chemokines, and its correlation with the disease severity, is not well defined. In this chapter, we report useful markers to identify lung infiltrating innate immune cells and define their activation status. We also describe a simple method to measure intracellular cytokine production to evaluate the inflammatory activity of neutrophils and IMMs in a mouse model of human coronavirus infection.

Chao, J. Y., et al. (2020). "Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City." Journal of Pediatrics.
Objective To describe the clinical profiles and risk factors for critical illness in hospitalized children and adolescents with COVID-19. Study design Children 1 month to 21 years with COVID-19 from a single tertiary care children's hospital between March 15-April 13, 2020 were included. Demographic and clinical data were collected. Results 67 children tested positive for COVID-19; 21 (31.3%) were managed as outpatients. Of 46 admitted patients, 33 (72%) were admitted to the general pediatric medical unit and 13 (28%) to the pediatric intensive care unit (PICU). Obesity and asthma were highly prevalent but not significantly associated with PICU admission (p=0.99). Admission to the PICU was significantly associated with higher C-reactive protein, procalcitonin, and pro-B type natriuretic peptide levels and platelet counts (p 0.05 for all). Patients in the PICU were more likely to require high-flow nasal cannula (p=0.0001) and were more likely to have received Remdesivir through compassionate release (p 0.05). Severe sepsis and septic shock syndromes were observed in 7 (53.8%) PICU patients. Acute respiratory distress syndrome (ARDS) was observed in 10 (77%) PICU patients, 6 of whom (46.2%) required invasive mechanical ventilation for a median of 9 days. Of the 13 patients in the PICU, 8 (61.5%) were discharged home, and 4 (30.7%) patients remain hospitalized on ventilatory support at day 14. One patient died after withdrawal of life-sustaining therapy because of metastatic cancer. Conclusions We describe a higher than previously recognized rate of severe disease requiring PICU admission in pediatric patients admitted to the hospital with COVID-19.

Chen, J., et al. (2020). "The clinical and immunological features of pediatric COVID-19 patients in China." Genes & Diseases.
In December 2019, the corona virus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) emerged in Wuhan,China and rapidly spread worldwide. Few information on clinical features and immunological profile of COVID-19 in paediatrics. The clinical features and treatment outcomes of twelve

paediatric patients confirmed as COVID-19 were analyzed. The immunological features of children patients was investigated and compared with twenty adult patients. The median age was 14.5-years (range from 0.64-17), and six of the patients were male. The average incubation period was 8 days. Clinically, cough (9/12, 75%) and fever (7/12, 58.3%) were the most common symptoms. Four patients (33.3%) had diarrhea during the disease. As to the immune profile, children had higher amount of total T cell, CD8+ T cell and B cell but lower CRP levels than adults (P 0.05). Ground-glass opacity (GGO) and local patchy shadowing were the typical radiological findings on chest CT scan. All patients received antiviral and symptomatic treatment and the symptom relieved in 3 to 4 days after admitted to hospital. The paediatric patients showed mild symptom but with longer incubation period. Children infected with SARS-CoV-2 had different immune profile with higher T cell amount and low inflammatory factors level, which might ascribed to the mild clinical symptom. We advise that nucleic acid test or examination of serum IgM/IgG antibodies against SARS-CoV-2 should be taken for children with exposure history regardless of clinical symptom.

Chen, X. B., et al. (2020). "Retrospective Analysis of 61 Cases of Children Died of Viral Pneumonia." Fa i Hsueh Tsa Chih Journal of Forensic Medicine **36**(2): 25.
Abstract: Objective To retrospectively analyze the forensic and pathological postmortem examination and clinical data of children who died of viral pneumonia in identification of cause of death cases and to discuss the clinical characteristics and pathological features of viral pneumonia in children, in order to provide reference to pathological diagnosis of viral pneumonia in children caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Methods In this study, postmortem examination data from the institute of 61 cases of children whose cause of death were identified as viral pneumonia in recent years were collected. The gender, age, clinical symptoms and pathological features were comparatively analyzed. Results Among the 61 cases of children who died of viral pneumonia, most were within 2 years old (83.61%), and a large proportion died within 2 weeks after the onset of the disease (91.80%). General changes in postmortem examination included respiratory mucosal hyperemia, pleural effusion, pulmonary swelling, variegated pulmonary pleura and serosa, focal hemorrhage and edema of the cut surface of the lung. A large proportion of children had enlarged mesenteric lymph nodes (83.61%), and 21.31% of children had thymic dysplasia. Histopathological changes included pulmonary alveoli and interstitial edema, pulmonary hemorrhage, alveolar epithelial shedding, serous and (or) fibrous exudation in the alveoli, formation of viral inclusions, formation of transparent membranes, infiltration of inflammatory cells that mainly consisted of macrophages and lymphocytes in interstitial substance and alveoli. Viral infections often affected the heart and gastrointestinal tract. Conclusion The clinical symptoms of children with viral pneumonia are difficult to notice, and because their immune system is not fully developed and they have poor autoimmunity, they can easily get into a critical condition and even die. Through analysis of the characteristics of forensic autopsy and histopathological changes, this study could provide reference for pathological diagnosis of viral pneumonia.

Ciurkiewicz, M., et al. (2020). "Beneficial and detrimental effects of regulatory T cells in neurotropic virus infections." International Journal of Molecular Sciences **21**(5).
Neurotropic viruses infect the central nervous system (CNS) and cause acute or chronic neurologic disabilities. Regulatory T cells (Treg) play a critical role for immune homeostasis, but may inhibit pathogen-specific immunity in infectious disorders. The present review summarizes the current knowledge about Treg in human CNS infections and their animal models. Besides dampening pathogen-induced immunopathology, Treg have the ability to facilitate protective responses by supporting effector T cell trafficking to the infection site and the development of resident memory T cells. Moreover, Treg can reduce virus replication by inducing apoptosis of infected macrophages and attenuate neurotoxic astrogliosis and pro-inflammatory microglial responses. By contrast, detrimental effects of Treg are caused by suppression of antiviral immunity, allowing for virus persistence and latency. Opposing disease outcomes following Treg manipulation in different models might be attributed to differences in technique and timing of intervention, infection route, genetic background, and the host's age. In addition, mouse models of virus-induced demyelination revealed that Treg are able to reduce autoimmunity and immune-mediated CNS damage in a disease phase-dependent manner. Understanding the unique properties of Treg and their complex interplay with effector cells represents a prerequisite for the development of new therapeutic approaches in neurotropic virus infections. © 2020 by the authors. Licensee MDPI, Basel, Switzerland.

Cordoro, K. M., et al. (2020). "Clustered Cases of Acral Perniosis: Clinical Features, Histopathology and Relationship to COVID-19." Pediatric dermatology.
BACKGROUND/OBJECTIVES: There has been a recent marked increase in pediatric and adult patients presenting with purpuric acral lesions concerning for ischemia, thrombosis and necrosis in COVID-19 prevalent regions worldwide. The clinical and histopathological features and relationship to COVID-19 have not been well described. The objective of this case series is to describe the clinical features and determine the histopathologic findings and clinical implications of the clusters of acral perniosis cases identified in pediatric patients. METHODS: We describe 6 otherwise healthy adolescents - 3 siblings per family from 2 unrelated families - presented within a 48-hour period in April, 2020, with acral perniosis-like lesions in the context of over 30 similar patients who were evaluated within the same week. RESULTS: Affected patients had mild symptoms of viral upper respiratory infection (URI) or contact with symptomatic persons 1-2 weeks preceding the rash. They all presented with red to violaceous macules and dusky, purpuric plaques scattered on the mid and distal aspects of the toes. Skin biopsies performed on each of the 6 patients demonstrated near identical histopathologic findings to those of idiopathic perniosis, with a lymphocytic inflammatory infiltrate without evidence of thromboembolism or immune complex vasculitis. While SARS-CoV-2 polymerase chain reaction was negative, testing was performed 1-2 weeks after URI symptoms or sick contact exposure. CONCLUSION: We offer a clinical approach to evaluation of patients with this presentation and discuss the possibility that these skin findings represent a convalescent-phase cutaneous reaction to SARS-CoV-2 infection.

DeBiasi, R. L., et al. (2020). "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region." The Journal of Pediatrics.

Dipasquale, V., et al. (2020). "Challenges in paediatric inflammatory bowel diseases in the COVID-19 time." Digestive and Liver Disease.

Du, W., et al. (2020). "Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China." Infection: 1-8.
The COVID-19 outbreak spread in China and is a threat to the world. We reported on the epidemiological, clinical, laboratory, and radiological characteristics of children cases to help health workers better understand and provide timely diagnosis and treatment. Retrospectively, two research centers' case series of 67 consecutive hospitalized cases including 53 adult and 14 children cases with COVID-19 between 23 Jan 2020 and 15 Feb 2020 from Jinan and Rizhao were enrolled in this study. Epidemiological, clinical, laboratory, and radiological characteristics of children and adults were analyzed and compared. Most cases in children were mild (21.4%) and conventional cases (78.6%), with mild clinical signs and symptoms, and all cases were of family clusters. Fever (35.7%) and dry cough (21.4%) were described as clinical manifestations in children cases. Dry cough and phlegm were not the most common symptoms in children compared with adults ($p = 0.03$). In the early stages of the disease, lymphocyte counts did not significantly decline but neutrophils count did in children compared with adults ($p = 0.02$). There was a lower level of CRP ($p = 0.00$) in children compared with adults. There were 8 (57.1%) asymptomatic cases and 6 (42.9%) symptomatic cases among the 14 children cases. The age of asymptomatic patients was younger than that of symptomatic patients ($p = 0.03$). Even among asymptomatic patients, 5 (62.5%) cases had lung injuries including 3 (60%) cases with bilateral involvement, which was not different compared with that of symptomatic cases ($p = 0.58$, $p = 0.74$). The clinical symptoms of children are mild, there is substantial lung injury even among children, but that there is less clinical disease, perhaps because of a less pronounced inflammatory response, and that the occurrence of this pattern appears to inversely correlate with age.

Du, W., et al. (2020). "Clinical Characteristics of COVID-19 in Children Compared with Adults Outside of Hubei Province in China." SSRN.
Aims &Background: The COVID-19 outbreak spread in China and is a threat to the world. We reported on the epidemiological, clinical, laboratory, and radiolog

Esteves, S. C., et al. (2020). "SARS-CoV-2 pandemic and repercussions for male infertility patients: a proposal for the individualized provision of andrological services." Andrology.

The prolonged lockdown of health facilities providing non-urgent gamete cryopreservation -as currently recommended by many reproductive medicine entities and regulatory authorities due to the SARS-CoV-2 pandemic will be detrimental for subgroups of male infertility patients. We believe the existing recommendations should be promptly modified and propose that the same permissive approach for sperm banking granted for men with cancer is expanded to other groups of vulnerable patients. These groups include male infertility patients (e.g., azoospermic men and cryptozoospermic) undergoing medical or surgical treatment to improve sperm quantity and quality, as well as males of reproductive age affected by inflammatory and systemic auto-immune diseases who are about to start treatment with gonadotoxic drugs or who are under remission. In both scenarios, the 'fertility window' may be transitory; postponing diagnostic semen analysis and sperm banking in these men could compromise the prospects of biological parenthood. Moreover, we provide recommendations on how to continue the provision of andrological services in a considered manner and a safe environment. Our opinion is timely and relevant given the fact that fertility services are currently rated as of low priority in most countries.

Filocamo, G., et al. (2020). "Absence of severe complications from SARS-CoV-2 infection in children with rheumatic diseases treated with biologic drugs." Journal of rheumatology.
We read with interest the Editorial by Cron and Chatam (1) suggesting a cytokine storm syndrome (CSS) occurring in response to SARS-CoV-2 infection and, consequently, a possible role for targeted approaches to blocking inflammatory cytokines.

Han, Y. N., et al. (2020). "A comparative-descriptive analysis of clinical characteristics in 2019-Coronavirus-infected children and adults." Journal of Medical Virology **06**: 06.
Acute respiratory disease (ARD) caused by 2019 novel coronavirus (2019-nCoV) has rapidly spread throughout China. Children and adults show a different clinical course. The purpose of the current study is to comparatively analyze the clinical characteristics of 2019-nCoV infection in children and adults and to explore the possible causes for the discrepancies present. The medical records of 25 adults and 7 children confirmed cases of 2019-nCoV ARD were reviewed retrospectively. All children were family clusters. The total adult patients were differentiated into: the local residents of Wuhan, a history of travel to Wuhan and direct contact with people from Wuhan. The numbers were 14 (56%), 10 (40%) & 1 (4%), respectively. The median incubation period of children and adults was 5 days (range 3-12 days) and 4 days (range 2-12 days), respectively. Diarrhoea and/or vomiting (57.1%) were more common in children, whereas for adults it was myalgia or fatigue (52%). On admission, the percentage of children having pneumonia (5, 71.4%) was roughly the same as adults (20, 80%). 20% of adults had leucopoenia, but leukocytosis was more frequently in children (28.6%, P=0.014). A higher number of children had elevated creatine kinase isoenzyme (57.1% vs. 4%, P=0.004). Antiviral therapy was given to all adult patients but to none of the children. In summary, knowledge of these differences between children and adults will not only be helpful for the clinical diagnosis of 2019 novel coronavirus disease (COVID-19), but also for a future discussion on age-specific coronavirus infection. This article is protected by copyright. All rights reserved.

Harahsheh, A. S., et al. (2020). "Missed or Delayed Diagnosis of Kawasaki Disease During the 2019 Novel Coronavirus Disease (COVID-19) Pandemic." Journal of Pediatrics **23**: 23.

Henderson, L. A., et al. (2020). "On the alert for cytokine storm: Immunopathology in COVID-19." Arthritis & Rheumatology.
Coronavirus disease 2019 (COVID-19) is sweeping across the globe. Most patients have mild to moderate symptoms, but a subgroup will become severely ill. Sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS) are common complications of the disease.(1) Factors associated with ICU admission and death include older age, comorbid conditions, elevated body mass index, lymphopenia, and elevated transaminases, LDH, D-dimer, ferritin, and soluble IL-2 receptor (sIL-2R).(1-4).

Hong, H., et al. (2020). "Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children." Pediatrics & Neonatology.

Hosoda, T., et al. (2020). "SARS-CoV-2 enterocolitis with persisting to excrete the virus for about two weeks after recovering from diarrhea: A case report." Infection Control & Hospital Epidemiology: 1-4.

Hospital, B. C. s., et al. (2020). Clinical Characteristics and Long-term Prognosis of 2019-nCoV Infection in Children. ClinicalTrials.

Hospital, S. J. C. s. R. (2020). Risk Factors, Clinical Characteristics and Outcomes of Acute Infection With Coronavirus 2019 (COVID-19) In Children. ClinicalTrials, https://ClinicalTrials.gov/show/NCT04371315.

Huang, H., et al. (2020). "Detection and clinical characteristics analysis of respiratory viruses in hospitalized children with acute respiratory tract infections by a GeXP-based multiplex-PCR assay." Journal of Clinical Laboratory Analysis **34**(4).
BackgroundThe information regarding viral epidemiology and clinical characteristics in hospitalized children with acute respiratory tract infection (ARTI) in central Fujian is limited. In this study, we aimed at analyzing the viral epidemiology and clinical characteristics of ARTI in hospitalized children admitted to The First Affiliated Hospital of Fujian Medical University.MethodsCohort of 386 hospitalized children (31 days to 15 years) diagnosed with ARTI admitted to the Department of Pediatrics from January 1, 2018, to December 31, 2018, was enrolled in this study. Nasopharyngeal swab or sputum samples on the day of hospitalization were tested for 11 viruses via a GeXP-based multiplex-PCR assay. The viral profiles and clinical characteristics were analyzed.ResultsThe overall positive rate of the samples was 43.26% (167/386). Among the 167 positive samples, 134 (80.24%, 134/167) had a single virus and 33 (19.76%, 33/167) had multiple viruses. There was a significant difference in the frequency of single vs mixed infections among positive samples (80.24% vs 19.76%; $\chi 2 = 122.168$, P = .000) as well as among the total examined samples (34.72% vs 8.55%; $\chi 2 = 77.945$, P = .000). Human rhinovirus was the most prevalent virus (17.36%, 67/386), followed by influenza A (5.96%, 23/386) and human adenovirus (5.70%, 22/386). There was no significant difference in the etiological distribution of viral pathogens between males and females ($\chi 2 = 0.480$, P = .489). Viral infections were more likely to occur in the winter-spring months than in the summer-autumn months (52.51% vs 33.53%, $\chi 2 = 13.830$, P = .000).ConclusionsThe GeXP-based multiplex PCR is an accurate and high-throughput assay allows us to quickly detect multiple respiratory viruses simultaneously in pediatric patients. Our study provides information on the viral profiles and clinical characteristics in hospitalized children with ARTI, which would help better effective prevention strategies.

Jesenak, M., et al. (2020). "COVID-19, chronic inflammatory respiratory diseases and eosinophils - Observationsfrom reported clinical case series." Allergy.
Currently, the world is facinga global pandemicwith a new coronavirus SARS-CoV- 2 (Severe Acute Respiratory Syndrome CoronaVirus Type 2) causing infectious disease named COVID-19 (CoronaVirus Infectious Disease 2019). Comparing the clinical presentation and epidemiological characteristics of COVID-19 with previous coronavirus-associated respiratory diseases (SARS-CoV1 and MERS) revealedsome remarkable findings and differences. Moreover, the clinical course of SARS-CoV-2 infection showed the complexity of COVID-19 profile with the variable clinical presentations.

Jiang, J., et al. (2020). "Epidemiological and clinical characteristics of novel coronavirus infection in children: Thoughts on the diagnostic criteria of suspected cases outside Hubei Province." Chinese Pediatric Emergency Medicine **27**(0): E003-E003.
Objective To improve the diagnostic criteria of suspected cases through investigating the epidemiological and clinical manifestations of confirmed cases of new-type coronavirus infection in children. Methods We retrospective analyzed the epidemiological and clinical manifestations of 6 children with new coronavirus infection diagnosed in Chongqing Three Gorges Central Hospital from February 3, 2020 to February 15, 2020 . Compared with the diagnostic criteria of suspected cases,we summarized the problems encountered in the application of this standard in clinical work and try to put forward Suggestions for improvement. Results Among the 6 children with confirmed cases: 5 males and 1 female; 3 from Hubei Province and 3 from Wanzhou ; 6 cases of clustered onset of the family; Visiting nature: 3 cases of suspected case income, 3 cases of community or outpatient screening . Three cases with fever and / or respiratory symptoms, one of which had symptoms of diarrhea; all children's blood routine and lymphocyte counts were within the normal range; chest CT imaging except for cases No. 1 and No. 5 were in line with typical new coronavirus pneumonia signs. In addition, the remaining 3 patients had abnormal imaging but did not have the characteristics of new coronavirus pneumonia, and 1 case was

normal. Comparison results:Only case 1 of all cases fully met the diagnostic criteria, and the remaining cases did not meet the diagnostic criteria of early suspected cases. Conclusion In order to improve the accuracy and practicality of the diagnosis of suspected cases in children, it is recommended to refine and standardize the diagnostic criteria of some suspected cases.

Jones, V. G., et al. (2020). "COVID-19 and Kawasaki Disease: Novel Virus and Novel Case." Hospital Pediatrics **07**: 07.

Jouanguy, E. (2020). "Human genetic basis of fulminant viral hepatitis." Human Genetics.
In rare cases, hepatitis A virus (HAV) and hepatitis B virus (HBV) can cause fulminant viral hepatitis (FVH), characterized by massive hepatocyte necrosis and an inflammatory infiltrate. Other viral etiologies of FVH are rarer. FVH is life-threatening, but the patients are typically otherwise healthy, and normally resistant to other microbes. Only a small minority of infected individuals develop FVH, and this is the key issue to be addressed for this disease. In mice, mouse hepatitis virus 3 (MHV3) infection is the main model for dissecting FVH pathogenesis. Susceptibility to MHV3 differs between genetic backgrounds, with high and low mortality in C57BL6 and A/J mice, respectively. FVH pathogenesis in mice is related to uncontrolled inflammation and fibrinogen deposition. In humans, FVH is typically sporadic, but rare familial forms also exist, suggesting that there may be causal monogenic inborn errors. A recent study reported a single-gene inborn error of human immunity underlying FVH. A patient with autosomal recessive complete IL-18BP deficiency was shown to have FVH following HAV infection. The mechanism probably involves enhanced IL-18- and IFN-gamma-dependent killing of hepatocytes by NK and CD8 T cytotoxic cells. Proof-of-principle that FVH can be genetic is important clinically, for the affected patients and their families, and immunologically, for the study of immunity to viruses in the liver. Moreover, the FVH-causing IL18BP genotype suggests that excessive IL-18 immunity may be a general mechanism underlying FVH, perhaps through the enhancement of IFN-gamma immunity. Copyright © 2020, Springer-Verlag GmbH Germany, part of Springer Nature.

Kammoun, R. and K. Masmoudi (2020). "Paediatric aspects of COVID-19: an update." Respiratory Medicine and Research: 100765.

Kennedy, N. A., et al. (2020). "British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic." Gut.
The COVID-19 pandemic is putting unprecedented pressures on healthcare systems globally. Early insights have been made possible by rapid sharing of data from China and Italy. In the UK, we have rapidly mobilised inflammatory bowel disease (IBD) centres in order that preparations can be made to protect our patients and the clinical services they rely on. This is a novel coronavirus; much is unknown as to how it will affect people with IBD. We also lack information about the impact of different immunosuppressive medications. To address this uncertainty, the British Society of Gastroenterology (BSG) COVID-19 IBD Working Group has used the best available data and expert opinion to generate a risk grid that groups patients into highest, moderate and lowest risk categories. This grid allows patients to be instructed to follow the UK government's advice for shielding, stringent and standard advice regarding social distancing, respectively. Further considerations are given to service provision, medical and surgical therapy, endoscopy, imaging and clinical trials.

Lenval, F. (2020). Incidence of Covid-19 in School Children. ClinicalTrials, https://ClinicalTrials.gov/show/NCT04377737.

Li, J., et al. (2020). "AVNP2 protects against cognitive impairments induced by C6 glioma by suppressing tumour associated inflammation in rats." Brain, Behavior, & Immunity **22**: 22.
Glioblastoma is a kind of malignant tumour and originates from the central nervous system. In the last century, some researchers and clinician have noticed that the psychosocial and neurocognitive functioning of patients with malignant gliomas can be impaired. Many clinical studies have demonstrated that part of patients, adults or children, diagnosed with glioblastoma will suffer from cognitive deficiency during their clinical course, especially in long-term survivors. Many nanoparticles (NPs) can inhibit the biological functions of tumours by modulating tumour-associated inflammation, which provokes angiogenesis and tumour growth. As one of the best antiviral nanoparticles (AVNPs), AVNP2 is the 2nd

generation of AVNP2 that have been conjugated to graphite-graphene for improving physiochemical performance and reducing toxicity. AVNP2 inactivates viruses, such as the H1N1 and H5N1influenza viruses and even the SARS coronavirus, while it inhibits bacteria, such as MRSA and E. coli. As antimicrobials, nanoparticles are considered to be one of the vectors for the administration of therapeutic compounds. Yet, little is known about their potential functionalities and toxicities to the neurotoxic effects of cancer. Herein, we explored the functionality of AVNP2 on inhibiting C6 in glioma-bearing rats. The novel object-recognition test and open-field test showed that AVNP2 significantly improved the neuro-behaviour affected by C6 glioma. AVNP2 also alleviated the decline of long-term potentiation (LTP) and the decreased density of dendritic spines in the CA1 region induced by C6. Western blot assay and immunofluorescence staining showed that the expressions of synaptic-related proteins (PSD-95 and SYP) were increased, and these findings were in accordance with the results mentioned above. It revealed that the sizes of tumours in C6 glioma-bearing rats were smaller after treatment with AVNP2. The decreased expression of inflammatory factors (IL-1beta, IL-6 and TNF-alpha) by Western blotting assay and ELISA, angiogenesis protein (VEGF) by Western blotting assay and other related proteins (BDNF, NF-kB, iNOS and COX-2) by Western blotting assay in peri-tumour tissue indicated that AVNP2 could control tumour-associated inflammation, thus efficiently ameliorating the local inflammatory condition and, to some extent, inhibiting angiogenesis in C6-bearing rats. In conclusion, our results suggested that AVNP2 could have an effect on the peri-tumor environment, obviously restraining the growth progress of gliomas, and eventually improving cognitive levels in C6-bearing rats.

Li, Y., et al. (2020). "Insight into COVID-2019 for pediatricians." Pediatric Pulmonology **18**: 18.
Since December 2019, patients with unexplained pneumonia have been found in Wuhan City, Hubei Province, China. The pathogen in these cases is a new type of coronavirus. The World Health Organization confirmed this diagnosis and named the pathogen SARSCoV-2. The disease caused by SARSCoV-2 is called Corona Virus Disease (COVID-2019). The virus is highly infectious and pathogenic, causing human-to-human transmission. At present, SARSCoV-2 is still rampant in the world. Zhengzhou City in Henan Province serves as an example, 102 people have been confirmed to be infected with SARSCoV-2 (at 24:00 on February 5th, 2020), including three children, the youngest is 4 years old. From the perspective of clinical pediatricians as the first line fighting the epidemic, this paper will discuss the clinical characteristics, prevention and control measures, outcomes, diagnosis, and treatment of pediatric cases.

Lindsley, A. W., et al. (2020). "Eosinophil Responses During COVID-19 Infections and Coronavirus Vaccination." Journal of Allergy and Clinical Immunology.
Eosinophils are circulating and tissue-resident leukocytes that have potent pro-inflammatory effects in a number of diseases. Recently, eosinophils have been shown to have a variety of other functions, including immunoregulation and antiviral activity. Eosinophil levels vary dramatically in a number of clinical settings, especially following eosinophil-targeted therapy, which is now available to selectively deplete these cells. There are key COVID-19-related questions concerning eosinophils whose answers affect recommended prevention and care. First, do patients with eosinophilia-associated diseases have an altered course of COVID-19? Second, do patients with eosinopenia (now intentionally induced by biological drugs) have unique COVID-19 susceptibility and/or disease course? This is a particularly relevant question as eosinopenia is associated with acute respiratory deterioration during infection with the Severe Acute Respiratory Syndrome (SARS)-Corona Virus (CoV)-2, the causative agent of COVID-19. Third, do eosinophils contribute to the lung pathology induced during COVID-19 and will they contribute to immunopotentiation potentially associated with emerging COVID-19 vaccines? Herein, we address these timely questions and project considerations during the emerging COVID-19 pandemic.

Lippi, G., et al. (2020). "Hypertension in patients with coronavirus disease 2019 (COVID-19): A pooled analysis." Polish Archives of Internal Medicine **130**(4): 304-309.
Introduction As the outbreak of coronavirus disease 2019 (COVID-19) was recognized, the clinical predictors of severe or fatal course of the disease should be identified to enable risk stratification and to allocate limited resources optimally. Hypertension has been widely reported to be associated with increased disease severity; however, some studies reported different findings. Objectives The study aimed to evaluate the association between hypertension and severe and fatal COVID-19. Methods The Scopus, Medline, and Web of Science databases were searched to identify studies reporting the rate of

hypertensive patients in the population diagnosed with severe or nonsevere COVID-19 or in COVID-19 survivors and nonsurvivors. The obtained data were pooled into a meta-analysis to calculate odds ratios (ORs) with 95% CIs. Results Hypertension was associated with a nearly 2.5-fold increased risk of severe COVID-19 (OR, 2.49; 95% CI, 1.98-3.12; I2 = 24%), as well as with a similarly significant higher mortality risk (OR, 2.42; 95% CI, 1.51-3.90; I2 = 0%). In a meta-regression analysis, a correlation was observed between an increase in the mean age of patients with severe COVID-19 and an increased log OR of hypertension and COVID-19 severity (P = 0.03). Conclusions This pooled analysis of the current literature would suggest that hypertension may be associated with an up to 2.5-fold higher risk of severe or fatal COVID-19, especially in older individuals. © Author(s), 2020.

Liu, M., et al. (2020). "Family cluster of child SARS-CoV-2 infections: a case report." Medical Journal of Wuhan University **41**(3): 362-365.
A case of child SARS-CoV-2 infection with family cluster was reported in this paper. The boy's father was the first case in this family. Then the boy, the grandmother and the mother were infected one by one. Combined with literature analysis, it suggested that SARS-CoV-2 infection could be transmitted from person to person, and it was highly contagious. However, the children's symptoms were mild and the prognosis was acceptable in general. © 2020, Editorial Board of Medical Journal of Wuhan University. All right reserved.

Liu, P., et al. (2020). "The immunologic status of newborns born to SARS-CoV2-infected mothers in Wuhan, China." Journal of Allergy and Clinical Immunology.
BACKGROUND: Immunologic dysfunction due to COVID-19 is closely related to clinical prognosis, and the inflammatory response of pregnant women may affect the directional differentiation and function of fetal immune cells. OBJECTIVE: To analyze the immune status of newborns from mothers with COVID-19 in the third trimester. METHODS: Along with collecting the clinical data from 51 newborns and their respective mothers, we also recorded the immunophenotypes and cytokine and immunoglobulin levels of the newborns. RESULTS: None of the 51 newborns showed fever or respiratory distress during hospitalization. Detection of SARS-CoV-2 nucleic acid in pharyngeal swabs was negative. Except for the low level of CD16-CD56 cells, the count and proportion of lymphocytes, CD3, CD4, CD8, and CD19 were all in the normal range. Moreover, the serum IgG and IgM levels were within the normal range, while IL-6 showed increased levels. There was no correlation between maternal COVID-19 duration and the lymphocyte subsets or cytokine levels (IFN-γ, IL-2, IL-4, IL-6, IL-10 and TNF-α). There was a positive correlation between IL-6 and IL-10 levels and CD16-CD56 cells. One (1.96%) infant with an extremely elevated IL-6 concentration developed necrotizing enterocolitis in the third week after birth, and the remaining 50 infants did not show abnormal symptoms through the end of the follow-up period. CONCLUSION: COVID-19 in the third trimester did not significantly affect the cellular and humoral immunity of the fetus, and there was no evidence that the differentiation of lymphocyte subsets was seriously unbalanced.

Lu, S., et al. (2020). "Effectiveness and Safety of Glucocorticoids to Treat COVID-19: A Rapid Review and Meta-Analysis." medRxiv: 2020.2004.2017.20064469.
Background: Glucocorticoids are widely used in the treatment of various pulmonary inflammatory diseases, but they are also often accompanied by significant adverse reactions. Published guidelines point out that low dose and short duration systemic glucocorticoid therapy may be considered for patients with rapidly progressing COVID-19 while the evidence is still limited. Methods: We comprehensively searched electronic databases and supplemented the screening by conducting a manual search. We included RCTs and cohort studies evaluating the effectiveness and safety of glucocorticoids in children and adults with COVID-19, SARS and MERS, and conducted meta-analyses of the main indicators that were identified in the studies. Results: Our search retrieved 23 studies, including one RCT and 22 cohort studies, with a total of 13,815 patients. In adults with COVID-19, the use of systemic glucocorticoid did not reduce mortality (RR=2.00, 95% CI: 0.69 to 5.75, I 2=90.9%) or the duration of lung inflammation (WMD=-1 days, 95% CI: -2.91 to 0.91), while a significant reduction was found in the duration of fever (WMD=-3.23 days, 95% CI: -3.56 to -2.90). In patients with SARS, glucocorticoids also did not reduce the mortality (RR=1.52, 95% CI: 0.89 to 2.60, I2=84.6%), duration of fever (WMD=0.82 days, 95% CI: -2.88 to 4.52, I2=97.9%) or duration of lung inflammation absorption (WMD=0.95 days, 95% CI: -7.57 to 9.48, I2=94.6%). The use of systemic glucocorticoid therapy prolonged the duration of hospital stay in all

patients (COVID-19, SARS and MERS). Conclusions: Glucocorticoid therapy was found to reduce the duration of fever, but not mortality, duration of hospitalization or lung inflammation absorption. Long-term use of high-dose glucocorticoids increased the risk of adverse reactions such as coinfections, so routine use of systemic glucocorticoids for patients with COVID-19 cannot be recommend. Keywords: COVID-19; glucocorticoids; meta-analysis; rapid reviewCompeting Interest StatementThe authors have declared no competing interest.Funding StatementThis work was supported by grants from National Clinical Research Center for Child Health and Disorders (Children's Hospital of Chongqing Medical University, Chongqing, China) (grant number NCRCCHD-2020-EP-01); Special Fund for Key Research and Development Projects in Gansu Province in 2020; The fourth batch of "Special Project of Science and Technology for Emergency Response to COVID-19" of Chongqing Science and Technology Bureau. Special funding for prevention and control of emergency of COVID-19 from Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province (grant number No. GSEBMKT-2020YJ01).Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe data used to support the findings of this study are included within the article.

Lu, Y., et al. (2020). "Clinical characteristics and radiological features of children infected with the 2019 novel coronavirus." Clinical Radiology **01**: 01.
AIM: To identify and summarise the common findings from 2019 novel coronavirus (2019-nCoV) infections in children. MATERIALS AND METHODS: The clinical characteristics and radiological findings (chest radiography and chest computed tomography [CT]) of nine children infected with the 2019-nCoV were reviewed in this retrospective case series. RESULTS: Among the children, six had fever (including two children with cough), one had only cough, one had a stuffy nose when initially diagnosed, and one was an asymptomatic carrier. Chest radiographs seemed mostly normal in six cases whereas increased and/or disordered bilateral bronchovascular shadows and dense hilar shadows were seen in three cases. Chest CT exhibited no obvious abnormal signs in four cases. Typical CT findings included patchy, peripheral ground-grass opacities, subpleural lamellar dense shadows, and parenchymal bands. Pleural effusions, mediastinal lymphadenopathy, cavitation, and pleural thickening were absent. CONCLUSION: The clinical manifestations and radiological findings of the 2019-nCoV-infected children were mild and lacked a typical pattern.

Ludvigsson, J. F. (2020). "Systematic review of COVID-19 in children show milder cases and a better prognosis than adults." Acta Paediatrica **23**: 23.
AIM: The coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people. Data on symptoms and prognoses in children are rare. METHODS: A systematic literature review was carried out to identify papers on COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the Medline and EMBASE databases between 1 January and 18 March 2020. RESULTS: The search identified 45 relevant scientific papers and letters. The review showed that children have so far accounted for 1-5% of diagnosed COVID-19 cases, they often have milder disease than adults and deaths have been extremely rare. Diagnostic findings have been similar to adults, with fever and respiratory symptoms being prevalent, but fewer children seem to have developed severe pneumonia. Elevated inflammatory markers were less common in children and lymphocytopenia seemed rare. Newborn infants have developed symptomatic COVID-19, but evidence of vertical intrauterine transmission was scarce. Suggested treatment included providing oxygen, inhalations, nutritional support and maintaining fluids and electrolyte balances. CONCLUSIONS: COVID-19 has occurred in children, but they seemed to have a milder disease course and better prognoses than adults. Deaths were extremely rare.

Luo, S., et al. (2020). "[Clinical observation of 6 severe COVID-19 patients treated with plasma exchange or tocilizumab]." Zhejiang da Xue Xue Bao. Yi Xue Ban/Journal of Zhejiang University. Medical Sciences **49**(2): 227-231.
OBJECTIVE: To observe the clinical effect of plasma exchange and tocilizumab in treatment of patients with severe coronavirus disease 2019 (COVID-19). METHODS: Six patients with severe COVID-19 admitted in First Affiliated Hospital of Bengbu Medical College from January 25 to February 25, 2020. Three patients were treated with plasma exchange and three patients were treated with tocilizumab. The effect on excessive inflammatory reaction of plasma exchange and tocilizumab was observed. RESULTS: The C-reactive protein (CRP) and IL-6 levels were significantly decreased and the lymphocyte and prothrombin time were improved in 3 patients after treatment with plasma exchange; while inflammation level was not significantly decreased, and lymphocyte and prothrombin time did not improve in 3 patients treated with tocilizumab. CONCLUSIONS: For severe COVID-19 patients with strong inflammatory reaction, plasma exchange may be preferred.

Ma, H., et al. (2020). "High resolution CT features of novel coronavirus pneumonia in children." Chinese Journal of Radiology **54**(0): E002-E002.
Objective To investigate the high resolution CT (HRCT) features of novel coronavirus pneumonia (NCP) in children . Methods A retrospective analysis was performed on the chest HRCT findings of 22 children diagnosed with 2019-nCov pneumonia by clinical and nucleic acid testing in Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 25, 2020 to February 5, 2020. There were 12 boys and 10 girls, aged from 2 months to 14 years old, with a median age of 4 years, and 14 patients were under 5 years old. The characteristics of lung lesions on HRCT imaging such as distribution, shape, density, etc. and whether there were hilar and mediastinal lymph node enlargement and pleural changes were observed by 2 radiologists. Results In all of the 22 patients, 3 patients (3/22) had normal chest CT, and 19 patients (19/22) had infiltrated lesions in lung. Among them, 7 patients had unilateral lung involvement, 12 patients had bilateral involvement. The HRCT manifestations were as follows. Six patients showed ground glass shadow, including 4 cases showed light ground glass shadow and 2 had typical crazy paving sign. Four patients showed lung consolidation, with localized strip shadow and patchy high-density shadow. Six patients showed patchy lesions with surrounding ground glass shadow, including 1 case with white lung in the right. The bronchopneumonia-like changes in 3 cases, showed scattered spot-like or patchy uneven high-density shadows. The lesions in the lower lobe were more serious than those in the upper lobe, and the lesions in the lateroposterior zone of the lung were more common than those in the apical and central area of the lung. No enlarged lymph nodes and pleural effusion were seen in all patients, and 1 case had thickened interlobar pleura. Conclusions The HRCT manifestations of NCP in children are diversified, comprehensive judgments need to be made in combination with epidemiological data, clinical manifestations, and laboratory tests, but the chest HRCT can be used as an important basis for early clinical diagnosis and prevention and control interventions.

Mahase, E. (2020). "Covid-19: concerns grow over inflammatory syndrome emerging in children." BMJ **369**: m1710-m1710.
Doctors in the UK have been warned over a rising number of children presenting with a multisystem inflammatory state and needing intensive care. In an urgent alert shared by North Central London Clinical Commissioning Group and the Paediatric Intensive Care Society,1 doctors were told that while the unspecified number of cases may be connected to the current pandemic, the symptoms have been observed in both children who have tested positive and negative for covid-19. "There is a growing concern that a SARS-CoV-2 related inflammatory syndrome is emerging in children in the UK or that there may be another as yet unidentified infectious pathogen associated with these cases," the letter said. Child health leaders have stressed that there is currently a small number of cases and that advice to …

Mailhot, G. and J. H. White (2020). "Vitamin D and immunity in infants and children." Nutrients **12**(5).
The last couple of decades have seen an explosion in our interest and understanding of the role of vitamin D in the regulation of immunity. At the molecular level, the hormonal form of vitamin D signals through the nuclear vitamin D receptor (VDR), a ligand-regulated transcription factor. The VDR and vitamin D metabolic enzymes are expressed throughout the innate and adaptive arms of the immune system. The advent of genome-wide approaches to gene expression profiling have led to the

identification of numerous VDR-regulated genes implicated in the regulation of innate and adaptive immunity. The molecular data infer that vitamin D signaling should boost innate immunity against pathogens of bacterial or viral origin. Vitamin D signaling also suppresses inflammatory immune responses that underlie autoimmunity and regulate allergic responses. These findings have been bolstered by clinical studies linking vitamin D deficiency to increased rates of infections, autoimmunity, and allergies. Our goals here are to provide an overview of the molecular basis for immune system regulation and to survey the clinical data from pediatric populations, using randomized placebo-controlled trials and meta-analyses where possible, linking vitamin D deficiency to increased rates of infections, autoimmune conditions, and allergies, and addressing the impact of supplementation on these conditions. © 2020 by the authors. Licensee MDPI, Basel, Switzerland.

Mao, L.-j., et al. (2020). "A child with household transmitted COVID-19." BMC Infectious Diseases **20**(1): 329-329.
Although people of all ages are susceptible to the novel coronavirus infection, which is presently named "Coronavirus Disease 2019" (COVID-19), there has been relatively few cases reported among children. Therefore, it is necessary to understand the clinical characteristics of COVID-19 in children and the differences from adults. We report one pediatric case of COVID-19. A 14-month-old boy was admitted to the hospital with a symptom of fever, and was diagnosed with a mild form of COVID-19. The child's mother and grandmother also tested positive for SARS-CoV-2 RNA. However, the lymphocyte counts were normal. The chest computed tomography (CT) revealed scattered ground glass opacities in the right lower lobe close to the pleura and resorption after the treatment. The patient continued to test positive for SARS-CoV-2 RNA in the nasopharyngeal swabs and stool at 17 days after the disappearance of symptoms. The present pediatric case of COVID-19 was acquired through household transmission, and the symptoms were mild. Lymphocyte counts did not significantly decrease. The RNA of SARS-CoV-2 in stool and nasopharyngeal swabs remained positive for an extended period of time after the disappearance of symptoms. This suggests that attention should be given to the potential contagiousness of pediatric COVID-19 cases after clinical recovery.

Matthai, J., et al. (2020). "Coronavirus Disease (COVID-19) and the Gastrointestinal System in Children." Indian Pediatrics **12**: 12.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), though primarily a respiratory pathogen, also involves the gastrointestinal tract. Similar to the respiratory mucosa, angiotensin converting enzyme-2 (ACE-2) receptor and transmembrane serine protease 2 TMPRSS2) co-express in the gastrointestinal tract, which facilitates viral entry into the tissue. Less than 10% of children with infection develop diarrhea and vomiting. Prolonged RT PCR positivity in the stool has raised the possibility of feco-oral transmission. Elevated transaminases are common, especially in those with severe coronavirus disease-2019 (COVID -19) disease. Children with inflammatory bowel disease and post liver transplant patients do not have an increased risk of disease, and should remain on medications they are already on. Children with chronic liver disease should continue their medications as usual. All elective procedures like endoscopy should be postponed.

Miles, B. A., et al. (2020). "Tracheostomy during COV-SARS-CoV-2 pandemic: Recommendations from the New York Head and Neck Society." Head and Neck.
The rapid spread of SARS-CoV-2 in 2019 and 2020 has resulted in a worldwide pandemic characterized by severe pulmonary inflammation, effusions, and rapid respiratory compromise. The result of this pandemic is a large and increasing number of patients requiring endotracheal intubation and prolonged ventilator support. The rapid rise in endotracheal intubations coupled with prolonged ventilation requirements will certainly lead to an increase in tracheostomy procedures in the coming weeks and months. Performing tracheostomy in the setting of active COV-SARS-CoV-2, when necessary, poses a unique situation, with unique risks and benefits for both the patient and the health care providers. The New York Head and Neck Society has collaborated on this document to provide guidance on the performance of tracheostomies during the SARS-CoV-2 pandemic. © 2020 Wiley Periodicals, Inc.

Molloy, E. J. (2020). "The Doctor's Dilemma: lessons from GB Shaw in a modern pandemic COVID-19." Pediatric Research.
In the current COVID 19 pandemic, the only treatments are supportive as no definitive pharmacological

intervention is available. The heterogeneity of the immune response in different patient groups is clear with less severe illness in children. Understanding these disparities is particularly important as severely affected patients with COVID19 cannot always be predicted before they experience a cytokine storm and multiorgan dysfunction. Over 100 years ago, the concept of individualised immunotherapy was introduced by Sir Almroth Wright and immortalised in GB Shaw's play The Doctor's Dilemma. Shaw's play The Doctor's Dilemma explores the issues of private medical practice, equality of health care delivery, rationing of scarce resources (intensive care) and high-risk therapies. The play also describes the dilemma of rationing of resources and selecting the correct patient for new experimental therapies. Immunological theories of the time are now reflected in current understanding of inflammatory responses in sepsis and immunomodulation during the COVID19 pandemic.

Molloy, E. J. and C. F. Bearer (2020). "COVID-19 in children and altered inflammatory responses." Pediatric Research.

Morand, A. U., D.; Fabre, A. 2020, 2020050160 (). (2020). "COVID-19 and Kawasaki Like Disease: The Known-Known, the Unknown-Known and the Unknown-Unknown." Preprints.
In the end of April nearly 100 cases of children aged between 6 month and 9 years with Kawasaki like disease were reported (mostly in Europe) probably linked to COVID-19. With the increasing awareness of this condition the number of cases reported is increasing worldwide. We aim to sum up the known data about this new entity based on published data (in a case report, a series of 8 cases and in newspapers and society statement) and using our knowledge of classical Kawasaki disease. It seems to be a post infectious disease with an onset between 2-4 weeks after the infection, probably in genetically predisposed children aged between 6 month to 17 years. A very rough estimation of incidence based on current data from Bergamo, Italy, and New York State and a lot assumption is between 0.016% (95% CI:0.013-0.02%) - 0.31% (95% CI: 0.2-0.47%) of infected children. Clinical signs overlaps with Kawasaki disease in some children, but another feature is prominent gastrointestinal manifestations. For the 9 detailed patients most had incomplete presentation for Kawasaki disease (with a mean 1.7 (+/-1.2) criteria per patient for the 5 non fever criterion) and only one had a classical form. In some cases, presentation is closer to toxic shock syndrome or isolated myocarditis. Persistent fever seems to be constant and biological exploration are consistent with inflammation (elevated CRP, ferritin and D-Dimers). Management is described as supportive and children seem to improve rapidly, but can require cardiac or respiratory support. In date of 11 may 2020 there is 4 deaths confirmed linked to these new entities (1 in UK and 3 in New York). Paediatricians and general practitioners need to be aware of these possible evolution following COVID-19 infection. However it seems to be rare and children are probably still spared from most morbidities and mortality linked to COVID-19 infection .There are need of published detailed cohorts to better delineate these entities.

Muus, C., et al. (2020). "Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells." bioRxiv: 2020.2004.2019.049254.
The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, creates an urgent need for identifying molecular mechanisms that mediate viral entry, propagation, and tissue pathology. Cell membrane bound angiotensin-converting enzyme 2 (ACE2) and associated proteases, transmembrane protease serine 2 (TMPRSS2) and Cathepsin L (CTSL), were previously identified as mediators of SARS-CoV2 cellular entry. Here, we assess the cell type-specific RNA expression of ACE2, TMPRSS2, and CTSL through an integrated analysis of 107 single-cell and single-nucleus RNA-Seq studies, including 22 lung and airways datasets (16 unpublished), and 85 datasets from other diverse organs. Joint expression of ACE2 and the accessory proteases identifies specific subsets of respiratory epithelial cells as putative targets of viral infection in the nasal passages, airways, and alveoli. Cells that co-express ACE2 and proteases are also identified in cells from other organs, some of which have been associated with COVID-19 transmission or pathology, including gut enterocytes, corneal epithelial cells, cardiomyocytes, heart pericytes, olfactory sustentacular cells, and renal epithelial cells. Performing the first meta-analyses of scRNA-seq studies, we analyzed 1,176,683 cells from 282 nasal, airway, and lung parenchyma samples from 164 donors spanning fetal, childhood, adult, and elderly age groups, associate increased levels of ACE2, TMPRSS2, and CTSL in specific cell types with increasing age, male gender, and smoking, all of which are epidemiologically linked to COVID-19 susceptibility and outcomes. Notably, there was a

particularly low expression of ACE2 in the few young pediatric samples in the analysis. Further analysis reveals a gene expression program shared by ACE2+TMPRSS2+ cells in nasal, lung and gut tissues, including genes that may mediate viral entry, subtend key immune functions, and mediate epithelial-macrophage cross-talk. Amongst these are IL6, its receptor and co-receptor, IL1R, TNF response pathways, and complement genes. Cell type specificity in the lung and airways and smoking effects were conserved in mice. Our analyses suggest that differences in the cell type-specific expression of mediators of SARS-CoV-2 viral entry may be responsible for aspects of COVID-19 epidemiology and clinical course, and point to putative molecular pathways involved in disease susceptibility and pathogenesis.Competing Interest StatementN.K. was a consultant to Biogen Idec, Boehringer Ingelheim, Third Rock, Pliant, Samumed, NuMedii, Indaloo, Theravance, LifeMax, Three Lake Partners, Optikira and received non-financial support from MiRagen. All of these outside the work reported. J.L. is a scientific consultant for 10X Genomics Inc A.R. is a co-founder and equity holder of Celsius Therapeutics, an equity holder in Immunitas, and an SAB member of ThermoFisher Scientific, Syros Pharmaceuticals, Asimov, and Neogene Therapeutics O.R.R., is a co-inventor on patent applications filed by the Broad Institute to inventions relating to single cell genomics applications, such as in PCT/US2018/060860 and US Provisional Application No. 62/745,259. A.K.S. compensation for consulting and SAB membership from Honeycomb Biotechnologies, Cellarity, Cogen Therapeutics, Orche Bio, and Dahlia Biosciences. S.A.T. was a consultant at Genentech, Biogen and Roche in the last three years. F.J.T. reports receiving consulting fees from Roche Diagnostics GmbH, and ownership interest in Cellarity Inc. L.V. is funder of Definigen and Bilitech two biotech companies using hPSCs and organoid for disease modelling and cell based therapy.

Novice, T., et al. (2020). "A Germline Mutation in the C2 Domain of PLCγ2 Associated with Gain-of-Function Expands the Phenotype for PLCG2-Related Diseases." Journal of Clinical Immunology **40**(2): 267-276.
We report three new cases of a germline heterozygous gain-of-function missense (p.(Met1141Lys)) mutation in the C2 domain of phospholipase C gamma 2 (PLCG2) associated with symptoms consistent with previously described auto-inflammation and phospholipase Cγ2 (PLCγ2)-associated antibody deficiency and immune dysregulation (APLAID) syndrome and pediatric common variable immunodeficiency (CVID). Functional evaluation showed platelet hyper-reactivity, increased B cell receptor-triggered calcium influx and ERK phosphorylation. Expression of the altered p.(Met1141Lys) variant in a PLCγ2-knockout DT40 cell line showed clearly enhanced BCR-triggered influx of external calcium when compared to control-transfected cells. Our results further expand the molecular basis of pediatric CVID and phenotypic spectrum of PLCγ2-related defects. © 2019, Springer Science+Business Media, LLC, part of Springer Nature.

Phillips, B. (2020). "Towards evidence-based medicine for paediatricians." Archives of disease in childhood **105**(5): 506.

Poh, C. M., et al. (2020). "Multiplex Screening Assay for Identifying Cytotoxic CD8+ T Cell Epitopes." Frontiers in Immunology **11**.
The cytotoxicity of epitope-specific CD8+ T cells is usually measured indirectly through IFNγ production. Existing assays that directly measure this activity are limited mainly to measurements of up to two specificities in a single reaction. Here, we develop a multiplex cytotoxicity assay that allows direct, simultaneous measurement of up to 23 different specificities of CD8+ T cells in a single reaction. This can greatly reduce the amount of starting clinical materials for a systematic screening of CD8+ T cell epitopes. In addition, this greatly enhanced capacity enables the incorporation of irrelevant epitopes for determining the non-specific killing activity of CD8+ T cells, thereby allowing to measure the actual epitope-specific cytotoxicity activities. This technique is shown to be useful to study both human and mouse CD8+ T cells. Besides, our results from human PBMCs and three independent infectious animal models (MERS, influenza and malaria) further reveal that IFNγ expression by epitope-specific CD8+ T cells does not always correlate with their cell-killing potential, highlighting the need for using cytotoxicity assays in specific contexts (e.g., evaluating vaccine candidates). Overall, our approach opens up new possibilities for comprehensive analyses of CD8+ T cell cytotoxicity in a practical manner. © Copyright © 2020 Poh, Zheng, Channappanavar, Chang, Nguyen, Rénia, Kedzierska, Perlman and Poon.

Porcelli, P. (2020). "Fear, anxiety and health-related consequences after the COVID-19 epidemic." Clinical

Neuropsychiatry **17**(2): 103-111.
The current COVID-19 pandemic is causing direct and indirect effects in the global population. In this paper, fear and its possible forthcoming consequences on health will be investigated and discussed. Fear is an innate reactive emotion to the immediate threats produced by danger. It is hardwired within subcortical survival circuits and originally had to defend the organism from predators. Besides, fear is a cognitive emotional process mediated by the cortical structures, and implies a subjective evaluation both at implicit (subsymbolic, unconscious) and explicit (symbolic, conscious) levels. Within a defensive taxonomy framework, fear can be defined as a reflex triggering a prompt behavior aimed at surviving from predating attacks (freezing), whereas anxiety as a deliberate pattern aimed at planning behaviors for anticipating and avoiding future harm. Fear and anxiety overlap at a subjective level, but are generated by different neurobiological networks and serve different evolutionary goals. The current viral danger and the need for social distancing worsen the sense of loneliness. A wide body of experimental and epidemiological literature evidence that psychological stress, social isolation, and loneliness have a detrimental effect on multiple health-related outcomes including comorbidity, multimorbidity, and mortality. The negative effects can be even higher for people currently living a massive limitation of physical and interpersonal contacts. A strong effort to integrate psychological and medical care is needed to face post-pandemic health issues. © Clinical Neuropsychiatry.

Potdar, A. A., et al. (2020). "Reduced expression of COVID-19 host receptor, ACE2 is associated with small bowel inflammation, more severe disease, and response to anti-TNF therapy in Crohn's disease." medRxiv: 2020.2004.2019.20070995.
Angiotensin-Converting Enzyme 2 (ACE2) has been identified as the host receptor for SARS-coronavirus 2 (SARS-CoV-2) which has infected millions world-wide and likely caused hundreds of thousands of deaths. Utilizing transcriptomic data from four cohorts taken from Crohn's disease (CD) and non-inflammatory bowel disease (IBD) subjects, we observed evidence of increased ACE2 mRNA in ileum with demographic features that have been associated with poor outcomes in COVID-19 including age and raised BMI. ACE2 was downregulated in CD compared to controls in independent cohorts. Within CD, ACE2 expression was reduced in inflamed ileal tissue and also remarkably, from uninvolved tissue in patients with a worse prognosis in both adult and pediatric cohorts. In active CD, small bowel ACE2 expression was restored by anti-TNF therapy particularly in anti-TNF responders. Collectively our data suggest that ACE2 downregulation is associated with inflammation and worse outcomes in CD.Competing Interest StatementCedars-Sinai has financial interests in Prometheus Biosciences, Inc., a company which has access to the data and specimens in Cedars-Sinai's MIRIAD Biobank (including the data and specimens used in this study) and seeks to develop commercial products. DPBM, JB, SRT own stock in Prometheus Biosciences Inc. AAP, DL, JB, SRT, DPBM are consultants for Prometheus Biosciences, Inc. DPBM has consulted for Gilead, Pfizer, Boehringer Ingelheim, Qu Biologics, Bridge Biotherapeutics, and received grant support from Janssen. TSS has consulted for Janssen, Boehringer Ingelheim, Genentech and Takeda.Funding StatementThis work was supported by internal funds from the F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute. The Cedars-Sinai MIRIAD IBD Biobank is supported by the F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases [NIH/NIDDK] [grants P01 DK046763 and U01 DK062413], and The Leona M and Harry B Helmsley Charitable Trust.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesTranscriptomics datasets used in this manuscript are available on public dataset (GEO, Accession #s: GSE120782, GSE57945, GSE16879,GSE100833). One is available at arrayExpress (E-MTAB-5783). One of the dataset is unpublished and will be deposited on GEO.

Queiroz, N. S. F., et al. (2020). "Management of inflammatory bowel disease patients in the COVID-19 pandemic era: a Brazilian tertiary referral center guidance." Clinics **75**: e1909.
The world is fighting the COVID-19 outbreak and health workers, including inflammatory bowel diseases specialists, have been challenged to address the specific clinical issues of their patients. We hereby summarize the current literature in the management of inflammatory bowel disease (IBD) patients during the COVID-19 pandemic era that support the rearrangement of our IBD unit and the clinical advice provided to our patients.

Reynolds, S. D., et al. (2020). "Systemic Immunosuppressive Therapy for Inflammatory Skin Diseases in Children: Expert-Consensus-Based Guidance for Clinical Decision Making During the COVID-19 Pandemic." Pediatric dermatology.
BACKGROUND/OBJECTIVES: The COVID-19 pandemic has raised questions about the approach to management of systemic immunosuppressive therapies for dermatologic indications in children. Given the absence of data to address concerns related to SARS-CoV-2 infection while on these agents in an evidence-based manner, a Pediatric Dermatology COVID-19 Response Task Force (PDCRTF) was assembled to offer time-sensitive guidance for clinicians. METHODS: A survey was distributed to an expert panel of 37 pediatric dermatologists on the PDCRTF to assess expert opinion and current practice related to three primary domains of systemic therapy: initiation, continuation, and laboratory monitoring. RESULTS: Nearly all respondents (97%) reported that the COVID-19 pandemic had impacted their decision to initiate immunosuppressive medications. The majority of pediatric dermatologists (87%) reported that they were pausing or reducing the frequency of laboratory monitoring for certain immunosuppressive medications. In asymptomatic patients, continuing therapy was the most popular choice across all medications queried. The majority agreed that patients on immunosuppressive medications who have a household exposure to COVID-19 or test positive for acute infection should temporarily discontinue systemic and biologic medications, with the exception of systemic steroids, which may require tapering. CONCLUSIONS: The ultimate decision regarding initiation, continuation and laboratory monitoring of immunosuppressive therapy during the pandemic requires careful deliberation, consideration of the little evidence available, and discussion with families. Consideration of an individual's adherence to COVID-19 preventive measures, risk of exposure, and the potential severity if infected must be weighed against the dermatological disease, medication, and risks to the patient of tapering or discontinuing therapies.

Riphagen, S., et al. (2020). "Hyperinflammatory shock in children during COVID-19 pandemic." The Lancet.

Rivera-Figueroa, E. I., et al. (2020). "Incomplete Kawasaki Disease in a Child with Covid-19." Indian Pediatrics **09**: 09.

Sardu, C., et al. (2020). "Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence." J Clin Med **9**(5).
The symptoms most commonly reported by patients affected by coronavirus disease (COVID-19) include cough, fever, and shortness of breath. However, other major events usually observed in COVID-19 patients (e.g., high blood pressure, arterial and venous thromboembolism, kidney disease, neurologic disorders, and diabetes mellitus) indicate that the virus is targeting the endothelium, one of the largest organs in the human body. Herein, we report a systematic and comprehensive evaluation of both clinical and preclinical evidence supporting the hypothesis that the endothelium is a key target organ in COVID-19, providing a mechanistic rationale behind its systemic manifestations.

Schroeder, A. R., et al. (2020). "COVID-19 and Kawasaki Disease: Finding the Signal in the Noise." Hosp Pediatr.

Seif, F., et al. (2020). "JAK Inhibition as a New Treatment Strategy for Patients with COVID-19." International archives of allergy and immunology: 1-9.
After the advent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the outbreak of coronavirus disease 2019 (COVID-19) commenced across the world. Understanding the Immunopathogenesis of COVID-19 is essential for interrupting viral infectivity and preventing aberrant immune responses before a vaccine can be developed. In this review, we provide the latest insights into the roles of angiotensin-converting enzyme II (ACE2) and Ang II receptor-1 (AT1-R) in this disease.

Novel therapeutic strategies, including recombinant ACE2, ACE inhibitors, AT1-R blockers, and Ang 1-7 peptides, may prevent or reduce viruses-induced pulmonary, cardiac, and renal injuries. However, more studies are needed to clarify the efficacy of these therapeutics. Furthermore, considering the common role of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway in AT1-R expressed on peripheral tissues and cytokine receptors on the surface of immune cells, potential targeting of this pathway using JAK inhibitors (JAKinibs) is suggested as a promising approach in patients with COVID-19 who are admitted to hospitals. In addition to antiviral therapy, potential ACE2- and AT1-R-inhibiting strategies, and other supportive care, we suggest other potential JAKinibs and novel anti-inflammatory combination therapies that affect the JAK-STAT pathway in patients with COVID-19. Since the combination of MTX and baricitinib leads to outstanding clinical outcomes, the addition of baricitinib to MTX might be a potential strategy.

Shneider, A., et al. (2020). "Can melatonin reduce the severity of COVID-19 pandemic?" International reviews of immunology: 1-10.
The current COVID-19 pandemic is one of the most devastating events in recent history. The virus causes relatively minor damage to young, healthy populations, imposing life-threatening danger to the elderly and people with diseases of chronic inflammation. Therefore, if we could reduce the risk for vulnerable populations, it would make the COVID-19 pandemic more similar to other typical outbreaks. Children don't suffer from COVID-19 as much as their grandparents and have a much higher melatonin level. Bats are nocturnal animals possessing high levels of melatonin, which may contribute to their high anti-viral resistance. Viruses induce an explosion of inflammatory cytokines and reactive oxygen species, and melatonin is the best natural antioxidant that is lost with age. The programmed cell death coronaviruses cause, which can result in significant lung damage, is also inhibited by melatonin. Coronavirus causes inflammation in the lungs which requires inflammasome activity. Melatonin blocks these inflammasomes. General immunity is impaired by anxiety and sleep deprivation. Melatonin improves sleep habits, reduces anxiety and stimulates immunity. Fibrosis may be the most dangerous complication after COVID-19. Melatonin is known to prevent fibrosis. Mechanical ventilation may be necessary but yet imposes risks due to oxidative stress, which can be reduced by melatonin. Thus, by using the safe over-the-counter drug melatonin, we may be immediately able to prevent the development of severe disease symptoms in coronavirus patients, reduce the severity of their symptoms, and/or reduce the immuno-pathology of coronavirus infection on patients' health after the active phase of the infection is over.

Sichitiu, J., et al. (2020). "Antenatal corticosteroid therapy and COVID-19 : pathophysiological considerations." Acta obstetricia et gynecologica Scandinavica.
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has presented many challenges in healthcare, including obstetrics. Therefore, we read with great interest the special editorial published in the AOGS regarding clinical recommendations for the management of coronavirus disease 2019 (COVID-19) in pregnant women.(1) As illustrated by the authors, the usefulness and safety of corticosteroids as an adjuvant therapy for COVID-19 pneumonia remains controversial. Corticosteroids may diminish the inflammatory response, a major factor for lung damage and acute respiratory distress syndrome in viral respiratory tract infection. However, previous studies on corticosteroid therapy in severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus illustrated delayed viral clearance, with no survival benefit and perhaps even adverse outcomes.(2) Some patients with COVID-19 exhibit biphasic disease evolution with a mild presentation followed by a secondary respiratory deterioration due to a cytokine storm, despite decreasing viral load.(2) Therefore, timing of corticosteroid therapy might be particularly consequential, with early administration reducing inflammatory response and viral clearance during the initial phase.

Silberstein, M. (2020). "Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?" Medical Hypotheses **140**.
There is anecdotal evidence that tocilizumab, an immunosuppressant drug, may be a potential therapeutic option for patients with severe manifestations of coronavirus disease 2019 (COVID-19). Like tocilizumab, Vitamin D appears to modulate the activity of an interleukin (IL-6), which may explain the seasonal variation in prevalence of influenza. While most cases of COVID-19 have, thus far, occurred in the Northern Hemisphere winter, limiting the ability to assess seasonal variation, there remains substantial variation in the severity of this condition that has yet to be explained. A retrospective

comparison of Vitamin D levels in previously obtained blood samples between survivors and confirmed fatalities could establish a rationale for implementation of widespread Vitamin D supplementation. This would be far cheaper and simpler than tocilizumab as a therapeutic option to trial. © 2020

Su, L., et al. (2020). "The different clinical characteristics of corona virus disease cases between children and their families in China - the character of children with COVID-19." Emerging Microbes & Infections **9**(1): 707-713.
This study aims to analyze the different clinical characteristics between children and their families infected with severe acute respiratory syndrome coronavirus 2. Clinical data from nine children and their 14 families were collected, including general status, clinical, laboratory test, and imaging characteristics. All the children were detected positive result after their families onset. Three children had fever (22.2%) or cough (11.2%) symptoms and six (66.7%) children had no symptom. Among the 14 adult patients, the major symptoms included fever (57.1%), cough (35.7%), chest tightness/pain (21.4%), fatigue (21.4%) and sore throat (7.1%). Nearly 70% of the patients had normal (71.4%) or decreased (28.6%) white blood cell counts, and 50% (7/14) had lymphocytopenia. There were 10 adults (71.4%) showed abnormal imaging. The main manifestations were pulmonary consolidation (70%), nodular shadow (50%), and ground glass opacity (50%). Five discharged children were admitted again because their stool showed positive result in SARS-CoV-2 PCR. COVID-19 in children is mainly caused by family transmission, and their symptoms are mild and prognosis is better than adult. However, their PCR result in stool showed longer time than their families. Because of the mild or asymptomatic clinical process, it is difficult to recognize early for pediatrician and public health staff.

Taghdir, M., et al. (2020). "A review on some nutrition-based interventions in Covid-19." Journal of Military Medicine **22**(2): 169-176.
Covid-19 is an emerging infectious disease caused by SARS-CoV-2 that can be transmitted to humans. There are currently no drug or vaccine for this disease. In the absence of treatment for this new virus, finding alternative methods to prevent and control of the disease is important. Having a well-functioning immune system is essential for the host's defense against pathogenic organisms. Malnutrition can lead to an impaired immune system during life. Even though the immune system response to infection, is itself a factor that could lead to nutritional status impairment. Deficiency of some nutrients can lead to disorders of immune system. Adequate intake of vitamins (A, D, Bs, C and E), minerals (selenium, zinc and iron) and omega-3 fatty acids are among the essential factors in proper immune system function. Therefore, it is recommended to follow a healthy diet to prevent the Covid-19. It is also suggested to assess the nutritional status of patients before prescribing treatments.

Toubiana, J., et al. (2020). "Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France." 2020.2005.2010.20097394.
Background: Acute clinical manifestations of SARS-CoV-2 infection are less frequent and less severe in children than in adults. However, recent observations raised concerns about potential post-viral severe inflammatory reactions in children infected with SARS-CoV-2. Methods: We describe an outbreak of cases of Kawasaki disease (KD) admitted between April 27 and May 7, 2020, in the general paediatrics department of a university hospital in Paris, France. All children prospectively underwent nasopharyngeal swabs for SARS-CoV-2 RT-PCR, SARS-CoV-2 IgG serology testing, and echocardiography. The number of admissions for KD during the study period was compared to that observed since January 1, 2018, based on discharge codes, using Poisson regression. Results: A total of 17 children were admitted for KD over an 11-day period, in contrast with a mean of 1.0 case per 2-week period over 2018-2019 (Poisson incidence rate ratio: 13.2 [95% confidence interval: 7.3-24.1], p <0.001). Their median age was 7.5 (range, 3.7-16.6) years, and 59% of patients originated from sub-Saharan Africa or Caribbean islands. Eleven patients presented with KD shock syndrome (KDSS) requiring intensive care support, and 12 had myocarditis. All children had marked gastrointestinal symptoms at the early stage of illness and high levels of inflammatory markers. Fourteen patients (82%) had evidence of recent SARS-CoV-2 infection (positive RT-PCR 7/17, positive IgG antibody detection 14/16). All patients received immunoglobulins and some received corticosteroids (5/17). The clinical outcome was favourable in all patients. Moderate coronary artery dilations were detected in 5 cases (29%) during hospitalisation. Conclusions: The ongoing outbreak of KD in the Paris might be related to SARS-CoV2, and shows an unusually high

proportion of children with gastrointestinal involvement, KDSS and African ancestry.Competing Interest StatementThe authors have declared no competing interest.Funding StatementNo specific funding for this studyAuthor DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe analyses as well as the anonymised database will be made available on reasonable request.

Trahern Jones of Pediatric Infectious Diseases Instructor of Pediatrics of Utah Health Lake, C. and F. Danielle Nahal Resident Physician Medical Center (2020). "Beating the Pandemic: What Emergency Providers Should Know About COVID-19." Pediatric Emergency Medicine Reports **25**(5).
AUTHORS Trahern (TW) Jones, MD, Fellow, Division of Pediatric Infectious Diseases, Adjunct Instructor, Department of Pediatrics, University of Utah Health, Salt Lake City Danielle Nahal, MD, Pediatric Resident Physician, UCSF Medical Center, San Francisco PEER REVIEWER James A. Wilde, MD, FAAP, Professor of Emergency Medicine, Associate Professor of Pediatrics, Augusta University, Augusta, GA

The disease associated with the 2019 novel coronavirus (COVID-19) is now a significant event in world history, with uncertain but likely major consequences for individuals, families, healthcare workers, health systems, and the global economy. There still is a great deal to be learned. Although COVID-19 appears to pose only a limited danger to children, older adults face the possibility of much more serious manifestations. In addition, healthcare professionals and systems are under serious threat of being overwhelmed. Staff may be in shortage because of illness or the need for isolation. Hospital systems may need to divert resources from areas and specialties under less strain than others. In short, at this time it seems COVID-19 will demand the attention of most practitioners and allied health providers over the next year. Thus, familiarization with what is known so far about its pathophysiology, epidemiologic risk factors, treatment, and future directions for research is important as we face and fight this crisis united as healthcare providers. Terminology During crisis situations, accurate communication is vital to ensure healthcare providers and the public are properly informed. Thus, consistent terminology should be used when discussing COVID-19. Because of the novel character of this virus and to ensure the proper epidemiologic terms are employed, the following definitions may be helpful: Severe acute respiratory syndrome (SARS): The infectious disease caused by a zoonotic coronavirus (SARS-CoV) that spread between multiple countries in East Asia and Canada in 2002-2003.1 Middle East respiratory syndrome (MERS): The infectious disease caused by a zoonotic coronavirus (MERS-CoV) that spread between multiple countries in the Middle East and South Korea from 2012 to the present.2 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): The currently proposed name of the virus related to the December 2019 outbreak in Wuhan, China.1 The name is proposed by the Coronavirus Study Group of the International Committee on the Taxonomy of Viruses. In materials distributed for the public, the World Health Organization (WHO) also will refer to the virus as "COVID-19 virus" to avoid confusion.3 Coronavirus Disease 2019 (COVID-19): The currently accepted name by WHO for the disease caused by SARS-CoV-2.3 The name was chosen following international guidelines to avoid stigmatizing any particular location, region, animals, or food items.4 Endemic: A disease that is constantly present, prevalent, and expected in a given area.5 Epidemic: A sudden rise in the cases of a disease beyond what normally is expected.5 Outbreak: The same definition as epidemic, but generally in a more limited area (such as a city or province).5 Pandemic: An epidemic that has spread across multiple countries.5 Microbiology of Coronaviruses Coronaviruses are named for the club-like projections of surface proteins from the virus particle that appear to create a crown, or "corona," on electron micrographs.6 (See Figures 1 and 2.) Coronaviruses are enveloped, nonsegmented, single-stranded, positive-sense ribonucleic acid (RNA) viruses, with the largest known genome among all viruses (approximately 30 kb).6,7 Figure 1. Transmission Electron Micrographs of SARS-CoV-2 Virus Particles Figure 2. Novel Coronavirus SARS-CoV-2 This scanning electron microscope image shows SARS-CoV-2 (yellow) — also known as 2019-nCoV, the

virus that causes COVID-19 — isolated from a patient in the United States, emerging from the surface of cells (blue/pink) cultured in the lab. Numerous coronaviruses are known to cause diverse clinical syndromes in humans and animals, includin mild to severe disease in such species as bats, rats, mice, chickens, turkeys, cattle, beluga whales, dogs, cats, rabbits, livestock, and pigs.7 In these animals, disease can manifest in the central nervous system, the respiratory tract, the gastrointestinal (GI) tract, the hepatobiliary system, and the renal system.7 Pathogenic human coronaviruses (HCoVs) were identified first in the 1960s.8 Four strains of community- transmitted, seasonal HCoVs now have been identified: HCoV 229E, OC43, NL63, and HKU1. Each of these coronaviruses is an endemic cause of generally mild, self-limited respiratory infections in children and adults. Notably, 60% to 90% of adults will become seropositive for at least one of these viruses in their lifetime.6 The novel coronaviruses SARS-CoV and MERS-CoV emerged in 2003 and 2012, respectively, causing major epidemics of severe respiratory illnesses. SARS-CoV was determined to have a natural reservoir in horseshoe bats, supported by findings of highly conserved SARS-related CoVs in bats that use the same cellular receptor as the human virus.9 There also were findings of similar viruses in palm civets and other mammals that were postulated to act as intermediate animal hosts in the "wet markets" (exotic animal and seafood markets) of China. MERS-CoV also has been linked to previously identified bat coronaviruses, with the dromedary camel acting as an intermediate host.10 After containment of both of these outbreaks, it was suggested that new, zoonotic coronaviruses would continue to emerge in the future, causing novel human and animal diseases through their ability to recombine and infect multiple species and cell types.7 Novel 2019 Coronavirus In December 2019, an outbreak of pneumonia of unknown etiology emerged in Wuhan, China, with a case cluster apparently linked to the Huanan Seafood Wholesale Market — a marketplace for seafood and various animals from regions throughout East and Southeast Asia.11 These cases were identified using a reporting mechanism for "pneumonia of unknown etiology" that originally had been developed in the wake of the previous SARS epidemic.12 Although retrospective case identification was able to pinpoint cases of pneumonia associated with the Huanan Seafood Wholesale Market as early as Dec. 13, 2019, further cases with no clear epidemiologic link were identified as early as Dec. 1, 2019.13 This suggested that transmission potentially had occurred as early as November 2019, but had been undetected. The China Center for Disease Control and Prevention (China CDC) conducted initial viral studies, which included lower respiratory tract samples, in four of the known patients from the December 2019 cluster. In these patients, no specific pathogens could be identified by the RespiFinderSmart22kit (including known HCoVs).11 Further genomic sequencing of extracted RNA revealed sequences that matched with betacoronavirus lineage genomes, including 85% identity with a previously published bat SARS-like CoV. Later confirmed by whole genome sequencing and viral culture, the newly isolated virus initially was named 2019-nCoV. 11,14 Although genetically distinct from SARS-CoV and MERS-CoV, it fell within the same genus. These studies were repeated and confirmed in samples from additional patients from hospitals in Wuhan, with continued phylogenetic analysis providing further evidence that 2019-nCOV was more similar to bat-derived coronavirus strains than strains known to infect humans.15,16 The data suggested a bat reservoir for coronaviruses in general, including 2019-nCoV; however, the data also suggested that an intermediate animal (not a bat) may have been infected and amplified the virus in the Huanan Seafood Wholesale Market, although this remains incompletely understood.16 Similarly, SARS-CoV and MERS-CoV were believed to pass through other intermediate host animals.17,18 This raised further questions about the transmission of 2019-nCoV and its emergence as a human pathogen. One study suggested that a snake species may have been an intermediate host (based on si ilar codon usage) and two others implicated pangolins; however, neither hypothesis has been widely accepted, and further research is needed.19,20,21 Ultimately, by Dec. 31, 2019, the China CDC announced an outbreak investigation was underway, and by Jan. 1, 2020, it had closed the Huanan Seafood Wholesale Market.12 This was followed by case investigation and contact tracing by the China CDC. By mid-January 2020, as cases accrued and the natural history of the pneumonia of unknown etiology became clear, the China CDC announced the outbreak response had been upgraded to "Level 1," the highest designation for such measures.12 Meanwhile, the China CDC also had developed primers for molecular identification of the novel coronavirus disease and released the virus's genetic sequence for distribution to health authorities globally. This ultimately served as a significant step forward for other nations to rapidly develop their own molecular identification assays. Nevertheless, human-to-human spread was well underway, as cases in other provinces in China were reported by the end of January, and cases associated with travel to Wuhan were reported abroad in Southeast Asia.12 On Jan. 22, 2020, the Chinese government issued a quarantine notice for the entire city of Wuhan, the center of the epidemic.22 However, at this point,

outbreak containment was complicated by the Chinese New Year travel plans of many Chinese citizens, many of whom had traveled before the quarantine went into effect, as well as likely asymptomatic or mildly symptomatic spread of the virus among the population at large.23-25 Several initial case series regarding the virus were published by late January 2020, providing the global community with a view into the epidemic and better delineating rates of severe disease, complications, and mortality among patients with confirmed infection.12,13,26 These studies emphasized that the burden of severe disease rested in particular with the elderly and those with comorbid conditions, but also provided early hints of the strain that healthcare facilities would face because of the need for drastic infection prevention measures, intensive care unit (ICU) support, and intensive ventilatory support measures, including extracorporeal membrane oxygenation. To alleviate these strains on the healthcare system, Chinese authorities undertook emergency measures of creating multiple facilities strictly dedicated to cohorting hundreds to thousands of COVID-19 patients, some of which were field hospitals constructed within days.27 The number of confirmed cases rose rapidly throughout February 2020, with Chinese cases numbering into the tens of thousands. WHO member states discovered and reported cases in rapid succession, frequently associated with travel from East Asia, but with many indicative of community spread within their borders. On Feb. 11, 2020, WHO announced that the label "COVID-19" should be applied to the new disease in an effort to avoid stigmatizing regions where it had been first identified.3 By Feb. 29, 2020, more than 85,000 cases had been identified between 54 countries, with the vast majority of confirmed cases (79,000) within China.28 Although sporadic clusters had appeared globally up to this point, Iran and Northern Italy faced sudden surges of COVID-19 patients in late February and early March 2020.29 Italian ICUs reported attempts to cohort hundreds of COVID-19 cases, but still were forced to transfer patients to unaffected regions to cope with the massive numbers of critically ill patients.30 Within the first two weeks of March 2020, COVID-19 patients were estimated to occupy more than 1,000 ICU beds out of a total of 5,200 in Italy, and intensivists were left to consider implementing triage principles (denying lifesaving care to the sickest and least likely to survive) when allocating ventilatory support.31,32 In the meantime, multiple European countries reported increasing numbers of COVID-19 patients, while China's extreme efforts at containment and quarantine had interrupted community transmission o new cases, thus shifting the center of the epidemic to the Western hemisphere.33 On March 11, 2020, WHO elevated COVID-19 to "pandemic" status.34 The United States began to see widespread community transmission in mid-March 2020, as patients began to number into the thousands and every state and U.S. territory reported cases.35 Mirroring European and Chinese efforts to curtail community transmission, U.S. authorities enacted closures of universities, school districts, bars, restaurants, gyms, and other locations of public gathering, while millions of Americans were asked to work from home or to forsake working altogether.36 At the time of this writing, the number of documented cases outside of China has overtaken those reported from within China, and global spread is recorded in more than 150 countries, with the number of new cases rising exponentially each day.37 Epidemiology and Risk Factors The epidemiology and risk factors for COVID-19 are evolving. Providers, healthcare systems, and governments are attempting to elucidate this information as the number of cases continues to rise. Initially, the risk factors for acquisition of the disease were understood to be focused around exposure to a possible mammalian host at the Huanan Seafood Wholesale Market; however, later investigation questioned whether the disease may have presented first in the community, because neither the first identified case nor 13 other initial patients visited the market in question.13 As the infection spread, it became clear that epidemiologic exposure to the seafood market alone could not explain all cases. Initial concern for human-to-human transmission was noted in the same study, based on known characteristics of the coronavirus group. Further studies described transmission of the virus among close contacts, including both family clusters and business contacts, suggesting the potential for index cases to transmit the disease asymptomatically.23,38 Since then, SARS-CoV-2 has been detected widely in individuals with no travel history or known contact with other individuals who have tested positive, confirming community spread of the virus. In addition, it is estimated that upward of 86% of cases in Wuhan prior to Jan. 23, 2020, were undetected, suggesting the pandemic is driven largely by asymptomatic spread or is spread by those with mild symptoms.25 It also should be noted that some data have suggested that healthcare workers can become disproportionately represented among COVID-19 cases, likely due to the virus's potential for nosocomial spread.39,40 The incubation period, defined as the period between exposure to the infection and the appearance of first symptoms, has been suggested as an average of five to six days, based on initial reports from SARS-CoV-2 and mirrored by other coronavirus diseases, including SARS and MERS.41 The range may extend to two to 14 days. Disease

severity and mortality are highest among the elderly.40,42 Individuals with comorbidities like hypertension, diabetes, and heart disease tend to be overrepresented among confirmed cases.12,13,26,43 U.S. data have estimated mortality rates to be highest among those older than 85 years of age (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), those aged 55 to 64 years (1% to 3%), and least among those aged 20 to 54 years (1%).42 Providers should take note that even among nongeriatric adults, hospitalizations and ICU admissions still are common, especially among those with underlying conditions. (See Figure 3 and Table 1.) Figure 3. Coronavirus Disease 2019 (COVID-19) Hospitalizations,* Intensive Care Unit Admissions,† and Deaths,§ by Age Group — United States, February 12–March 16, 2020 Table 1. Hospitalization with and Without Intensive Care Unit (ICU) Admission, by Age Group Among COVID-19 Patients Aged ≥19 Years with and Without Reported Underlying Health Conditions — United States, February 12–March 28, 2020 * Age Group (yrs) Hospitalized Without ICU Admission, No. (% Range†) ICU Admission, No. (% Range†) Underlying condition pr sent/reported§ Underlying condition present/reported§ Yes No Yes No 19-64 285 (18.1–19.9) 197 (6.2–6.7) 134 (8.5–9.4) 58 (1.8–2.0) ≥ 65 425 (41.7–44.5) 58 (16.8–18.3) 212 (20.8–22.2) 20 (5.8–6.3) Total ≥ 19 710 (27.3–29.8) 255 (7.2–7.8) 346 (13.3–14.5) 78 (2.2–2.4) Overall disease incidence among pediatric patients has been difficult to assess, as each affected region has followed different approaches to testing populations. In one of the largest datasets from China (including 72,314 patients), only about 2% of documented cases occurred in patients younger than 19 years of age (965 patients).44 Initial reports from Italy demonstrated that out of 22,512 cases, only 1.2% (70 cases) were documented among patients younger than 18 years of age, and there were no reported deaths in this age group.40 Recent data described 4,226 cases in the United States and noted that only 5% of documented cases occurred in patients younger than 19 years of age (123 cases).42 Further features of identified pediatric patients have been reported variably. The China CDC detailed features of 2,143 cases, of which 34% had a positive real-time polymerase chain reaction (RT-PCR) test and 66% were suspected cases (high risk by exposure to a known COVID-19 case with clinical symptoms, laboratory features, or imaging findings).45 However, these data were limited somewhat because of the overrepresentation of suspected cases, especially since this time period overlapped with influenza and respiratory syncytial virus season. Among these children, the median age was 7 years, with the age range from 1 day to 18 years. Biological males and females were represented equally. The majority of cases (90%) were asymptomatic or of mild to moderate severity; however, it was observed that more critical features were observed in children younger than 1 year of age (involving acute respiratory distress syndrome or respiratory failure with possible additional features of end organ dysfunction). There are no current comprehensive data to suggest which comorbidities in children increase the risk of severe disease. The authors of one study found that those who required an ICU stay and mechanical ventilation had coexisting conditions, such as hydronephrosis, leukemia, and complicated intussusception.46 Pathophysiology and Transmission The pathophysiology of coronavirus infections has been characterized largely by studies of the milder human coronaviruses and SARS-CoV. Human coronaviruses HCoV-NL63 and SARS-CoV both enter host cells through interaction with human angiotensin-converting enzyme 2 (ACE2), which is found throughout the body, including the respiratory and GI tracts. It is thought that ACE2 normally has a protective role in the inflamed lung, and as such, SARS-CoV's interaction with this may contribute to disease severity.47 The newly identified coronavirus, SARS-CoV-2, shows structural similarity to SARS-CoV in the receptor binding domains, which suggests that this new virus also binds at ACE2 sites.15 ACE2 is found primarily in the lower respiratory tract instead of the upper, which may account for why proportionally fewer patients have presented with symptoms of typical upper respiratory tract infection.48 Upon infection of alveolar epithelial cells, the virus may cause cell lysis and sloughing of the respiratory epithelium. Similar to other viral infections, it is thought that the host response is responsible for many of the disease manifestations. In studies of SARS-CoV, researchers have suggested that damage to the lungs of infected patients occurs both directly, by viral destruction of alveolar and bronchial epithelial cells and macrophages, and indirectly, through production of immune mediators, although the exact role of these mechanisms remains controversial.49 Viral transmission of the known human coronaviruses (HCoVs 229E, OC43, NL63, and HKU1) has not been well studied. Based on the behavior of other respiratory tract viruses, coronaviruses are believed to spread mainly through respiratory droplets, along with direct a d indirect contact with infected persons.6 SARS-CoV primarily was transmitted directly through mucous membrane contact with infectious respiratory droplets, as well as through exposure to fomites, with most cases occurring in people who had close contact with those affected by the illness.50 It has been established previously that both SARS-CoV and SARS-CoV-2 use ACE2 to enter cells; the presence of the receptor in

the GI tract has led to questions regarding fecal-oral spread of the virus. In a study of 73 patients hospitalized with COVID-19 (ages 10 months to 78 years), investigators found that 53% of patients had a stool positive for SARS-CoV-2 RNA. Notably, 17 patients continued to demonstrate positive stool RNA after developing negative respiratory samples.51 Further studies have looked for evidence of live virus in stool samples with mixed results.52,53 The Report of the WHO-China Joint Mission on COVID-19 did not identify the fecal-oral route as a main driver of SARS-CoV-2 transmission.54 Airborne spread has not yet been reported; however, the authors of one study in laboratory conditions suggested that aerosol transmission of the virus is plausible, with a similar aerosolized stability to that of SARS-CoV.55 In addition, fomite transmission via contaminated surfaces is believed to be a potential route of transmission, with results of one study demonstrating stability of potentially viable virus on surfaces like plastic and stainless steel for up to 72 hours.56 There have been concerns about vertical transmission of infection, especially after reports of infection detected in a 36-hour-old infant in China. This child's mother had tested positive by nasopharyngeal swab, but cord blood, placental specimens, and breast milk did not have the virus present.57 In a later case series of nine pregnant women who tested positive for SARS-CoV-2 late in pregnancy, all delivered healthy infants via cesarean delivery and had negative testing of throat swabs, cord blood, amniotic fluid, and breast milk.58 These findings were repeated in a larger series of 38 pregnant women and infants.59 One case report has suggested that a neonate born to a mother with active COVID-19 developed an elevated immunoglobulin M (IgM) response to SARS-CoV-2, which is suggestive of vertical transmission because maternal IgM is not passed through the placenta, although the infant's nasopharyngeal RT-PCR results for the virus remained repeatedly negative.60 Elevations in immunoglobulin G and IgM also have been reported among other newborns of mothers with COVID-19.61 Further investigation is warranted, but it remains unclear if vertical transmission is a significant mechanism of infection of neonates at this time.62 Clinical Manifestations The first described manifestations of COVID-19 in hospitalized adult patients were reported as "pneumonia of unknown cause."13 This was defined as an illness without a causative pathogen with clinical features of fever (≥ 38° C), radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for three to five days following standard clinical guidelines; or as the first three criteria, plus an epidemiologic link to the Huanan Seafood Wholesale Market or a sick contact with similar symptoms.63 Later reports described the most prominent early symptoms as fever (98% of patients), cough (76%), and myalgia/fatigue (44%).63 Laboratory findings among adult patients included lymphopenia (83.2%), thrombocytopenia (36.2%), elevated C-reactive protein (60.7%), elevated lactate dehydrogenase (41%), and elevated aminotransferases (AST/ALT, 22.2% and 21.3%, respectively). More than 23% of patients had at least one coexisting illness. The presence of coexisting illness was more common among patients with severe disease than among those with non-severe disease (38.7% vs. 21%). Age also was a predictor of disease severity; patients with severe disease were a median of seven years older than those with non-severe disease. Pediatric patien s diagnosed with COVID-19 have had somewhat more diverse clinical presentations, with a significant number of patients remaining asymptomatic, and far fewer patients with severe disease. It is important to note that the bulk of data describing clinical symptoms in pediatric populations are from hospitalized children in China. Fever has been reported in 41% to 65% of cases and cough in 38% to 65% of cases.41,46,64,65 Features of upper respiratory infection have been less prevalent, reported at 15% to 19%, with pharyngeal erythema specifically identified in 46% of cases.46,65 As noted previously, the virus has the ability to infect the GI tract; however, few pediatric patients presented with GI symptoms: 8% to 15% were noted to develop diarrhea and 6% to 10% to develop vomiting.46,64,65 Few pediatric patients have severe manifestations. Three severe cases were described in one large review of 171 children with COVID-19; all three had coexisting conditions (hydronephrosis, leukemia on maintenance chemotherapy, and intussusception), and ultimately the child with intussusception had multi-organ failure, which resulted in death.46 Although further pediatric deaths have been reported, details of the patients have not been adequately clarified to determine if specific risk factors were present. There have been several additional reports focusing on infants and neonates. A case series of hospitalized infants only included nine cases in China (age 28 days to 1 year), with the youngest being just 1 month of age. All had a sick family contact, and none experienced severe complications or required intensive care treatment. Of these cases, four had fever, three others had mild disease or no symptoms, and the last two had an unknown presentation.66 A later case series of four neonates born to mothers with known COVID-19 showed no manifestations of disease in any neonate. Three of the four patients' parents consented to testing and tested negative.67 One of the largest studies on pediatric patients

described an increased severity of disease in infants younger than 1 year of age; however, more than 70% of these patients were diagnosed on clinical symptoms alone, without SARS-CoV-2 testing to verify suspected COVID-19 disease.45 Rates of asymptomatic infection have been reported as high as 13% to 23%.46,64 It is likely that early in the epidemic's investigation, many children who were tested were known contacts of a positive case. Of children represented in the data, 65% to 90% had a close contact who tested positive or were part of a family cluster.46,64,65,68 Laboratory findings among pediatric patients have been variable. The authors of a review article focused on pediatric laboratory findings in COVID-19 found a normal leukocyte count in almost 70% of patients, while only 15% of patients mounted leukocytosis.69 Leukopenia is more variable, reported in 5% to 26% of cases.46,69 Procalcitonin was found to be elevated in 64% of patients in one large case series of SARS-CoV-2 positive children (n = 171).46 However, smaller studies have demonstrated lower percentages of children with elevated procalcitonin. Radiographic findings on chest X-ray or chest computed tomography (CT) are common among individuals with COVID-19, and even those with asymptomatic or mild disease may have abnormalities suggestive of infection. Among adult and pediatric patients with disease, 75% to 98% are reported to have evidence of pneumonia on imaging, particularly with bilateral lobular and subsegmental consolidations described on CT scans, as well as multifocal ground glass opacities.12,26,65 Pediatric patients also may demonstrate consolidation with a surrounding halo sign.65 Overall, pediatric patients with COVID-19 are less likely to have fewer findings on CT, and lesser extent of disease on radiography.70 Diagnosis and Testing In mid-January 2020, the China CDC developed primers for molecular identification of the novel coronavirus disease and released the virus's genetic sequence for distribution to global health authorities.12 This was an important co tribution to the global health community, allowing other nations to rapidly develop their own molecular identification assays to track and control new cases abroad. Using these sequencing data, new cases in the United States are diagnosed primarily based on RT-PCR testing, available through multiple commercial laboratory suppliers under the Emergency Use Authorization of the Food and Drug Administration (FDA).71 Viral genetic material has been detected in bronchoalveolar lavage fluid, sputum, nasal and pharyngeal swabs, bronchoscope brush biopsies, feces, and blood, while urine appears to be routinely negative.53 For the time being, the U.S. Centers for Disease Control and Prevention (U.S. CDC) recommends collecting nasopharyngeal swabs as the preferred choice for initial diagnostic testing, with oropharyngeal, nasal mid-turbinate, and anterior nare swabs as acceptable alternatives.72 Collection of sputum is an option for patients with productive cough, although sputum induction is not recommended. Local and national test reagents and infrastructure have been outpaced by spreading community transmission and local surges of cases. Although tests remain scarce, the U.S. CDC recommends prioritizing testing according to the following categories of patients:73 * hospitalized patients and symptomatic healthcare workers; * symptomatic patients in long-term care facilities, symptomatic patients aged 65 years and older, symptomatic patients with underlying conditions, and symptomatic first responders; * symptomatic critical infrastructure workers; individuals who are not any of the above but present with symptoms; and mildly symptomatic individuals in communities with high COVID-19 hospitalizations. Testing for other pathogens also should be performed during initial evaluation, but codetection between SARS-CoV-2 and other respiratory viruses has been reported.74 In one small study of pediatric patients with SARS-CoV-2, coinfection with other respiratory pathogens (namely influenza A and B, mycoplasma, respiratory syncytial virus, and cytomegalovirus) was found in 40% of patients.65 Thus, the presence of influenza or other respiratory pathogens does not rule out COVID-19, and the U.S. CDC recommends that specific testing for SARS-CoV-2 should not be delayed.72 In one analysis of patients who underwent serial RT-PCR tests and serial chest CT scans, the sensitivity of an initial CT scan at presentation was estimated to be upward of 97%, albeit with greater accuracy in patients older than 60 years of age.75 Management At the time of this writing, there is no FDA-approved drug specific for treating COVID-19.75 Emphasis currently is placed on supportive care of complications, as well as strict infection control practices. Many individuals with COVID-19 will be able to manage their illness on their own at home, which may be preferable as a means of case isolation. However, some patients may have progression of symptoms to moderate or severe disease, especially older individuals with cardiovascular disease, renal disease, diabetes, or immunocompromising conditions. The decision to admit and monitor patients at higher risk for severe complications must be made at the discretion of the provider on a case-by-case basis. Patients with COVID-19 who are discharged home should be warned that increasing shortness of breath or worsening symptoms may require re-evaluation by a healthcare provider. Current guidelines from the U.S. CDC emphasize that corticosteroids may be harmful and should not be given when managing

COVID-19 infections, unless otherwise indicated by another condition.75 This recommendation is based on data from other coronavirus outbreaks (SARS and MERS) and influenza studies that demonstrated that corticosteroid use could prolong viral replication in patients and ostensibly delay or hamper recovery.75,76 Multiple other medications are under investigation or consideration as potential therapies for COVID-19 infection. Recently, chloroquine and hydroxychloroquine (already approved by the U.S. FDA for other uses) have been cited as romising therapies, although their ultimate benefit remains unknown.77 Their method of action is believed to be based on alteration of phagolysosome pH in human cells, thus interfering with SARS-CoV-2's (or any intracellular organism's) ability to reproduce within host cells.78 In vitro testing supported this rationale, and 20 clinical studies were launched at multiple Chinese hospitals to evaluate the efficacy of chloroquine in COVID-19.78,79 Some investigators have claimed the initial data demonstrated that chloroquine may reduce patients' length of stay and ameliorate the progression of COVID-19 pneumonia,78,79 but this remains controversial. In another study, investigators claimed that the combination of hydroxychloroquine and azithromycin led to a reduction of viral load in COVID-19 patients, but this study was nonrandomized and extremely small.80 Thus, there are no U.S. recommendations at the time of this writing to use these agents in COVID-19 patients. Several other medications already marketed as antivirals also are under consideration for the treatment of COVID-19. Remdesivir is a nucleoside analogue previously used in Ebola treatment (albeit with no improvement in outcomes compared to placebo), but in vitro data support its efficacy against a variety of coronaviruses.81,82,83 Lopinavir and ritonavir (Kaletra) are protease inhibitors with some data supporting their efficacy against SARS and MERS, but recent data in the current COVID-19 pandemic suggest they are not useful.84,85,86 Darunavir/cobicistat also are protease inhibitors considered in the treatment of COVID-19, but there are no in vitro or clinical data to support their use at this time.87 Ribavirin is another nucleoside analogue that has been considered; however, it was found to have little effect on outcomes in SARS and MERS.84,88 Other therapies considered in the treatment of COVID-19 include tocilizumab (interleukin-6 inhibitor)89 and aerosolized alpha-interferon,90 but there are no recommendations from the U.S. CDC to use these therapies. The FDA is facilitating access to convalescent serum/plasma (antibodies harvested from COVID-19 survivors) as an investigational therapy,91 but with significant side effects and no firm evidence to support its efficacy against COVID-19, there is no recommendation for its use at this time. Recently, there has been discussion of whether angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) increase the risk of infection and severity of COVID-19, primarily because of SARS-CoV-2's previously described mechanism of binding to ACE2 to facilitate cell entry.92 No evidence has been found to support this hypothesis, and on the contrary, some animal studies suggest these medications actually may be protective against severe disease. At this time, discontinuation of these medications in COVID-19 disease is not recommended. Likewise, because SARS-CoV-2 binds to ACE2, some have suggested that medications that lead to upregulation of this enzyme, such as nonsteroidal anti-inflammatory drugs (NSAIDs), could lead to more severe disease.93 This supposition was followed by statements from the French Ministry of Health that patients with COVID-19 should avoid NSAIDs.94 However, at this time there is no published clinical evidence to recommend discontinuation or avoidance of NSAIDs in COVID-19 patients.95 Infection Prevention and Precautions Strategies to prevent community and nosocomial spread of COVID-19, as well as to minimize exposure of at-risk populations, are paramount. The U.S. CDC has provided comprehensive, updated recommendations for community mitigation strategies aimed at slowing the transmission of COVID-19 and reducing illness and death, while minimizing social and economic impacts.96 For all individuals, it is recommended people avoid close contact with others; avoid touching the eyes, nose, and mouth; and clean hands frequently, either using soap and water for 20 seconds or using hand sanitizer that is at least 60% alcohol.97 Because of the known problem of asymptomatic s read, recommendations have expanded beyond the simple message of staying home when symptomatic to practicing "social isolation." On an individual level, this includes encouraging individuals to maintain a distance of three to six feet apart from each other. On a larger scale, this has led to the systematic closure of schools, businesses, gymnasiums, restaurants, and bars, and the cancellation of large community events. There have been calls for widespread community quarantine, recommending that all individuals "shelter in place" and avoid all possible interaction with others. The U.S. CDC recommends minimizing potential healthcare exposures to contagious cases of COVID-19 through a variety of tactics, 98 including the following: * asking patients with symptoms of cough, sore throat, or fever to reschedule appointments for routine care; * using telehealth and telephone triage protocols to determine if symptomatic patients can be managed from home; * requesting patient

transport and emergency medical services to contact receiving emergency departments on transport protocols of symptomatic patients; * limiting points of entry to healthcare facilities, and posting visual materials and handwashing/sanitizer stations at these points, as well as throughout hallways; * enforcing cough etiquette and studious masking of all symptomatic patients; * designating separate waiting areas for patients with respiratory symptoms in coordination with the facility's infection prevention specialists; * ensuring patients in such waiting areas are separated by at least six feet; * ensuring patients with respiratory symptoms (including suspected or confirmed COVID-19) are transported and triaged efficiently and quickly through specially designated areas. There is no approved vaccine available for the prevention of COVID-19 at this time. The discovery and production of such a vaccine is a national and international public health priority to control the pandemic. Recently, the U.S. National Institutes of Health has initiated a Phase I clinical trial of an investigational vaccine.99 Efforts to produce a vaccine also are underway in China and Europe.100 Personal Protective Equipment As in all situations in which a patient presents with a potentially contagious infectious disease, practitioners confronting potential cases of COVID-19 should contact their institutional infection prevention specialists for specific guidance. In general, the U.S. CDC recommends that all healthcare personnel entering the room of a patient with known or suspected COVID-19 use a respirator or facemask, gown, gloves, and eye protection.98 Staff should ensure they follow personal protective equipment (PPE) donning and doffing procedures correctly to ensure contaminated droplets are not passed onto the hands, face, or eyes.101 (See Figures 4-6.) Figure 4. Sequence for Putting on Personal Protective Equipment Figure 5. How to Safely Remove Personal Protective Equipment: Example 1 Figure 6. How to Safely Remove Personal Protective Equipment: Example 2 When possible, and when supplies are adequate, respirators designated for airborne precautions are preferred. Understandably, these may become scarce in surge scenarios, and still may need to be prioritized for other patients with conditions that absolutely demand airborne precautions (such as varicella, tuberculosis, etc.). If respirators are scarce in the event of a surge scenario, facemasks are believed to be acceptable for all non-aerosol-generating situations among COVID-19 patients.98 In surge scenarios, institutions may choose to prioritize disposable and reusable respirators only for aerosol-generating procedures, such as intubation and bronchoscopy, among others. For a standardized list of all aerosol-generating procedures, providers should contact their facility's infection prevention specialist. In the event of a surge scenario, when community-transmitted cases of COVID-19 threaten to overwhelm the healthcare system, tactics must be employed to conserve PPE. Respirators should be prioritized for known aeroso -generating procedures and patients with a clearly delineated need for airborne precautions.98 Similarly, gowns should be prioritized. The U.S. CDC provides multiple suggestions for using and reusing respirators and facemasks in crisis scenarios:102,103 * using respirators that have exceeded the manufacturer's expiration date for fit-testing and training when supplies must be conserved; * following limited reuse policies of face masks and respirators between COVID-19 patients in crisis situations; * designating convalescent healthcare personnel (providers who have already been sick with, recovered, and ostensibly gained immunity to SARS-CoV-2) to provide care to COVID-19 patients. In crisis situations, the creation of facemasks from available materials (such as paper, cloth, or plastic) may be necessary. These clearly are not up to ordinary national standards of care, do not qualify as true PPE, and should be employed only as a last resort. In these situations, the U.S. CDC recommends combining their use with a face shield when possible.102 Conclusion The final costs and outcomes of the COVID-19 pandemic cannot be predicted, but its current implications are historic in scope. Some efforts at modeling the pandemic have predicted that without appropriate action, millions of lives could be lost in the United States and Europe.104 Healthcare workers already are tasked with extremely high patient volumes in heavily impacted regions, and many have become separated from their families for the sake of isolation and protecting the vulnerable. There are few, if any, individuals in the world who will not have some personal connection to this pandemic. However, while anxieties and doubts multiply in the face of such grave predictions, providers should remind themselves that this pandemic ultimately will pass. Although the immediate effects of COVID-19 may seem overwhelming, the courage and efforts of healthcare workers will outlast the disease. Indeed, the day may not be so distant when this pandemic is relegated to mere historical interest, and humanity will have learned an essential lesson in vigilance against infectious diseases. Acknowledgement The authors would like to extend their appreciation to Anne Blaschke-Bonkowsky, MD, PhD, for her support and advice throughout the writing of this manuscript.

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Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19. ClinicalTrials.

Turner, D., et al. (2020). "COVID-19 and Paediatric Inflammatory Bowel Diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto group of ESPGHAN." Journal of Pediatric Gastroenterology & Nutrition **31**: 31.
INTRODUCTION: With the current COVID-19 pandemic, concerns have been raised about the risk to children with inflammatory bowel diseases (IBD). We aimed to collate global experience and provide provisional guidance for managing paediatric IBD (PIBD) in the era of COVID-19. METHODS: An electronic reporting system of children with IBD infected with SARS-CoV-2 has been circulated among 102 PIBD centres affiliated with the Porto and Interest-group of ESPGHAN. A survey has been completed by major PIBD centres in China and South-Korea to explore management during the pandemic. A third survey collected current practice of PIBD treatment. Finally guidance points for practice have been formulated and voted upon by 37 PIBD authors and Porto group members. RESULTS: Eight PIBD children had COVID-19 globally, all with mild infection without needing hospitalization despite treatment with immunomodulators and/or biologics. No cases have been reported in China and South Korea but biologic treatment has been delayed in 79 children, of whom 17 (22%) had exacerbation of their IBD. Among the Porto group members, face-to-face appointments were often replaced by remote consultations but almost all did not change current IBD treatment. Ten guidance points for clinicians caring for PIBD patients in epidemic areas have been endorsed with consensus rate of 92-100%. CONCLUSIONS: Preliminary data for PIBD patients during COVID-19 outbreak are reassuring. Standard IBD treatments including biologics should continue at present through the pandemic, especially in children who generally have more severe IBD course on one hand, and milder SARS-CoV-2 infection on the other.

Verdoni, L., et al. (2020). "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study." The Lancet.
Summary Background The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic. Methods All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki- like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively. Findings Group 1 comprised 19 patients (seven boys, 12 girls; aged 3·0 years [SD 2·5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7·5 years [SD 3·5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 vs group 2, 0·3 vs ten per month), mean age (3·0 vs 7·5 years), cardiac involvement (two of 19 vs six of ten), KDSS (zero of 19 vs five of ten), MAS (zero of 19 vs five of ten), and need for adjunctive steroid treatment (three of 19 vs eight of ten; all $p<0·01$). Interpretation In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic. Funding None.

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Wampler Muskardin, T. L. (2020). "Intravenous Anakinra for Macrophage Activation Syndrome May Hold Lessons

for Treatment of Cytokine Storm in the Setting of Coronavirus Disease 2019." ACR Open Rheumatology **08**: 08.
Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are increasingly recognized as being on a continuum of cytokine storm syndromes, with different initiating pathways culminating in cytotoxic dysfunction and uncontrolled activation and proliferation of T lymphocytes and macrophages. The activated immune cells produce large amounts of proinflammatory cytokines, including interleukin 1beta (IL)-1beta. Management depends on the recognized diagnosis. In the setting of a cytokine storm syndrome and infection, collaborative involvement of specialists, including infectious disease and rheumatology is ideal. Anakinra, a recombinant IL-1 receptor antagonist, has been used subcutaneously and intravenously in pediatric patients and is considered a first-line treatment for MAS and secondary HLH (sHLH) among many pediatric rheumatologists. Previous reports of anakinra used in adults for treatment of MAS or sHLH are limited to subcutaneous administration. In this issue, Moneagudo et al. present a series of adult patients with sHLH treated with intravenous anakinra, including patients in whom subcutaneous anakinra was insufficient. As the authors suggest, there is a potential therapeutic use for anakinra in sHLH or the cytokine storm syndrome triggered by COVID19. Trial design will be key, with the patient subpopulation, timing of intervention, and doses tested important.

Wampler Muskardin, T. L. (2020). "IV anakinra for macrophage activation syndrome may hold lessons for treatment of cytokine storm in the setting of COVID19." ACR Open Rheumatology **08**: 08.
Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are increasingly recognized as being on a continuum, with different initiating pathways culminating in cytotoxic dysfunction and uncontrolled activation and proliferation of T lymphocytes and macrophages. The activated immune cells produce large amounts of proinflammatory cytokines, including IL-1s and IL-6, creating a "cytokine storm" (1, 2). HLH can be familial (primary) or acquired (secondary to conditions such as infection, malignancy, or active autoimmune or autoinflammatory disease). Secondary HLH (sHLH) in association with autoimmune or autoinflammatory disease is referred to as macrophage activation syndrome (MAS).

Wang, J., et al. (2020). "ACE2 expression by colonic epithelial cells is associated with viral infection, immunity and energy metabolism." medRxiv: 2020.2002.2005.20020545.
Respiratory disease caused by the 2019 novel coronavirus (2019-nCoV) pneumonia first emerged in Wuhan, Hubei Province, China, in December 2019 and spread rapidly to other provinces and other countries. Angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV and has been suggested to be also the receptor for 2019-nCoV. Paradoxically, ACE2 expression in the lung protects mice from SARS-CoV spike protein induced lung injury by attenuating the renin-angiotensin system. In the intestine, ACE2 also suppresses intestinal inflammation by maintaining amino acid homeostasis, antimicrobial peptide expression and ecology of the gut microbiome. Upon analysis of single cell-RNA sequencing data from control subjects and those with colitis or inflammatory bowel disease (IBD), we found that ACE2 expression in the colonocytes was positively associated with genes regulating viral infection, innate and cellular immunity, but was negatively associated with viral transcription, protein translation, humoral immunity, phagocytosis and complement activation. In summary, we suggest that ACE2 may play dual roles in mediating the susceptibility and immunity of 2019-nCoV infection.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThe National Natural Science Foundation of China (91742109, 31770978, 31722003, 31770925, 31370847, 81770552), National Key Research and Development Program (2016YFC0900102), National Science and Technology Major Project (2018ZX10302205), Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease (2019B030301004), Guangzhou Women and Children's Medical Center Fund (5001-3001032) and National Health and Medical Research Council of Australia (1037321, 1105209, 1143976, and 1080321 to A.L.) funded this study. Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively,

please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe single-cell RNAseq data was from our recently published work entitled "Profiling of Pediatric-Onset Colitis and IBD Reveals Common Pathogenics and Therapeutic Pathways"(Cell, 2019. 179(5): p. 1160-1176 e24.)

Wang, Y., et al. (2020). "Epidemiological and clinical characteristics analysis of 30 childhood cases with 2019 novel coronavirus infection in Shenzhen." Chinese Journal of Infectious Diseases **38**(0): E012-E012.
Objectives;To analyze the epidemiological and clinical characteristics of children with 2019 novel coronavirus (2019-nCoV) infection in Shenzhen.;;Methods;The data of 30 children diagnosed with 2019-nCoV infection in the Third People’s Hospital of Shenzhen from 16th January 2020 to 9th February 2020were collected.;;Results;Among the 30 children, 14 were boys and 16 were girls. There were 10 mild cases, 13 common cases and one severe case, and six cases with asymptomatic infection. The age ranged from 7 months to 18 years old with the median age of 7 years old. Twenty out of 30 cases (66.7%) were school children. The common clinical characteristics were fever (30.0%, 9/30) and cough (23.3%, 7/30). The body temperature waved below 37.5 ℃. Mostly the auscultations of the lungs were no rales and there was no extrapulmonary complication. A total number of one case had wheezes and hypoxia, and one case had diarrhea and vomiting. There was no critical and death case. There were 29 cases with travelling experience in Hubei province within two weeks, and 24 cases (80.0%) had relatives (parents or grandparents) diagnosed with 2019-nCoV infection. Elevated white blood cell counts (﹥12×10⁹/L), C reaction protein level, lactate dehydrogenase level and the low proportion of T help cells occurred in three, five, five and three cases, respectively. Some cases were coinfected with human respiratory syncytial virus, mycoplasma pneumonia, human herpesvirus, influenza B virus and rubella virus. The predominant pattern of computed tomography findings of childhood patients with 2019-nCoV infection presented with patchy film and ground-glass opacities in bilateral or unilateral lung. The median time for nucleic acid to turn negative was eight days among the enrolled cases. All the cases were cured and discharged home, and the days in hospital waved from 5 - 16 days (the median time was 12 days).;;Conclusions;The majority of the childhood cases are the school-age children with family cluster. Most cases present mild and common symptoms with good prognosis. Some patients may be complicated with multiple infections. ;

Wang, Y., et al. (2020). "Epidemiological and Clinical Characteristics of 74 Children Infected with SARS-CoV-2 in Family Clusters in Wuhan, China." SSRN.
Background: The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is ongoing globally. Limited data are available for children with SARS-

Wilk, A. J., et al. (2020). "A single-cell atlas of the peripheral immune response to severe COVID-19." medRxiv: 2020.2004.2017.20069930.
There is an urgent need to better understand the pathophysiology of Coronavirus disease 2019 (COVID-19), the global pandemic caused by SARS-CoV-2. Here, we apply single-cell RNA sequencing (scRNA-seq) to peripheral blood mononuclear cells (PBMCs) of 7 patients hospitalized with confirmed COVID-19 and 6 healthy controls. We identify substantial reconfiguration of peripheral immune cell phenotype in COVID-19, including a heterogeneous interferon-stimulated gene (ISG) signature, HLA class II downregulation, and a novel B cell-derived granulocyte population appearing in patients with acute respiratory failure requiring mechanical ventilation. Importantly, peripheral monocytes and lymphocytes do not express substantial amounts of pro-inflammatory cytokines, suggesting that circulating leukocytes do not significantly contribute to the potential COVID-19 cytokine storm. Collectively, we provide the most thorough cell atlas to date of the peripheral immune response to severe COVID-19.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThe Stanford ICU Biobank and A.J.R. are funded by NIH/NHLBI K23 HL125663. A.J.W. is supported by the Stanford Medical Scientist Training Program (T32 GM007365-44) and the Stanford Bio-X Interdisciplinary Graduate Fellowship; A.R. is supported by the Applied Genomics in Infectious Diseases training grant T32 AI007502-23; N.Q.Z. is supported by a National Science Scholarship from A*STAR Singapore; J.L.M. is supported by National Science Foundation Graduate Research Fellowship DGE-1656518; J.L.M. and G.I. are supported by NIH training grant T32 AI007290-35. C.A.B. is supported by NIH/NIDA DP1

DA04608902, a 2019 Sentinel Pilot Project from the Bill & Melinda Gates Foundation, and Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Diseases #1016687. C.A.B. is the Tashia and John Morgridge Faculty Scholar in Pediatric Translational Medicine from the Stanford Maternal Child Health Research Institute and an Investigator of the Chan Zuckerberg Biohub.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesRaw sequencing data will be deposited on GEO. Processed count matrices will be hosted on and available for download from the publicly accessible cellxgene platform by the Chan Zuckerberg Biohub Initiative.

Wollenberg, A., et al. (2020). "European Task Force on Atopic Dermatitis (ETFAD) statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2)-infection and atopic dermatitis." Journal of European Academy of Dermatology & Venereology **29**: 29.
Atopic dermatitis (AD) is a complex disease with elevated risk of respiratory comorbidities. sup 1,2 /sup Severely affected patients are often treated with immune-modulating systemic drugs. sup 3,4 /sup On March 11th 2020, the World Health Organization declared the 2019 novel coronavirus severe acute respiratory syndrome (SARS-Cov-2) epidemic to be a pandemic. The number of cases worldwide is increasing exponentially and poses a major health threat, especially for those who are elderly, immuno-compromised, or have comorbidities. This also applies to AD patients on systemic immune-modulating treatment. In these days of uncertainty, reallocation of medical resources, curfew, hoarding, and shutdown of normal social life, patients, caregivers and doctors ask questions regarding the continuation of systemic immune-modulating treatment of AD patients. The ETFAD decided to address some of these questions here.

World Health, O. (2020). The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. Background Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a wide range of uses. NSAIDs include nonselective cyclooxygenase (COX) inhibitors (such as ibuprofen, aspirin (acetylsalicylate), diclofenac, and naproxen), as well as selective COX2 inhibitors (such as celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valecoxib). Concerns have been raised that NSAIDs may be associated with an increased risk of adverse effects when used in patients with acute viral respiratory infections, including COVID-19.1,2 This review aimed to assess the effects of prior and current use of NSAIDs in patients with acute viral respiratory infections on acute severe adverse events (including mortality, the acute respiratory distress syndrome (ARDS), acute organ failure, and opportunistic infections), on acute health care utilization (including hospitalization, intensive care unit (ICU) admission, supplemental oxygen therapy, and mechanical ventilation) as well as on quality of life and long-term survival. Methods A rapid systematic review was carried out on 20 March 2020 on NSAIDs and viral respiratory infections using MEDLINE, EMBASE, and WHO Global Database. The review included studies conducted in humans of any age with viral respiratory infections exposed to systemic NSAIDs of any kind. All studies on COVID-19, the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) were included irrespective of their sample size. Review of the evidence A total of 73 studies were included (28 studies in adults, 46 studies in children, and one study in adults and children). All studies were concerned with acute viral respiratory infections or conditions commonly caused by respiratory viruses, but none specifically addressed COVID-19, SARS, or MERS. The review showed very low certainty evidence on mortality among adults and children.3 Effects of NSAIDs on the risk for ischemic and haemorrhagic stroke and myocardial infarction in adults with acute respiratory infections are unclear.4,5 Moderate to high certainty evidence showed little or no difference between ibuprofen and acetaminophen (paracetamol) among children with fever with regard to effects on death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding.6-9 Most studies report that no severe adverse events occurred, or that only mild or moderate adverse events were

observed. 10-13 There was no evidence regarding the effects of NSAID use on acute health care utilization, explicit quality of life measures, or long-term survival. Limitations No direct evidence from patients with COVID-19, SARS, or MERS was available. Therefore, all evidence included should be considered indirect evidence with respect to the use of NSAIDs prior to or during the management of COVID-19. Only one randomized controlled trial included a sufficiently large number of participants to identify rare severe adverse events. The remaining evidence derives from smaller randomized controlled trials, which are likely to be underpowered for detecting rare severe adverse events, and from case-control and cohort studies with methodological limitations. Studies included not only patients with confirmed viral respiratory infections and known pathogens, but also those with conditions commonly caused by respiratory viruses, such as upper respiratory tract infections and fever in children. It is likely that not all participants had viral respiratory infections. NSAIDs are a diverse set of drugs with different risk profiles for different populations and conditions. Not all studies distinguished between different types of NSAIDs. Some of the older studies are likely to have included patients taking specific NSAIDs that are no longer available owing to adverse effects. Conclusion At present there is no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs. References Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting?. Ecancermedicalscience. 2020;14:1023. Published 2020 Mar 30. doi:10.3332/ecancer.2020.1023 Non-steroidal anti-inflammatory drugs and covid-19. BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.m1185 (Published 27 March 2020) Epperly H, Vaughn FL, Mosholder AD, Maloney EM, Rubinson L: Nonsteroidal Anti-Inflammatory Drug and Aspirin Use, and Mortality among Critically Ill Pandemic H1N1 Influenza Patients: an Exploratory Analysis. Japanese journal of infectious diseases 2016, 69(3):248-251 Wen Y-C, Hsiao F-Y, Lin Z-F, Fang C-C, Shen L-J: Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode. Pharmacoepidemiology and drug safety 2018, 27(6):645-651 Wen Y-C, Hsiao F-Y, Chan KA, Lin Z-F, Shen L-J, Fang C-C: Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study. The Journal of infectious diseases 2017, 215(4):503-509 Grimaldi-Bensouda L, Abenhaim L, Michaud L, Mouterde O, Jonville-Béra AP, Giraudeau B, David B, Autret-Leca E: Clinical features and risk factors for upper gastrointestinal bleeding in children: A case-crossover study. European Journal of Clinical Pharmacology 2010, 66(8):831-837. Le Bourgeois M, Ferroni A, Leruez-Ville M, Varon E, Thumerelle C, Bremont F, Fayon MJ, Delacourt C, Ligier C, Watier L et al: Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. J Pediatr 2016, 175:47-53.e43. Lesko SM, Mitchell AA: Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997, 100(6):954-957. Lesko SM, Mitchell AA: An Assessment of the Safety of Pediatric Ibuprofen: A Practitioner-Based Randomized Clinical Trial. JAMA: The Journal of the American Medical Association 1995, 273(12):929-933. Moore N, Charlesworth A, Van Ganse E, LeParc JM, Jones JK, Wall R, Schneid H, Verriere F: Risk factors for adverse events in analgesic drug users: results from the PAIN study. Pharmacoepidemiol Drug Saf 2003, 12(7):601-610. Narayan K, Cooper S, Morphet J, Innes K: Effectiveness of paracetamol versus ibuprofen administration in febrile children: A systematic literature review. J Paediatr Child Health 2017, 53(8):800-807. Pierce C, Voss B: Efficacy and safety of ibuprofen and acetaminophen in children and adults: A meta-analysis and qualitative review. Annals of Pharmacotherapy 2010, 44(3):489-506. Rainsford KD, Adesioye J, Dawson S: Relative safety of NSAIDs and analgesics for non-prescription use or in equivalent doses. InflammoPharmacology 2000, 8(4):351-359.

Wu, G. (2020). "Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health." Amino Acids **52**(3): 329-360.
Taurine (a sulfur-containing beta-amino acid), creatine (a metabolite of arginine, glycine and methionine), carnosine (a dipeptide; beta-alanyl-L-histidine), and 4-hydroxyproline (an imino acid; also often referred to as an amino acid) were discovered in cattle, and the discovery of anserine (a methylated product of carnosine; beta-alanyl-1-methyl-L-histidine) also originated with cattle. These five nutrients are highly abundant in beef, and have important physiological roles in anti-oxidative and anti-inflammatory reactions, as well as neurological, muscular, retinal, immunological and cardiovascular function. Of particular note, taurine, carnosine, anserine, and creatine are absent from plants, and hydroxyproline is negligible in many plant-source foods. Consumption of 30 g dry beef can fully meet daily physiological needs of the healthy 70-kg adult human for taurine and carnosine, and can also

provide large amounts of creatine, anserine and 4-hydroxyproline to improve human nutrition and health, including metabolic, retinal, immunological, muscular, cartilage, neurological, and cardiovascular health. The present review provides the public with the much-needed knowledge of nutritionally and physiologically significant amino acids, dipeptides and creatine in animal-source foods (including beef). Dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline are beneficial for preventing and treating obesity, cardiovascular dysfunction, and ageing-related disorders, as well as inhibiting tumorigenesis, improving skin and bone health, ameliorating neurological abnormalities, and promoting well being in infants, children and adults. Furthermore, these nutrients may promote the immunological defense of humans against infections by bacteria, fungi, parasites, and viruses (including coronavirus) through enhancing the metabolism and functions of monocytes, macrophages, and other cells of the immune system. Red meat (including beef) is a functional food for optimizing human growth, development and health.

Wu, Q., et al. (2020). "Co-infection and Other Clinical Characteristics of COVID-19 in Children." Pediatrics **06**: 06.

Wu, Q., et al. (2020). "Epidemiological and Clinical Characteristics of Children with Coronavirus Disease 2019." SSRN.
Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly identified pathogen which mainly spreads by droplets. Most published studies

Xiong, X., et al. (2020). "Are COVID-19 infected children with gastrointestinal symptoms different from those without symptoms? A comparative study of the clinical characteristics and epidemiological trend of 244 pediatric cases from Wuhan." medRxiv: 2020.2004.2029.20084244.
Objective: COVID-19 patients presenting with gastrointestinal (GI) symptoms occur in both adults and children. To date, however, no large sample size study focusing on gastrointestinal symptoms in pediatric cases has been published. We analyzed COVID-19 infected children in Wuhan who presented with initial GI symptoms to determine the GI characteristics and epidemiological trend of the disease. Design: We retrospectively analyzed 244 children patients confirmed with COVID-19 at Wuhan Children's Hospital from 21 Jan to 20 Mar 2020. Symptomatic cases were divided into two groups according to whether the patients presented with or without GI symptoms on admission. Demographic, epidemiological, symptoms, and laboratory data were compared. We also analyzed the respective trends of case number changes of GI cases and asymptomatic cases. Results: 34 out of 193 symptomatic children had GI symptoms. They had lower median age and weight, a higher rate of fever, a longer length of stay and more hematological and biochemical abnormalities than patients without GI symptoms. There was no significant difference in chest CT findings or stool SARS-CoV-2 test positive percentages between the two groups. The number of patients admitted with GI symptoms showed an overall downward trend with time. At the time of writing, 242 patients were discharged, one died, and one critically ill patient was still in the intensive care unit. Conclusion: COVID-19 infected children with GI symptoms are prone to presenting with more clinical and laboratory abnormalities than patients without GI symptoms. More attention and timely hospital admission are needed for these patients.Competing Interest StatementThe authors have declared no competing interest.Funding StatementNo external funding was receivedAuthor DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe availability of all data referred to in the manuscript can be obtained via the corresponding authors

Ye, Q., et al. (2020). "Cytokine Storm in COVID-19 and Treatment." Journal of Infection.
Cytokine storm is an excessive immune response to external stimuli. The pathogenesis of the cytokine storm is complex. The disease progresses rapidly, and the mortality is high. Certain evidence shows that,

during the coronavirus disease 2019 (COVID-19) epidemic, the severe deterioration of some patients has been closely related to the cytokine storm in their bodies. This article reviews the occurrence mechanism and treatment strategies of the COVID-19 virus-induced inflammatory storm in attempt to provide valuable medication guidance for clinical treatment.

Zhang, C., et al. (2020). "Clinical Characteristics of 34 Children with Coronavirus Disease-2019 in the West of China: a Multiple-center Case Series." medRxiv: 2020.2003.2012.20034686.
BACKGROUND Up to 9 March, 2020, 109577 patients were diagnosed with coronavirus disease-2019 (COVID-19) globally. The clinical and epidemiological characteristics of adult patients have been revealed recently. However, the information of paediatric patients remains unclear. We describe the clinical and epidemiological characteristics of paediatric patients to provide valuable insight into early diagnosis of COVID-19 in children, as well as epidemic control policy making. METHODS and FINDINGS This retrospective, observational study was a case series performed at 4 hospitals in the west of China. Thirty-four paediatric patients with COVID-19 were included from January 1 to February 25, 2020. And the final follow-up visit was completed by February 28, 2020. Clinical and epidemiological characteristics were analyzed on the basis of demographic data, medical history, laboratory tests, radiological findings, and treatment information. Data analysis was performed on 34 paediatrics patients with COVID-19 aged from 1 to 144 months (median 33.00, IQR 10.00 - 94.25), among whom 14 males (41.18%) were included. 47.60% of patients were noticed without any exposure history. The median incubation period was 10.50 (7.75 - 25.25) days. Infections of other respiratory pathogens were reported in 16 patients (47.06%). The most common initial symptoms were fever (76.47%), cough (58.82%), and expectoration (20.59%). Vomiting (11.76%) and diarrhea (11.76%) were also reported in a considerable portion of cases. A remarkable increase was detected in serum amyloid A for 17 patients (85.00%) and high-sensitivity C-reactive protein for 17 patients (58.62%), while a decrease of prealbumin was noticed in 25 patients (78.13%). In addition, the levels of lactate dehydrogenase was increased significantly in 28 patients (82.35%), as well as α-hydroxybutyrate dehydrogenase in 25 patients (73.53%). Patchy lesions in lobules were detected by chest computed tomographic scans in 28 patients (82.36%). The typical feature of ground-glass opacity for adults was rare in paediatric patients (2.94%). A late-onset pattern of lesions in lobules were also noticed. Stratified analysis of the clinical features were not performed due to relatively limited samples. CONCLUSIONS Our data presented the clinical and epidemiological features of paediatric patients systemically. The findings offer new insight into the early identification and intervention of paediatric patients with COVID-19.Competing Interest StatementThe authors have declared no competing interest.Funding StatementNo funding was received.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesIndividual participant data that underlie the results reported in this article are available after deidentification for investigational purpose. Data are available in our hospital's clinical trial medical records managed by GCP office with investigator's support.

Zheng, F., et al. (2020). "Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China." Current Medical Science **24**: 24.
Since December 2019, COVID-19 has occurred unexpectedly and emerged as a health problem worldwide. Despite the rapidly increasing number of cases in subsequent weeks, the clinical characteristics of pediatric cases are rarely described. A cross-sectional multicenter study was carried out in 10 hospitals across Hubei province. A total of 25 confirmed pediatric cases of COVID-19 were collected. The demographic data, epidemiological history, underlying diseases, clinical manifestations, laboratory and radiological data, treatments, and outcomes were analyzed. Of 25 hospitalized patients with COVID-19, the boy to girl ratio was 1.27:1. The median age was 3 years. COVID-19 cases in children aged 3 years, 3.6 years, and =6-years patients were 10 (40%), 6 (24%), and 9 (36%), respectively. The most

common symptoms at onset of illness were fever (13 [52%]), and dry cough (11 [44%]). Chest CT images showed essential normal in 8 cases (33.3%), unilateral involvement of lungs in 5 cases (20.8%), and bilateral involvement in 11 cases (45.8%). Clinical diagnoses included upper respiratory tract infection (n=8), mild pneumonia (n=15), and critical cases (n=2). Two critical cases (8%) were given invasive mechanical ventilation, corticosteroids, and immunoglobulin. The symptoms in 24 (96%) of 25 patients were alleviated and one patient had been discharged. It was concluded that children were susceptible to COVID-19 like adults, while the clinical presentations and outcomes were more favorable in children. However, children less than 3 years old accounted for majority cases and critical cases lied in this age group, which demanded extra attentions during home caring and hospitalization treatment.

Zhong, Z., et al. (2020). "Chest CT findings and clinical features of coronavirus disease 2019 in children." Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences **45**(3): 236-242.
OBJECTIVES: To describe the CT features and clinical characteristics of pediatric patients with coronavirus disease 2019 (COVID-19). METHODS: A total of 9 COVID-19 infected pediatric patients were included in this study. Clinical history, laboratory examination, and detailed CT imaging features were analyzed. All patients underwent the first CT scanning on the same day of being diagnosed by real-time reverse-transcription polymerase chain reaction (rRT-PCR). A low-dose CT scan was performed during follow-up. RESULTS: All the child patients had positive results. Four patients had cough and one patient had fever. One patient presented both cough and fever. Two children presented other symptoms like sore throat and stuffy nose. One child showed no clinical symptom. Five patients had positive initial CT findings with subtle lesions like ground-glass opacity (GGO) or spot-like mixed consolidation. Three patients were reported with negative results in the initial and follow-up CT examination. One patient was reported with initial negative CT findings but turning positive during the first follow-up. All patients had absorbed lesions on follow-up CT images after treatment. CONCLUSIONS: Pediatric COVID-19 patients have certain imaging and clinical features as well as disease prognosis. Children with COVID-19 tend to have normal or subtle CT findings and relatively better outcome.

Zhou, M.-Y., et al. (2020). "From SARS to COVID-19: What we have learned about children infected with COVID-19." International Journal of Infectious Diseases.
Coronaviruses, both SARS-CoV and SARS-CoV-2 were firstly appeared in China. They have certain similarities in biological, epidemiological and pathological. To data, the researches have shown that their gene exhibit 79% of identical sequence and the receptor-binding domain structure is also very similar. There have been extensive research performed on SARS, however, the understanding of pathophysiology impact of Corona Virus Disease 2019(COVID-19) is still limited. In the review, we draw upon the lessons learnt from SARS in the epidemiology, clinical characteristics and pathogenesis for further understand the features of COVID-19. By comparing these two diseases, we found, COVID-19 has quicker and wider transmission, obvious family agglomeration, higher morbidity and mortality. Newborns, asymptomatic children and normal chest imaging cases were emerged in COVID-19. Children started with gastrointestinal symptoms may progress to severe condition and newborn whose mother was infected with COVID-19 could have severe complications. The laboratory test data showed, the percentage of neutrophils and the level of LDH is higher, otherwise the number of CD4+ and CD8+T cells is decreased in children's COVID-19 cases. Based on these early observations, as pediatrician, we put forward some thoughts on children's COVID-19 and give some recommendations to contain the disease.

Zhu, L., et al. (2020). "Clinical characteristics of a case series of children with coronavirus disease 2019." Pediatric Pulmonology **08**: 08.
We reported the clinical characteristics of a case series of 10 patients with coronavirus disease 2019 (COVID-19) aged from 1 year to 18 years. Seven patients had contact with confirmed COVID-19 family members before onset. Fever (4 [40.0%]) and cough (3 [30.0%]) were the most common symptoms. No patient showed leucopenia and lymphopenia on admission. Pneumonia was observed in chest CT images in 5 (50.0%) patients. Five (50.0%) patients received antiviral treatment. No patient had severe complications or developed a severe illness in our study. Our study indicated that COVID-19 children present less severe symptoms and have better outcomes.

Zimmermann, P. and N. Curtis (2020). "Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children." Pediatr

Infect Dis J **39**(5): 355-368.
Coronaviruses (CoVs) are a large family of enveloped, single-stranded, zoonotic RNA viruses. Four CoVs commonly circulate among humans: HCoV2-229E, -HKU1, -NL63 and -OC43. However, CoVs can rapidly mutate and recombine leading to novel CoVs that can spread from animals to humans. The novel CoVs severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The 2019 novel coronavirus (SARS-CoV-2) is currently causing a severe outbreak of disease (termed COVID-19) in China and multiple other countries, threatening to cause a global pandemic. In humans, CoVs mostly cause respiratory and gastrointestinal symptoms. Clinical manifestations range from a common cold to more severe disease such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure and even death. SARS-CoV, MERS-CoV and SARS-CoV-2 seem to less commonly affect children and to cause fewer symptoms and less severe disease in this age group compared with adults, and are associated with much lower case-fatality rates. Preliminary evidence suggests children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms. However, the importance of children in transmitting the virus remains uncertain. Children more often have gastrointestinal symptoms compared with adults. Most children with SARS-CoV present with fever, but this is not the case for the other novel CoVs. Many children affected by MERS-CoV are asymptomatic. The majority of children infected by novel CoVs have a documented household contact, often showing symptoms before them. In contrast, adults more often have a nosocomial exposure. In this review, we summarize epidemiologic, clinical and diagnostic findings, as well as treatment and prevention options for common circulating and novel CoVs infections in humans with a focus on infections in children.

From: Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE)
Sent: Wed, 26 Aug 2020 14:05:21 +0000
To: Brooks, John T. (CDC/DDID/NCHHSTP/DHP); Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHP); Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE); White, Jianglan Z. (CDC/DDID/NCHHSTP/DVH); Dunne, Eileen F. (CDC/DDID/NCHHSTP/DHP); Courtenay-Quirk, Cari (CDC/DDID/NCHHSTP/DHPIRS); Schieber, Richard A. (CDC/DDPHSS/CSELS/OD); Ao, Trong (CDC/DDPHSIS/CGH/DGHT); Ackers, Marta (CDC/DDPHSIS/CGH/DGHT); Ende, Zachary (CDC/DDID/NCIRD/ID); Dowell, Deborah (Debbie) (CDC/DDNID/NCIPC/DOP); Welsh, Clement (ATSDR/OAD/OIA); Eisenberg, Judith (CDC/NIOSH/DFSE/HETAB); Beavers, Suzanne (CDC/DDPHSS/CSELS/DSEPD); McDonald, Clifford (CDC/DDID/NCEZID/DHQP)
Subject: IM slides for August 26.
Attachments: COVID-19 IM 2020-08-26 FINAL.pdf

CMO Colleagues,
Please see attached for daily IM slides for August 26. Briefing time is 10AM-11AM ET.
It is not required or expected that you call-in to these daily briefings. However, they may be helpful to put the work we do into context – the CMO unit (John) gives an updates as part of this call. To that end, if you're interested in listening in while multi-tasking, the call-in information is below:
Join by phone:
US: (b)(6)
Webinar ID: (b)(6)
All participants will be muted, except pre-designated presenters.
Renee

COVID-19 Response
Incident Manager Meeting

Tuesday, 26 August 2020

Day 234 of Response, Day 219 of IMS Activation

(Click Here to Bring up the Time Tracker Application)

Priorities of the Week, August 23rd-August 29th

- Refine models to prioritize populations for initial doses of vaccines
- Develop bridging plans for alternate extraction platforms/reagents for the CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay
- Stand up school field evaluation unit in STLT OD, focused on rapid data collection in K-12 schools and institutes of higher education
- Clear (CMAR) Tool, assesses IPC risk in correctional/detention facilities
- Launch <18 yr. old decision algorithm for Clara, the online self-checker
- Lead investigation into SARS-CoV-2 in individuals/animals on mink farms
- Conduct mitigation session for countries focused on schools/lessons learned
- Deploy staff to support states and local jurisdictions
- Disseminate key findings through *MMWR*, CDC.gov, and partner calls

Case Surveillance

Daily change in COVID-19 case & death counts

Daily change in COVID-19 case counts

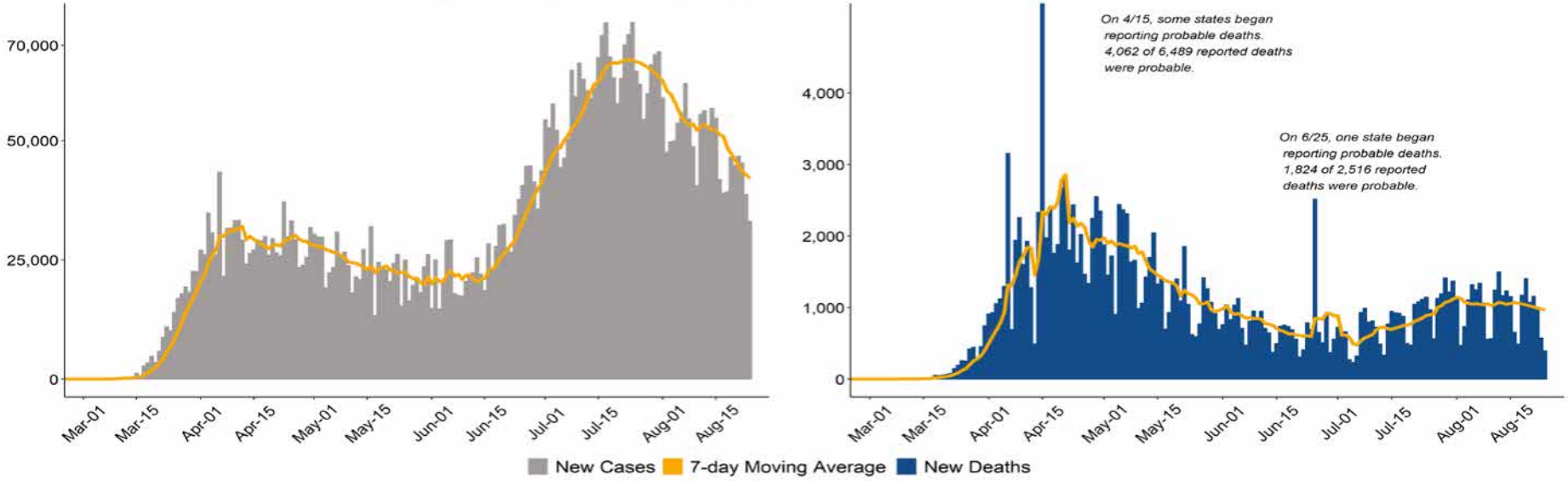
As of August 24 N= 5,715,567 (new: 33,076)

42,065 average over past 7 days vs. 50,991 over 7 previous days (-18%) vs. 66,960 over peak week (-37%)

Daily change in COVID-19 death counts

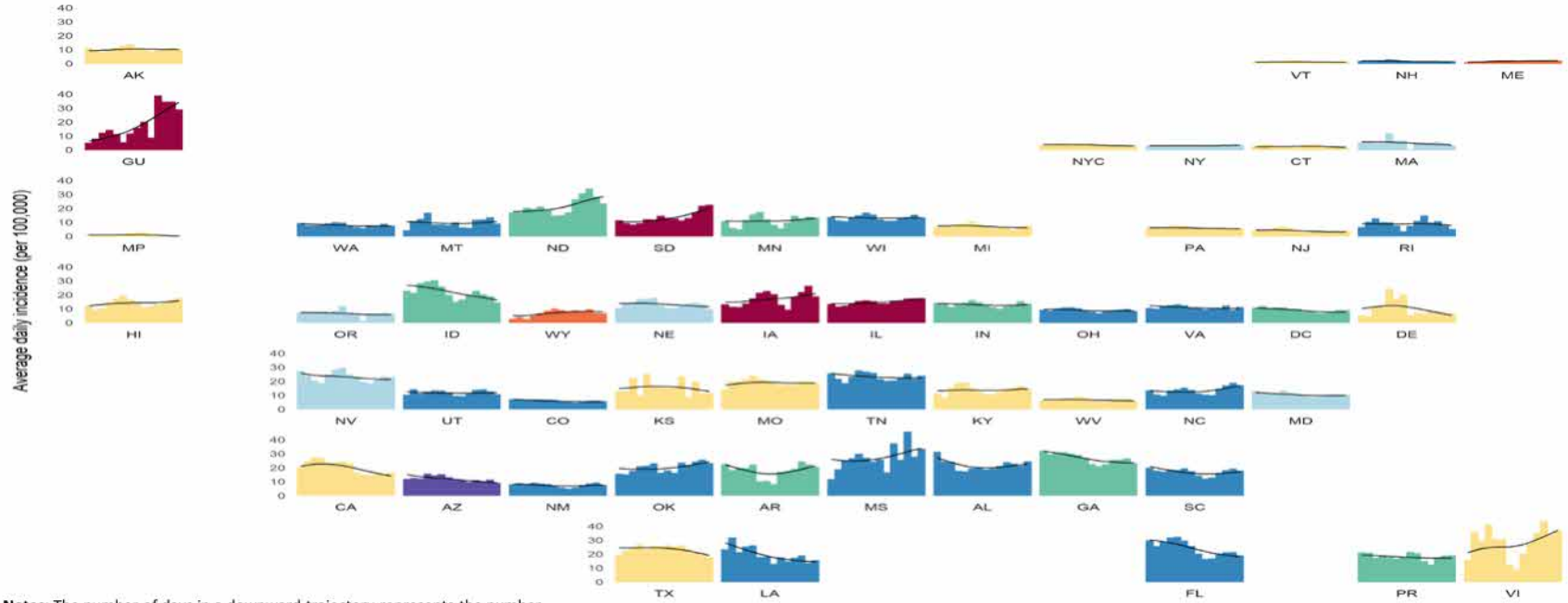
As of August 24 N=176,617 (new: 394)

968 average over past 7 days vs. 1,062 over 7 previous days (-9%)



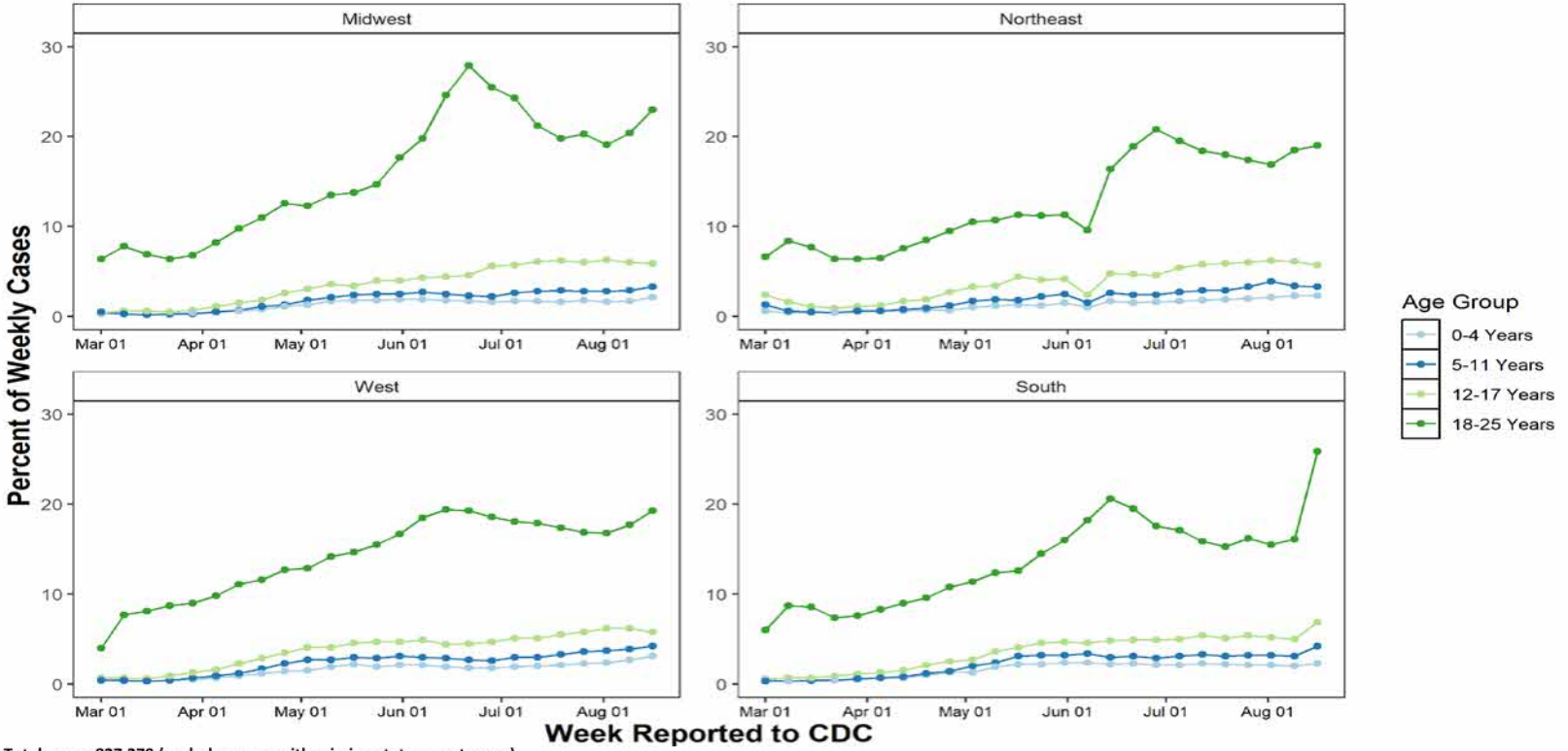
Note, as of April 12th, totals and figures include confirmed and probably cases and deaths reported from states

Incidence by Jurisdiction, 8/10/2020–8/23/2020 (preliminary)



Notes: The number of days in a downward trajectory represents the number of consecutive days for which the jurisdiction experienced either a negative slope or a low incidence plateau (two-week incidence ≤10 cases per 100,000 and slope >−0.1 and ≤0.1). Jurisdictions are allowed a 5-day grace period of departure from downward trajectory before the downward trajectory is considered over. **Data:** Jurisdiction-validated case counts

Distribution of cases of reported COVID-19 among persons 25 years and under by census region and age group, March 1 – August 20, 2020



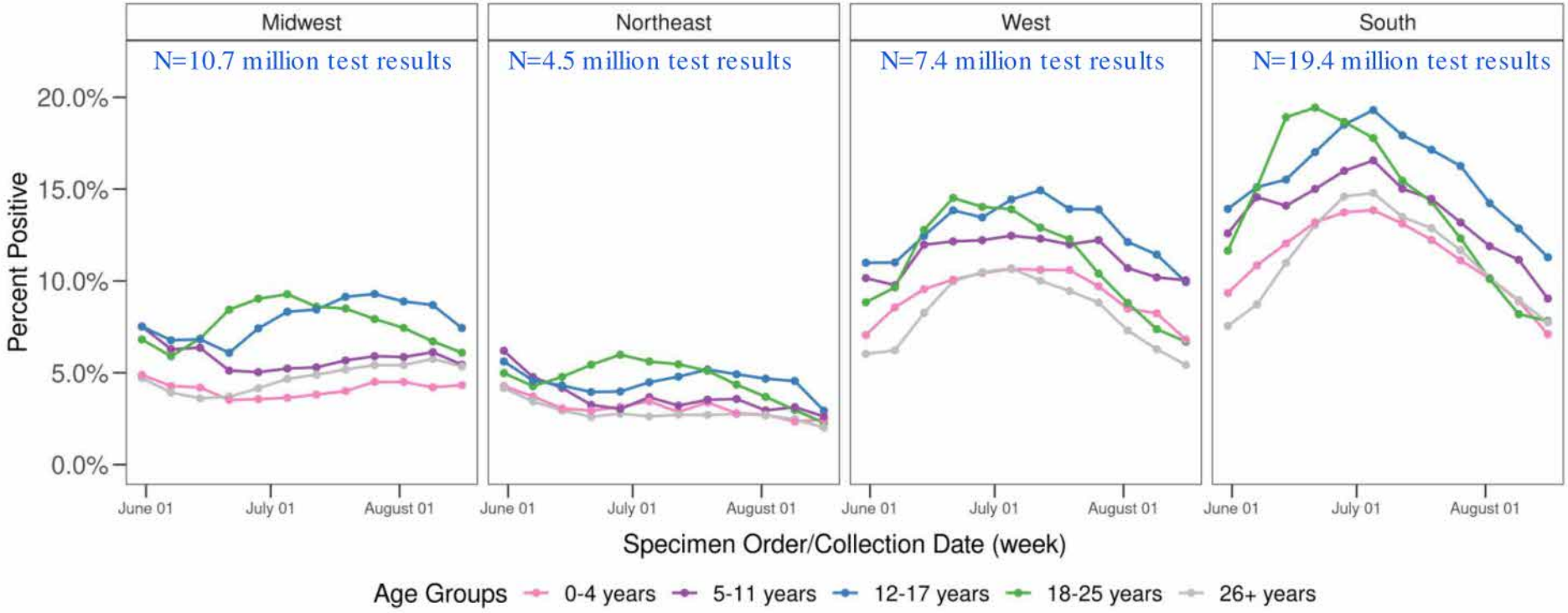
Total cases=827,279 (excludes cases with missing state, county, age)

Case-based surveillance summary

- 4/56 (7%) jurisdictions are upward trajectory
- 2/56 (4%) jurisdictions in plateau
- 50/56 (89%) in downward trajectory
- **Improved**
  - CT → plateau to downward trajectory
  - None→ upward trajectory to plateau
  - None → upward trajectory to downward
- **Worsened**
  - None→ downward trajectory to plateau
  - None → plateau to upward trajectory
  - None → downward to upward trajectory
- **COVID-19 by Region and Age Group**
  - Among persons ≤25, highest proportion of cases among persons aged 18-25 years across all regions
  - Proportion of all cases among 18-25 age group peaked mid-June (Midwest, West, South) but slightly later in the Northeast

Analytics

SARS-CoV-2 RT-PCR Weekly Percent Positivity by Census Region School Age Groups; May 31 – August 22, 2020 (data still coming in for most recent week)*



* Data from the unified dataset: CELR Line Level data and Federal Direct Report data (6 Commercial/Reference laboratories & Public Health laboratories)

Summary of SARS-CoV-2 RT-PCR Test Results

- In all regions, 12-17 year olds are demonstrating the highest percent positivity throughout August
  - In the South and West, this is followed by 5-11 year olds as second highest
  - In the Midwest this is followed by 18-25 year olds
- Overall percent positivity is highest in the South, followed by the West, then Midwest, and is lowest in the Northeast

Vaccine Planning Unit

Topline findings from Qualitative Research on a Future COVID-19 Vaccine

Qualitative Methods

- Purpose: Explore attitudes and beliefs about COVID vaccine, *including who should be among the first to get the vaccine once available*
- Online focus groups (via Zoom) - 60 minutes
- 2 primary audiences – Mixed Ethnicities and African American
- 6 segments
  - Older adults (60+) low SES range
  - Older adults (60+) in median SES range
  - Parents with children <18 in home
  - Adults 20–30 without children
  - Essential workers (non-medical)
  - Nurses (practice and hospital-based RNs)
- Quota sampling of participants via professional recruitment company
- Led by trained qualitative moderators

R

Personal Attitudes About Getting COVID-19 Vaccine

- Most participants generally open to receiving a COVID-19 vaccine *eventually*
- However, many participants hesitant to get the COVID-19 vaccine when first available
  - Many adopted a "wait and see" approach
  - 6 months commonly cited time period
- Reasons to delay/not get vaccine
  - Safety and side effects
  - Effectiveness of vaccine
  - Whether vaccine can be thoroughly tested in shortened timeframe
  - Sufficient testing in my demographic group (e.g., age, race/ethnicity)
- Reasons to get the COVID vaccine
  - Desire to get back to normal life (work, see family and friends)
  - Trust in vaccines and vaccine development process generally and COVID-19 vaccine specifically

Sources of Information

Sources of *and* trusted sources of information varied by audience segment

- Older segments
  - Relied on news establishments for information
  - Personal doctor was especially trusted
- Younger segments
  - Social media commonly cited as a source of information – not always trusted
  - Distrusted established news organizations
- **Trusted organizations included**
  - CDC
  - NIH
  - WHO
  - State or local health departments (by some participants)
- **Individuals cited varied widely and included:**
  - Dr. Fauci
  - Relatives who were health care workers
  - Certain media figures and celebrities

I do not trust the news. The media takes advantage of the situation.
Caucasian Male

Epidemiology

Transmission Dynamics of COVID-19 Outbreaks Associated with Daycare Centers and Schools, Salt Lake County, Utah

Salt Lake County Context

- 1.6 million people, 36% of Utah's population
- Investigate all SARS-CoV-2 lab-confirmed cases, their close contacts (first generation), and close contacts of any positive contacts or symptomatic contacts for all subsequent generations
- Utah's Electronic Disease Surveillance System, EpiTrax tracks all cases and their contacts, maintains linkage
- Testing availability and guidance changed over time

17 Childcare Center Outbreaks April–July 2020

- Reconstructed contact tracing trees for positive individuals using EpiTrax
- 12 centers involved 38 lab-confirmed COVID-19 staff members
- None of these centers had documented transmission to children within the center
- 2 centers included possible transmission within the centers but had incomplete contact investigation information to construct the transmission chains
- **3 centers (2 daycares and 1 school) had transmission in centers and complete contact tracing data**

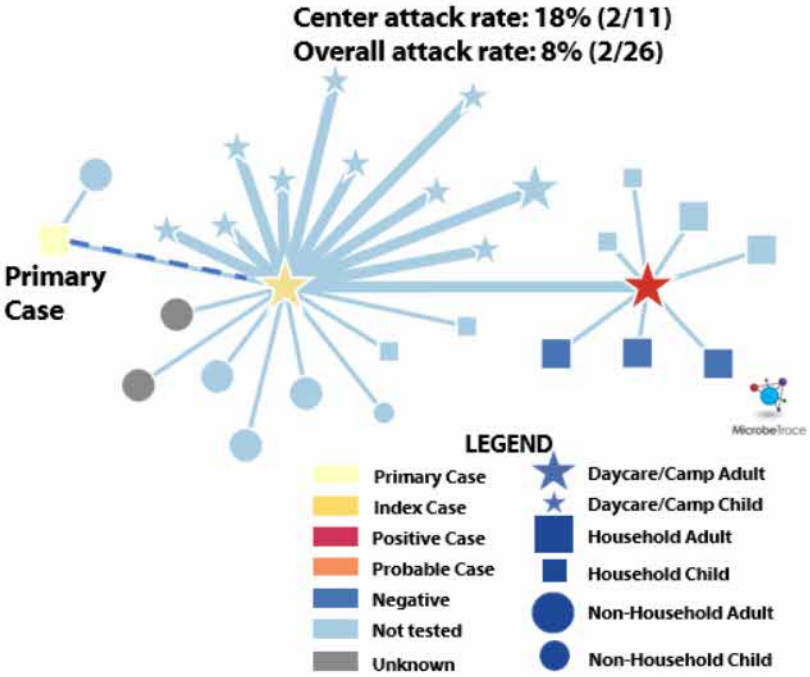
Center A Outbreak

2 Cases (both symptomatic) and 24 Contacts

- 2 adult cases (staff) associated with center
  - **Primary case:** household contact of index case (onset 3/23/2020)
  - **Index case:** teacher (onset 4/2/2020)
  - **Case 2:** teacher (onset 4/5/2020)
- 24 center and non-center contacts
  - No known transmission to contacts
  - Percent positivity during this outbreak: 6.8%, early in the outbreak

Mitigation strategies

- Staff required to wear masks
- Daily temperature and symptom screening required for staff and children



Center B Outbreak

5 Cases (all symptomatic) and 31 Contacts

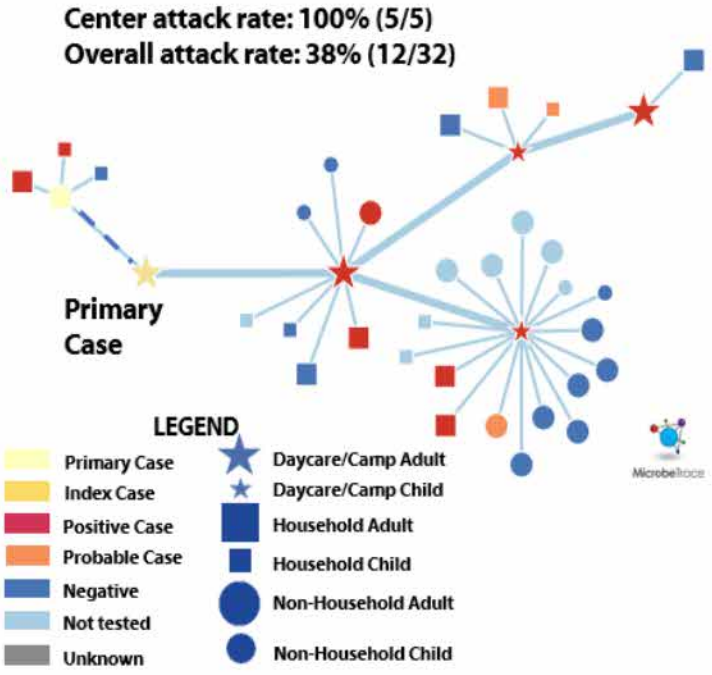
- 5 cases (3 teachers, 2 children) associated with center
  - **Primary case:** household contact of index case (onset 5/26/2020)
  - **Index case:** teacher (tested + 5/31/2020, onset 6/3/2020)
  - **Cases 2–5:** 2 teachers and 2 children (8 months old, 8 years old) with onsets 6/8-25/2020)

Transmission occurred to 3 of 4 households

- 2 pediatric cases led to 2 confirmed (mother and father) and 3 probable (2 adults [1 mother], 1 child) cases
- 3 adult cases resulted in 3 confirmed adult cases
- Percent positivity during this outbreak: 11.2%

Mitigation strategies

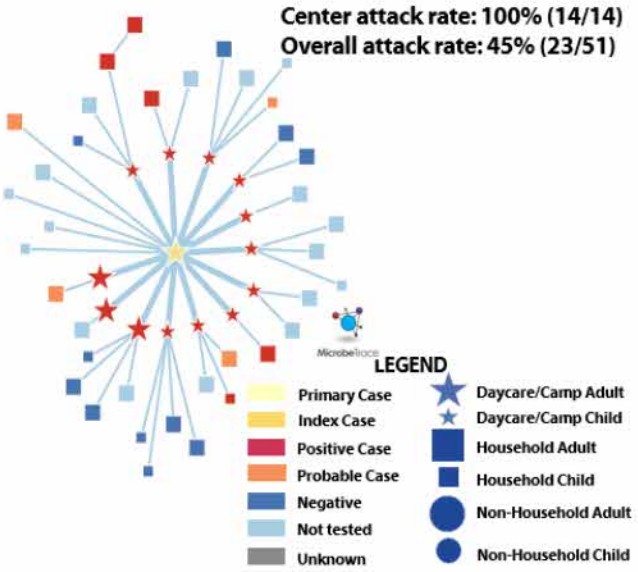
- Closed from 3/13–5/4/2020
- Staff required to wear masks
- Daily temperature screening for staff and children



Center C Outbreak

14 cases (11 symptomatic, 3 asymptomatic) and 37 known linked contacts

- 14 cases (4 teachers, 10 children) associated with center
  - **Primary case:** unknown
  - **Index case:** teacher (onset 6/24/2020, tested + 6/25/2020); 1 other teacher & 2 students had onsets on 6/24/2020
  - **Cases 5-14:** 8 students (aged 6-10 years; 3 asymptomatic) and 2 teachers with onset over next 8 days
- Transmission occurred to 7 of 14 households
  - Child cases led to 5 confirmed (3 mothers, 1 aunt, 1 child) and 2 probable household cases (1 mother and 1 child)
    - One positive mother of asymptomatic child was hospitalized
  - Adult cases led to 2 probable household cases (both adults)
  - Percent positivity during this outbreak: 12%



Mitigation strategies

- Closed from 3/13–6/17/2020
- Masks not required
- Requested daily temperature and symptom check for staff and children

Y

Summary: Transmission Dynamics of COVID-19 Outbreaks Associated with Daycare Centers and Schools, Salt Lake County, Utah

- **57% of cases linked to 3 centers were children (aged 8 month – 10 years)**
- **Transmission from children occurred to 26% of their contacts after exposures at centers**
  - Most children had mild disease and **25% were asymptomatic but still resulted in transmission to contacts**
  - 50% of infected contacts were mothers
- **52% of contacts were not tested**
  - Testing all contacts of COVID-19 positive cases, regardless of symptoms, is important to help limit spread and better understand how children contribute to transmission
- **2 of 3 centers required staff to wear masks; no children, even those ≥2 years, were required to wear masks**
  - Use of face masks, particularly among staff (adults), may help reduce transmission especially when children are too young to wear masks

STLT Support Task Force:
Health Department Section

JCC COVID-19 Response Assistance Field Teams (CRAFT): Virginia Beach Technical Assistance

Virginia Beach CRAFT 4 Mission (July 20–24):

- Challenges included increasing cases, test result delays, and staffing needs

CDC Mission Objectives (Aug 3–Sep 22):

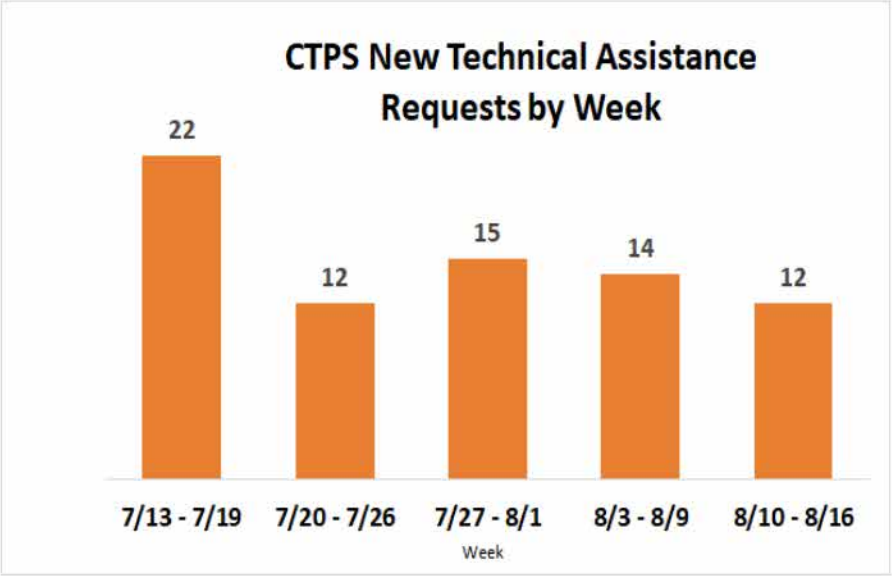
- Conduct local contact tracing and case investigations
- Conduct limited field visits
- Train local health department staff

Accomplishments to Date:

- Trained **24 staff** at **5 local health departments**
- Completed **~300 case investigations**
- Reduced case investigation interview scripts by **20 minutes**
- Improved workflow of case information
- Increased use of electronic systems for contract tracing

STLT Support Task Force:
Workforce Development & Innovation

Contact Tracing Program Support (CTPS) - TA Requests



What groups ask for TA?

- State & Local Health Departments
- CDC Response Groups
- Tribal Nations
- Non-Profit/NGO

What are we asked about?

1. Case Specific one-on-one guidance
2. Guideline and Definition Clarification
3. Monitoring & Evaluation of Case Investigation and Contact Tracing Activities
4. Testing
5. Special Populations (schools, sports teams)

G

Contact Tracing Program Support (CTPS) Example and Impact

TA Example

- CTPS received scenario from HD Section about contact tracing on a 2-hour school bus ride
- Outcome: CTPS and HDS identified that all students on school bus met criteria for close contact due to length of bus ride and exposure

TA Impact: Feedback loop as information flows into CDC from partners and programs and out of CDC in the form of guidance

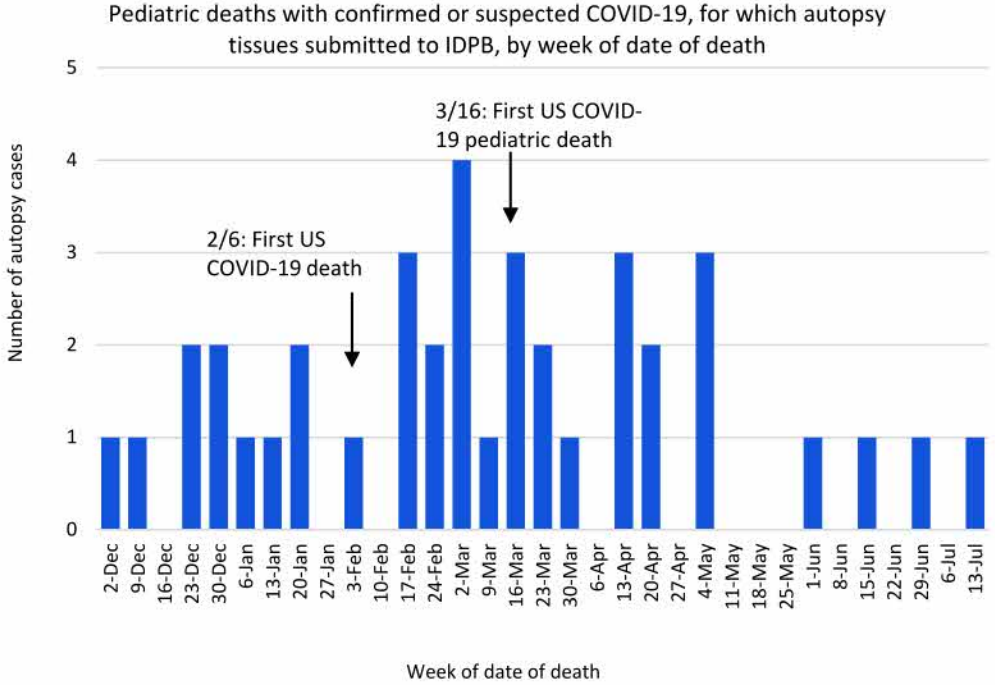
- Informs COVID-19 response about guidance needs and priorities
- Stimulates new guidance development for CI and CT based on emerging needs
- Highlights needed clarifications to guidance for specific scenarios and settings
- Assists in resource allocation decisions for TA and guidance work

Health Systems and Worker Safety

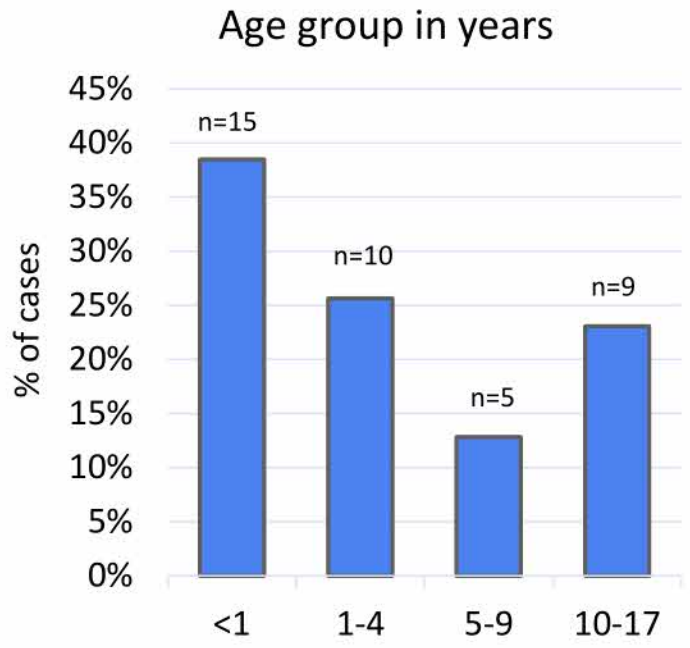
R

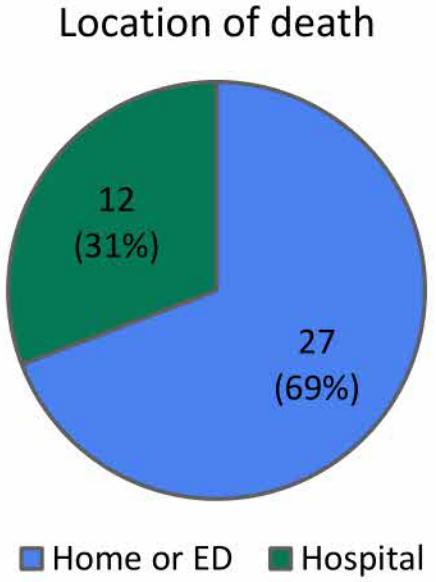
Evaluation of autopsy tissues for SARS-CoV-2, pediatric deaths, Infectious Diseases Pathology Branch (n=39)

- CDC's Infectious Diseases Pathology Branch (IDPB) developed COVID-19 assays for fixed tissue specimens for postmortem diagnosis
- States can submit tissue specimens to IDPB for postmortem diagnosis
  - Histopathologic evaluation
  - Molecular testing (nucleic acid)
    - RT-PCR and sequencing
    - In-situ hybridization (ISH)
    - Immunohistochemistry (IHC; antigen)
- As of 8/19/20, 212 autopsy cases submitted from 36 states
  - 39 (18%) from pediatric deaths (<18 years of age)



Evaluation of autopsy tissues for SARS-CoV-2, pediatric deaths, Infectious Diseases Pathology Branch (n=39)





R

Results of evaluation of autopsy tissues, pediatric deaths, Infectious Diseases Pathology Branch (n=22)

IDPB results on autopsy tissues	Lab evidence of SARS-CoV-2 prior to submission to IDPB (n=6)	No prior lab evidence of SARS-CoV-2 (n=16)
SARS-CoV-2 positive	3	1
SARS-CoV-2 negative, other pathogen(s) identified	2	9
SARS-CoV-2 negative, no other pathogens identified	1	6

R

Pediatric deaths with laboratory evidence of SARS-CoV-2 (n=7)

Age	Location of death	SARS-CoV-2 NP swab	IDPB SARS-CoV-2 results in respiratory tissues	Histopathology and alternative diagnoses/coinfections
1 month	Home/ED	Positive	RT-PCR positive IHC, ISH negative	Interstitial pneumonitis, aspiration
1 month	Home/ED	Positive	RT-PCR and IHC negative	Interstitial pneumonitis, aspiration
9 months	Home/ED	Positive	RT-PCR positive IHC, ISH negative	Aspiration
3 years	Home/ED	Positive	RT-PCR and IHC negative	Bronchopneumonia due to *Streptococcus pneumoniae*
5 years	Hospital	Positive	RT-PCR and IHC negative	Tuberculous meningitis
11 years	Home/ED	Negative	RT-PCR positive IHC, ISH negative	Tracheobronchitis, interstitial pneumonitis, pulmonary hemorrhage; no myocarditis
17 years	Home/ED	Positive	RT-PCR positive IHC, ISH negative	Eosinophilic myocarditis, tracheobronchitis, aspiration, pulmonary hemorrhage

Text Illness Monitoring (TIM)

- TIM monitors individuals for COVID-19 symptoms via SMS text messaging
- Participants receive:
  - A welcome message the first day
  - A daily message asking if they have COVID-19 symptoms
- Jurisdictions using TIM are alerted to individuals:
  - Reporting symptoms
  - Non-responders, and
  - Those who opt out

TIM Users

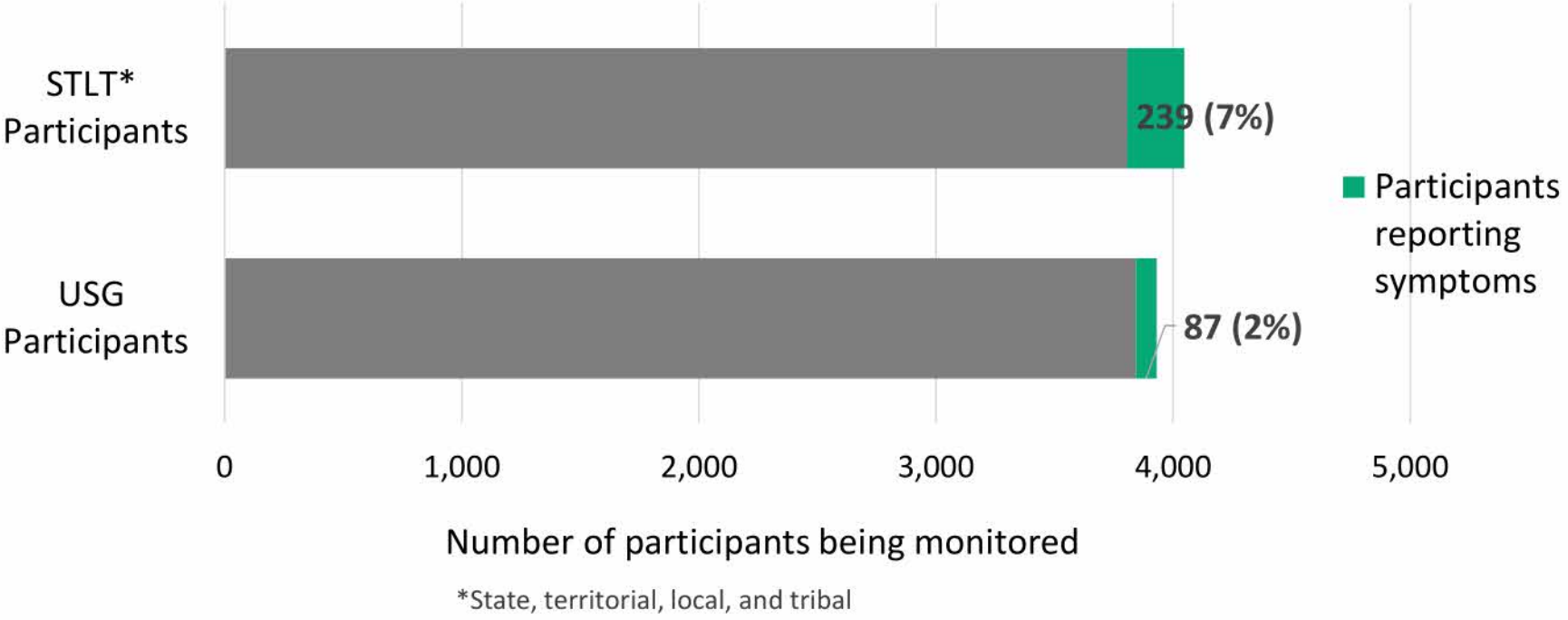
Organization type	# of organizations
USG agencies	6
State health departments	8
Tribal programs	28
Local health departments	73
TOTAL	**115**

Types of participants:

- Contacts of infected persons
- Employees
- Deployed staff
- Firefighters*
- Students*

*onboarding

Number of Participants Reporting Symptoms (8/17/20–8/23/20)



*State, territorial, local, and tribal

TIM: Continuously Improving

- Enhancements to TIM are continuously implemented to improve functionality, including the ability to:
  - Export data for analysis at the jurisdiction level
  - Send text messages to non-U.S. phone numbers
  - Adjust message timing to different time-zones
- Future plans:
  - TIM External SharePoint site
  - Onboarding new users
  - Evaluation

Send questions to: eocevent340@cdc.gov

Hospital Data

Creation of COVID-19 Unified Priority Hospital Dataset

Unified Time Series Dataset, HHS Protect (N = 6,458)

- Data collected from hospitals via TeleTracking, state reporting and NHSN (prior to July 15, 2020)
- Reported data on hospital supply needs capacity, occupancy, staffing and PPE supply needs

Unified Denominator Dataset, HHS Protect (N = 6,430)

Includes:

- All hospitals registered with CMS as of June 1, 2020
- Non-CMS hospitals that have reported capacity data since July 15, 2020
- IHS and VA hospitals

COVID-19 Unified Priority Hospital analytic dataset (N = 5,290)

- Can be used to perform analyses showing percent occupancy, capacity, proportion with COVID-19, and staffing and PPE supply needs by jurisdiction

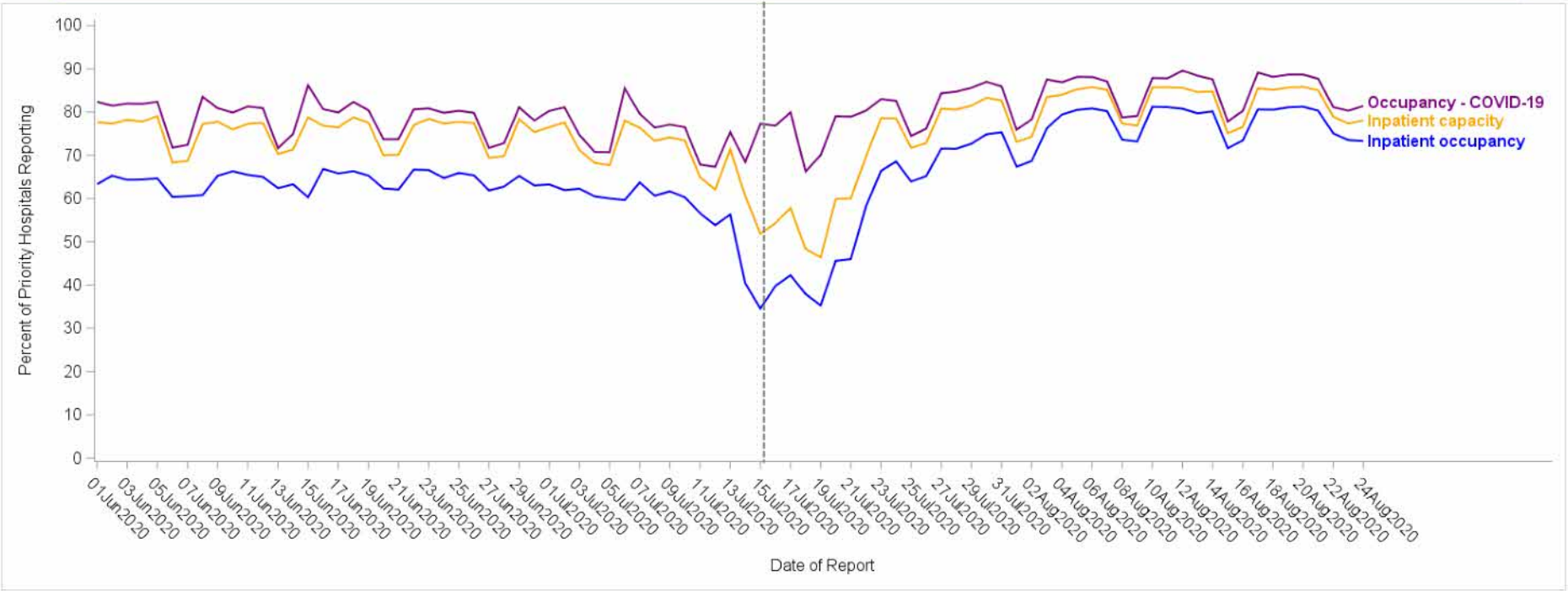
R

Completeness of Reporting of Select Metrics, August 18–24, 2020
Priority Hospitals* (N=5,290), COVID-19 Unified Priority Hospital Dataset

Metric	No. (%) of priority hospitals reporting at least once during August 18-24, 2020
Any data element	4,959 (93.7)
Total beds	4,789 (90.5)
Inpatient capacity (No. beds)	4,735 (89.5)
Inpatient occupancy, any patient	4,513 (85.3)
Inpatient occupancy, COVID-19 patients (confirmed and suspected)	4,864 (91.9)
ICU capacity (No. beds)	4,725 (89.3)
ICU occupancy, any patient	4,731 (89.4)
Ventilator capacity (No. ventilators)	4,825 (91.2)
Ventilator occupancy, any patient	4,848 (91.6)
Ventilator occupancy, COVID-19 patients (confirmed and suspected)	4,726 (89.3)
No. new COVID-19 admissions (confirmed and suspected) during preceding day	4,611 (87.2)
No. deaths due to COVID-19 (confirmed and suspected) during preceding day	4,574 (86.5)

Priority hospitals include those hospitals registered with Centers for Medicare & Medicaid Services (CMS) as of June 1, 2020 and non-CMS hospitals that have reported data since July 15th and exclude psychiatric, rehabilitation, or religious non-medical facilities.

Completeness of Reporting of Select Metrics by Day, June 1–August 24, 2020
Priority Hospitals* (N=5,290), COVID-19 Unified Priority Hospital Dataset

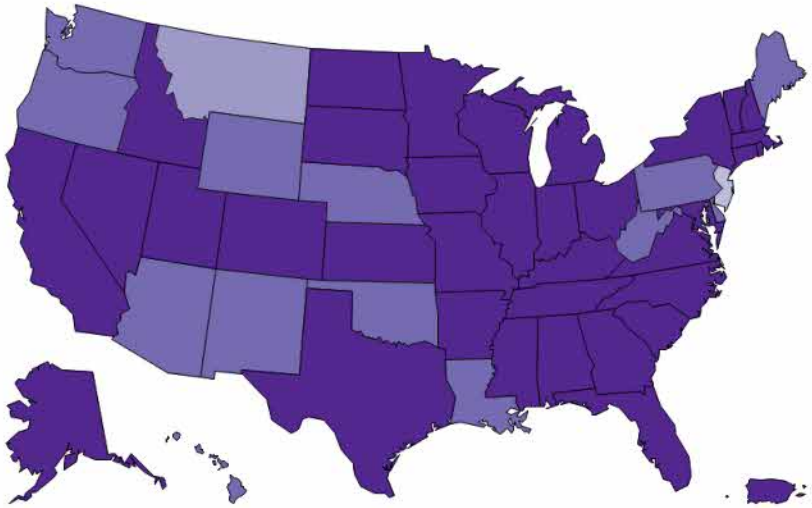


** Priority hospitals include those hospitals registered with Centers for Medicare & Medicaid Services (CMS) as of June 1, 2020 and non-CMS hospitals that have reported data since July 15th and exclude psychiatric, rehabilitation, or religious non-medical facilities.*

R

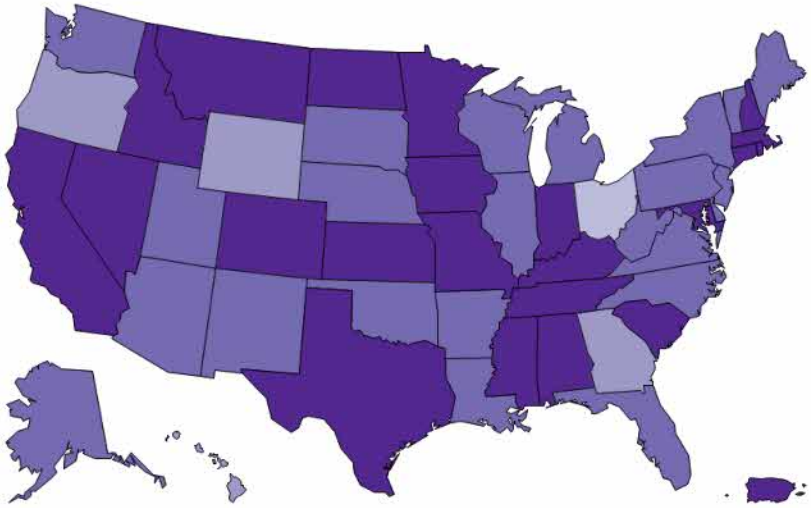
Completeness of Reporting of Select Metrics by State, August 18–24, 2020
Priority Hospitals* (N=5,290), COVID-19 Unified Priority Hospital Dataset

Percent of Hospitals Reporting Data Element:
Inpatient Beds Occupied by COVID-19 Patients



10 to <50%
50 to <75%
75 to <90%
90% or more

Percent of Hospitals Reporting Data Element:
In-hospital Deaths, COVID-19 Patients



** Priority hospitals include those hospitals registered with Centers for Medicare & Medicaid Services (CMS) as of June 1, 2020 and that CMS hospitals that have reported data since July 15 and exclude psychiatric, rehabilitation, or religious non-medical facilities*

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Summary

- Most hospitals (>85-90%) are reporting metrics for hospital capacity and occupancy at least once a week
- Reporting completeness varies by data element, reporting day, and jurisdiction
- Next steps include:
  - Continuing analyses on the completeness and quality of hospital data reported to HHS
  - Conducting outreach via hospital data liaisons to improve completeness and quality of reporting of all data elements
  - Working with partners to improve and align data cleaning best practices

Associate Director of Science

Upcoming *MMWRs*

MMWR Title	Task Force	Release Date
Preventing and Mitigating SARS-CoV-2 Transmission at Four Overnight Summer Camps—Maine, June–August, 2020	Epi	8/26/2020
Universal Laboratory Testing for SARS-CoV-2 at Long-Term Care Facilities Statewide—West Virginia, 2020	HDTF	8/27/2020
Mask wearing is associated with knowledge of risk of common activities among adults in the US	CICP	8/28/2020
Seroprevalence of SARS-CoV-2 among frontline healthcare personnel in a multistate hospital network—April–June 2020, United States	Epi	8/31/2020
Delay or avoidance of medical care due to concerns related to COVID-19—United States, June 24–30, 2020	CICP	9/1/2020

JCC Update

Chief of Staff

Questions/Comments

For more information, contact CDC Emergency Operations Center
770-488-7100
www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Backup Slides

Incident Manager

Do Not Distribute

- These slides are for internal use only.
- All content sides are color coded to indicate sharing instructions

– **Red = internal IMS only, close hold** – e.g., Information is sensitive and should not be shared

– **Yellow = needs approval before distribution** – e.g., Mix of public and non-public info/unofficial sources; slide concept/idea is new or still forming

– **Green = public information/okay for wider distribution**. – e.g., All info is available on CDC website or is public

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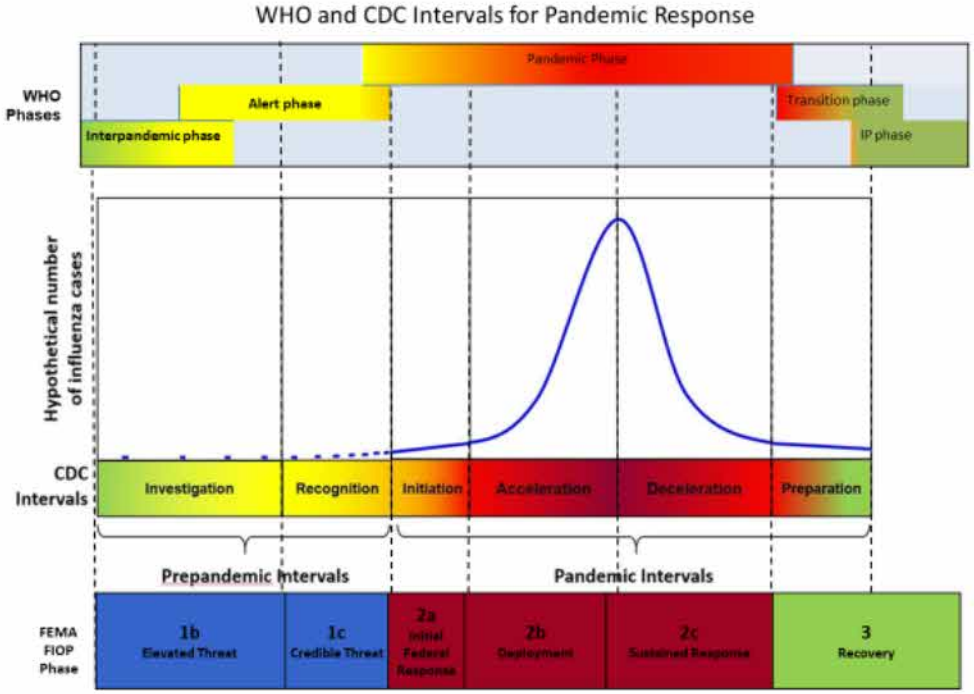
Agenda

- Incident Manager
- Case Surveillance
- Analytics
- NHSN Data
- Modeling
- Epidemiology
- Laboratory
- STLT Support
- Health Systems and Worker Safety
- Food Systems
- Community Interventions and Critical Populations
- One Health
- Global/International
- Chief Health Equity Officer
- Associate Director for Science
- Chief Medical Officer
- Communication
- Policy
- Chief of Staff
- JCC

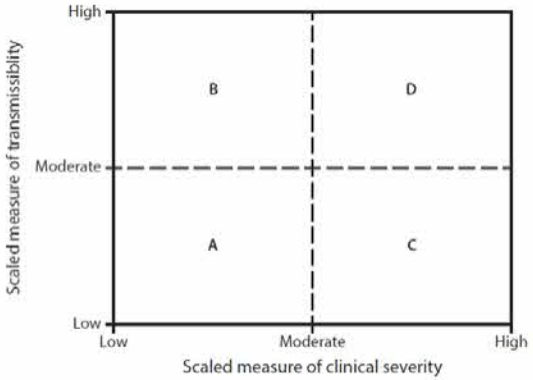
Incident Manager Priorities



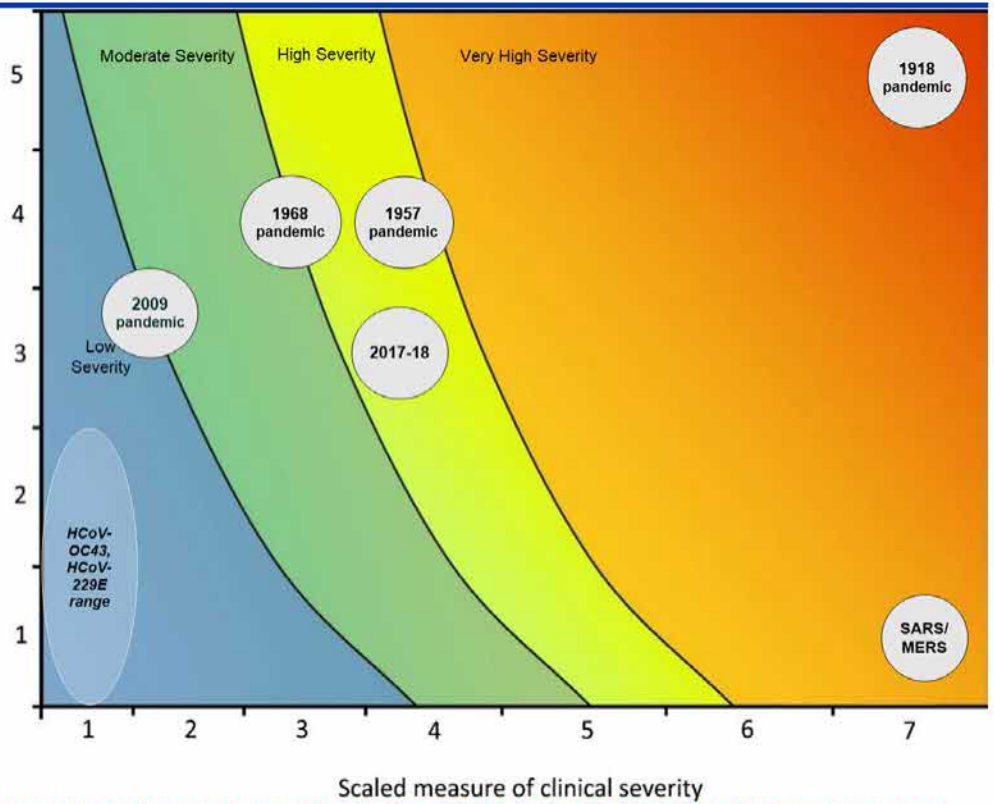
Adapted from: MMWR Recomm Rep. 2014 Sep 26;63(RR-06):1-18. **Updated preparedness and response framework for influenza pandemics.** Holloway R et al

Incident Manager Priorities

FIGURE 3. Pandemic Severity Assessment Framework for the initial assessment of the potential impact of an influenza pandemic



Source: Reed C, Biggerstaff M, Finelli L, et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 2013;19:85–91.



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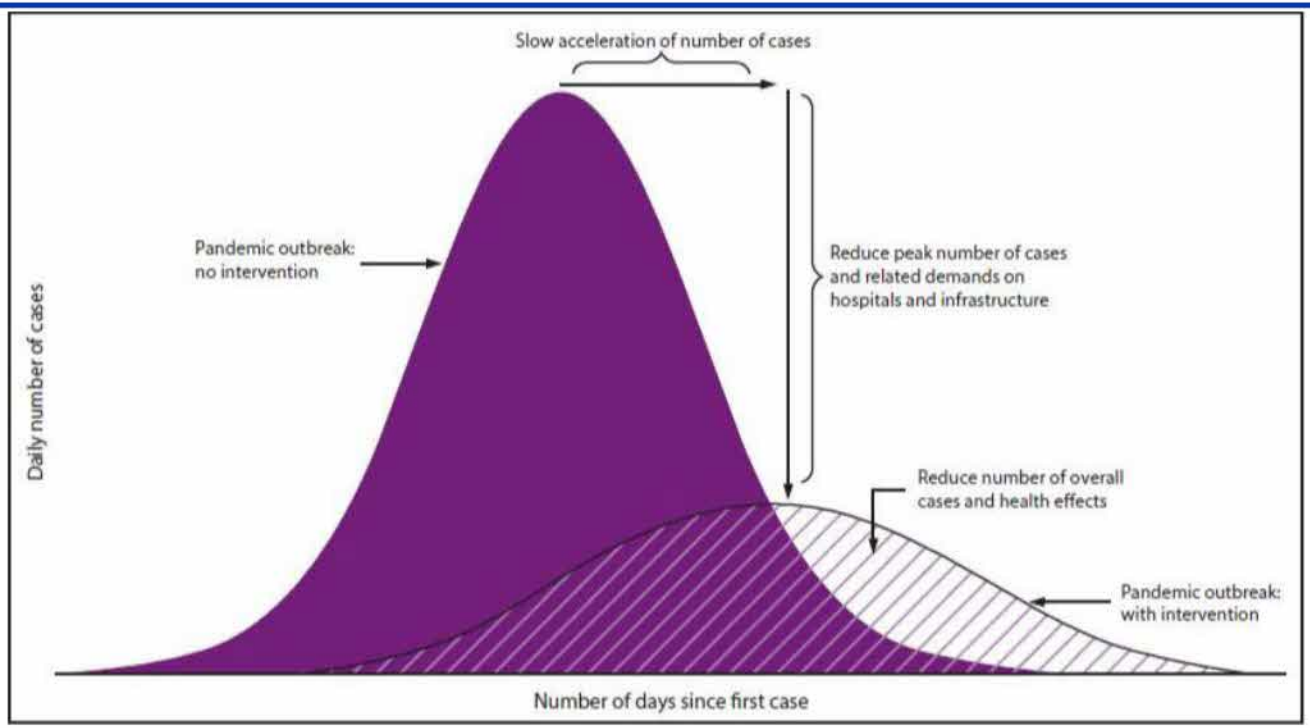
Incident Manager Priorities



Source: Adapted from: CDC. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States—early, targeted, layered use of nonpharmaceutical interventions. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. https://stacks.cdc.gov/view/cdc/11425.

G

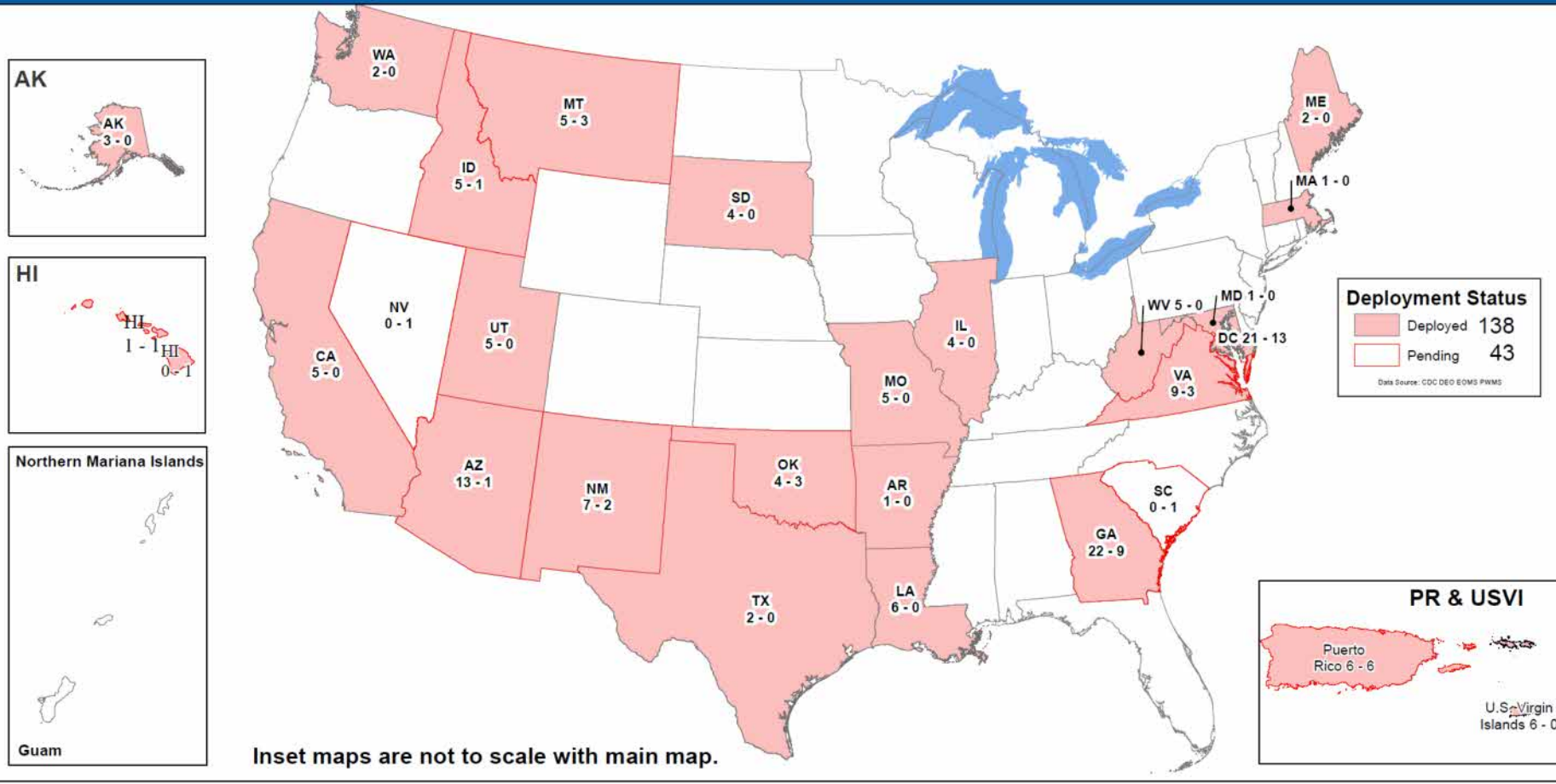
CDC Response Mission Statement

- CDC will implement strategies to slow the introduction and impact of COVID-19 in the United States. CDC will coordinate with international and domestic partners to provide clinical and infection control guidance and implement other methods to mitigate the impact of this virus.

COVID-19 Response: CDC US Deployments

Wednesday, August 26, 2020

SITUATIONAL AWARENESS GIS

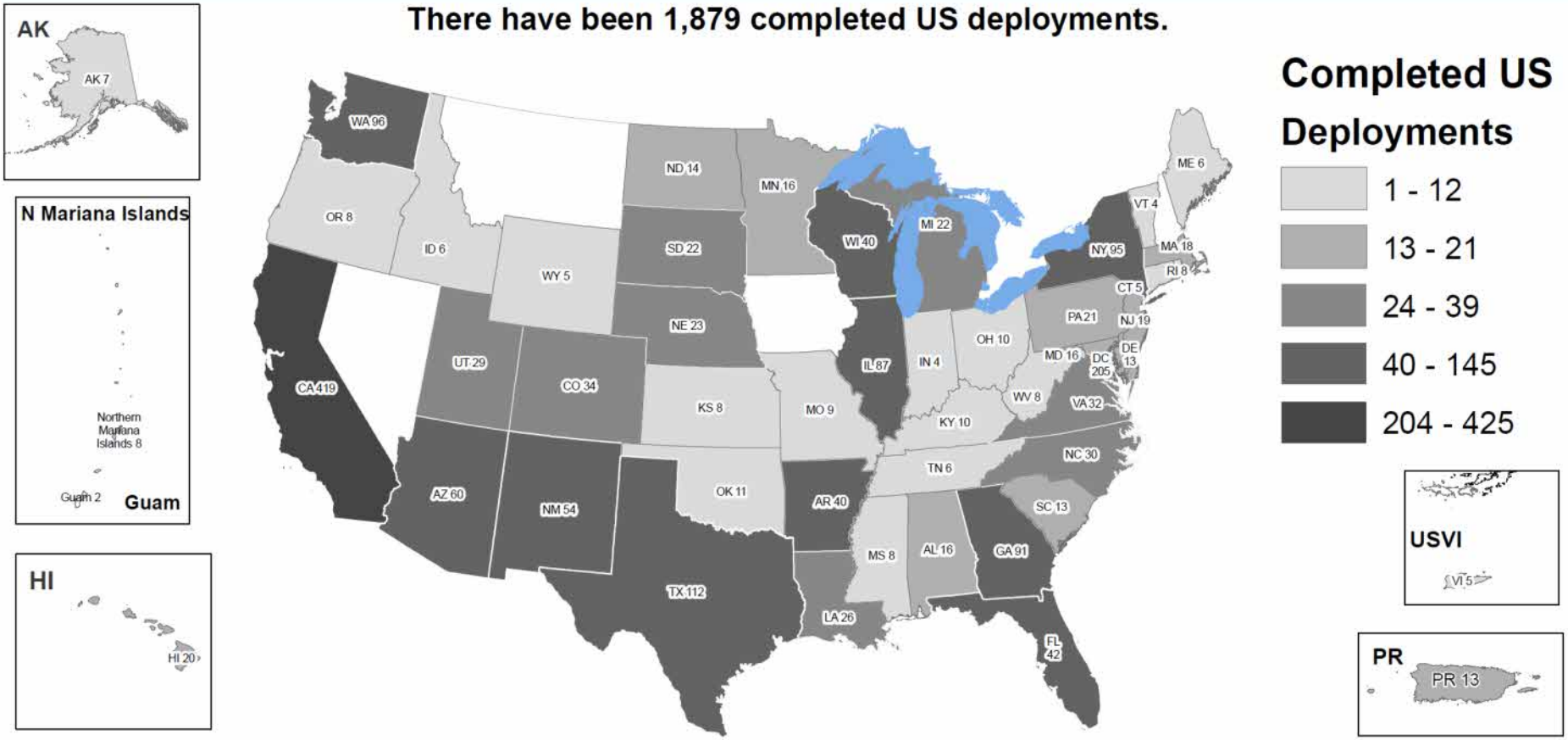


COVID-19 Response: CDC Completed US Deployments by State / Territory

Wednesday, August 26, 2020

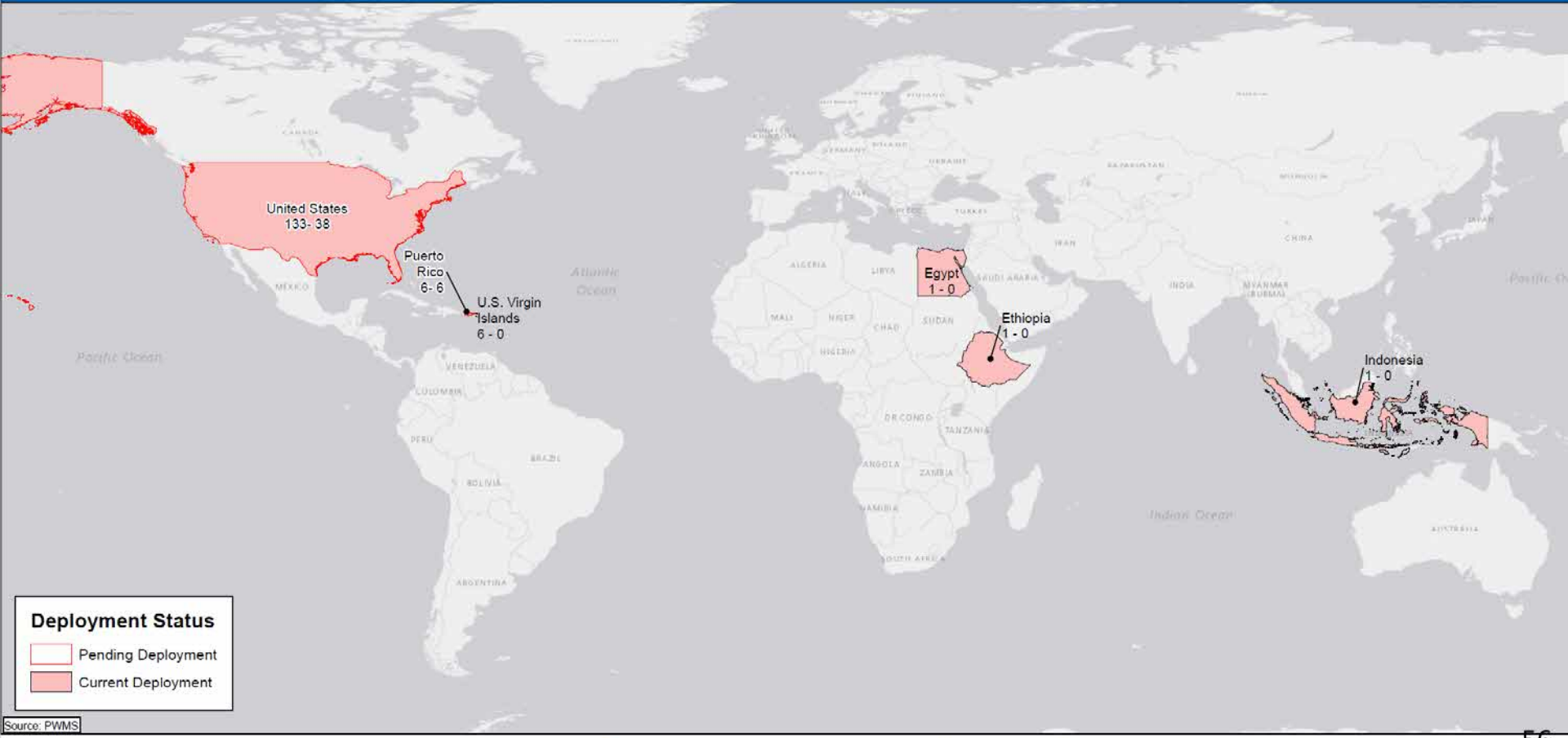
SITUATIONAL AWARENESS GIS

There have been 1,879 completed US deployments.



Data Source: CDC DEO EOMS PWMS

COVID-19 Response: CDC Deployments by Country
Wednesday, August 26, 2020



MXD Name: COVID-19 PERSTAT by Country Map, Prepared 8/26/2020: 12:06:19 AM, Document Path: \\cdc.gov\project\NMTC-T100-SRV1\Emergency Operations\SA\2020 Novel Coronavirus Response\GIS\MXD\Deployments\COVID-19 PERSTAT by Country Map.mxd

COVID-19 Response: CDC Completed Global Deployments
Wednesday, August 26, 2020

SITUATION AWARENESS GIS

There have been 1,911 completed global deployments.

Source: PWMS

MXD Name: COVID-19 PERSTAT by Country Completed Map, Prepared 8/26/2020: 12:22:30 AM, Document Path: \\cdc.gov\project\NMTC-T100-SRV1\Emergency Operations\SA\2020 Novel Coronavirus Response\GIS\MXD\Deployments\COVID-19 PERSTAT by Country Completed Map.mxd

Case Surveillance

Daily change in COVID-19 case & death counts

Daily change in COVID-19 case counts

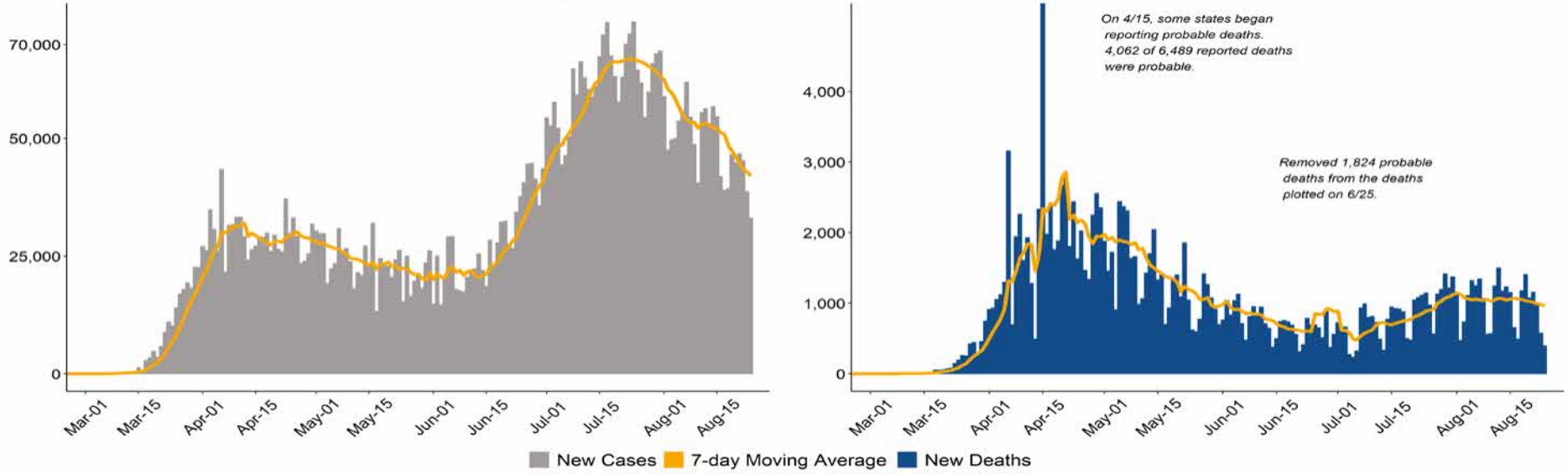
As of August 24 N= 5,715,567 (new: 33,076)

42,065 average over past 7 days vs. 50,991 over 7 previous days (-18%) vs. 66,960 over peak week (-37%)

Daily change in COVID-19 death counts

As of August 24 N=176,617 (new: 394)

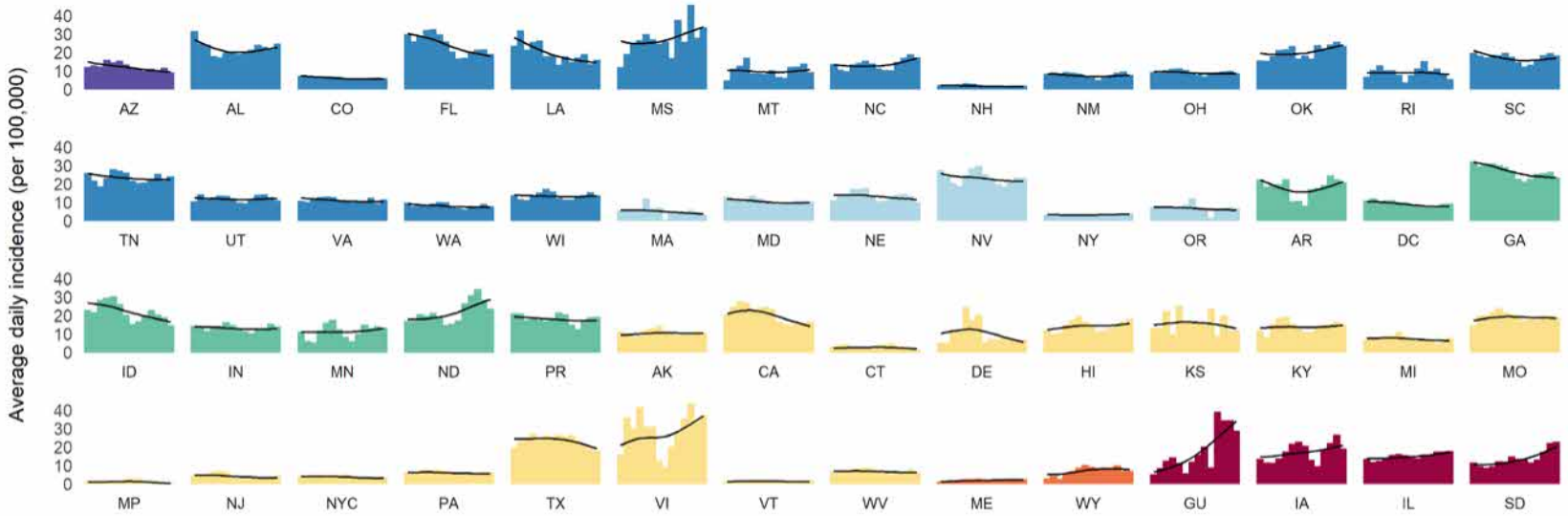
968 average over past 7 days vs. 1,062 over 7 previous days (-9%)



Note, as of April 12th, totals and figures include confirmed and probably cases and deaths reported from states

Y

Incidence by Jurisdiction, 8/10/2020–8/23/2020 (preliminary)



Status of incidence trajectory

- ≥42 days downward
- 21-41 days downward
- 14-20 days downward
- 7-13 days downward
- 1-6 days downward
- Plateau
- Upward trajectory

Notes: The number of days in a downward trajectory represents the number of consecutive days for which the jurisdiction experienced either a negative slope or a low incidence plateau (two-week incidence ≤10 cases per 100,000 and slope >−0.1 and ≤0.1). Jurisdictions are allowed a 5-day grace period of departure from downward trajectory before the downward trajectory is considered over.

Data: Jurisdiction-validated case counts

From: Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE)
Sent: Mon, 8 Jun 2020 14:00:01 +0000
To: Town, Katherine (CDC/DDID/NCHHSTP/DSTDP); Dasgupta, Sharoda (CDC/DDID/NCHHSTP/DHP); Panneer Chelvam, Nivedha (CDC/DDID/NCHHSTP/DHP); Learner, Emily (CDC/DDID/NCHHSTP/DSTDP); Kirkcaldy, Bob (CDC/DDID/NCHHSTP/DSTDP); Furukawa, Nathan (CDC/DDID/NCHHSTP/DVH); Wesolowski, Laura (CDC/DDID/NCHHSTP/DHPIRS); Barry, Vaughn (CDC/DDNID/NCIPC/DIP); McKay, Susannah (CDC/DDID/NCEZID/DHQP); Li, Jun (CDC/DDID/NCHHSTP/DHP); Ridzon, Renee (CDC/DDID/NCHHSTP/DHPSE); Peruski, Anne (CDC/DDID/NCHHSTP/DHP); Chavez, Pollyanna R. (CDC/DDID/NCHHSTP/DHP); Brooks, John T. (CDC/DDID/NCHHSTP/DHP)
Subject: Fwd: IM slides June 8
Attachments: COVID-19 IM 2020-06-08 FINAL.pdf

CMO Colleagues,

Please see attached for daily IM slides for June 8. Briefing time is 10AM-11AM ET.

It is not required or expected that you call-in to these daily briefings. However, they may be helpful to put the work we do into context – the CMO unit (John) gives an update daily as part of this call. To that end, if you're interested in listening in while multi-tasking, the call-in information is below:

Join by phone:

US: (b)(6)

Webinar ID: (b)(6)

All participants will be join muted, except pre-designated presenters.

Renee

COVID-19 Response
Incident Manager Meeting

Monday, 08 June 2020

Day 155 of Response, Day 140 of IMS Activation

(Click Here to Bring up the Time Tracker Application)

Priorities of the Week, June 7-13

- Assess state and local health department capacity for Contact Tracing/Case Investigation
- Finalize planning for deployment of teams to improve contact tracing practices and overcome barriers in local jurisdictions
- Complete review and provide guidance on jurisdictional testing plans
- Synchronize data across reports
- Report race/ethnicity data on the CDC website
- Finalize answers to questions about the use of thermal scanners
- Complete toolkit for state public health veterinarians to address animals positive for SARS-CoV-2
- Support whole of government sustainment planning and review CDC IMS structure to optimize coordination and workflow efficiency
- Disseminate key findings through MMWR, CDC.gov, and partner callss

NRCC Update

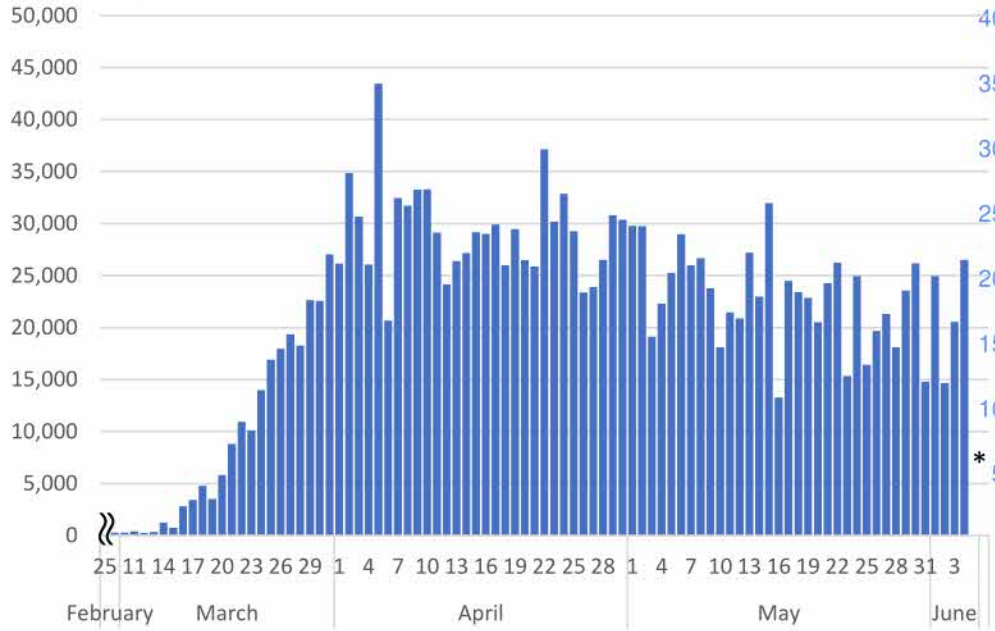
Case Surveillance

Daily change in cumulative COVID-19 case and death counts

Daily change in cumulative COVID-19 case counts

As of June 7 (preliminary) N=x,xxx,xxx (xx,xxx new)

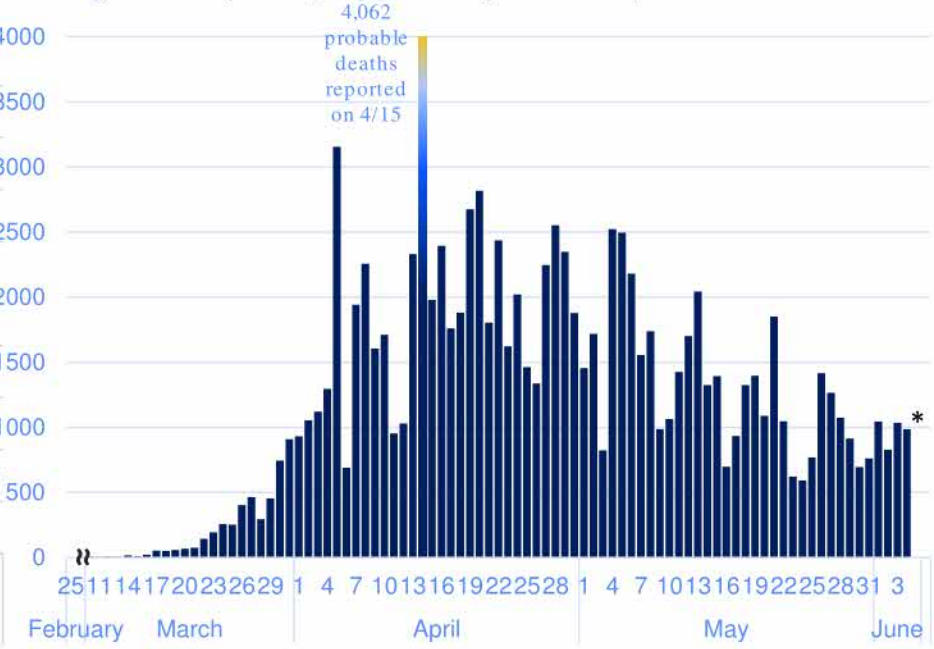
% change in last day: x.x% (*range last 7 days: x.x%-x.x%*)



Daily change in cumulative COVID-19 death counts

As of June 7 (preliminary) N=xxx,xxx (xxx new)

% change in last day: x.x% (*range last 7 days: x.x%-x.x%*)

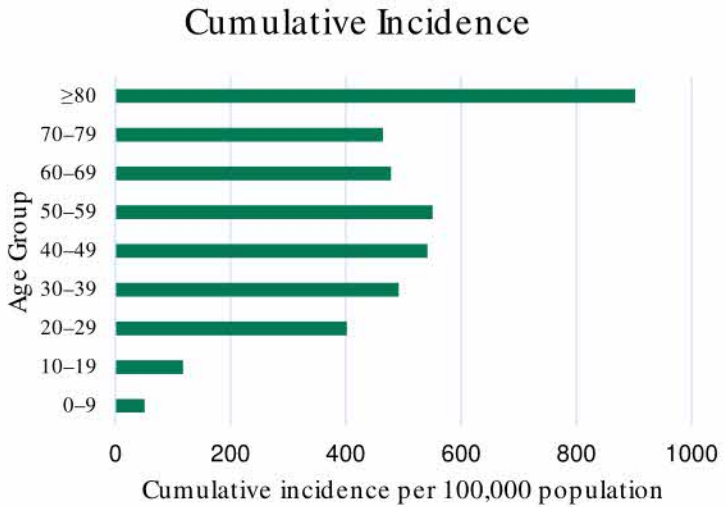


Note, as of 12 April, totals and figures include confirmed and probable cases and deaths reported from states

*Preliminary

Case Surveillance *MMWR* Report: Overview and distribution of cases

- Analyzed individual case data for **1,320,488 laboratory-confirmed** cases reported by jurisdictions during January 22–May 30, 2020.
- Describes underlying health conditions, symptoms, and severe outcomes in cases by age/sex
  - Distribution of cases by racial and ethnic group also reported (**55% missing**)



- Median age **48** (IQR=33-63 years)
- Similar incidence among females (**406.0**) and males (**401.1**)
- Racial and ethnic groups in COVID-19 case population disproportionately affected:
  - Hispanic / Latino: (**33% of cases**)
  - American Indian / Alaska Native, Non-Hispanic: (**1.3% of cases**)
  - Black, Non-Hispanic: (**22% of cases**)

Stokes E, Zambrano L, et al. Coronavirus Disease 2019 (COVID-19) — United States, January 22–May 30, 2020 (pending publication)

Case Surveillance *MMWR*: Underlying health conditions and symptoms

- Most commonly reported underlying health conditions (**287,320 cases**)
  - Cardiovascular disease **32%** (56% among severe cases)
  - Diabetes mellitus **30%** (45% among severe cases)
  - Chronic lung disease **18%** (22% among severe cases)
- Most commonly reported symptoms (**373,883 cases**)
  - Fever, cough, or shortness of breath **70%**
  - Muscle aches **36%**
  - headache **34%**
  - Loss of smell or taste **8%**, most common among **persons aged 20-29 years**
- Among women 15-44 years old, **11%** were reported to be pregnant

Stokes E, Zambrano L, et al. Coronavirus Disease 2019 (COVID-19) — United States, January 22–May 30, 2020 (pending publication)

Case Surveillance *MMWR*: Severe outcomes

- Severe outcome highest among: males, older persons, those with underlying conditions.
  - **ICU admissions** were highest among persons **aged 70-79 years**.
  - **Deaths** were highest among persons **80 years and older**.

Outcome	All patients	Any underlying health condition	No underlying health condition
Hospitalization	184,673 (31%)	90,201 (54%)	6,683 (8%)
ICU admission	29,837 (16%)	16,974 (26%)	1,343 (3%)
Deaths	71,116 (15%)	38,812 (36%)	1,431 (3%)

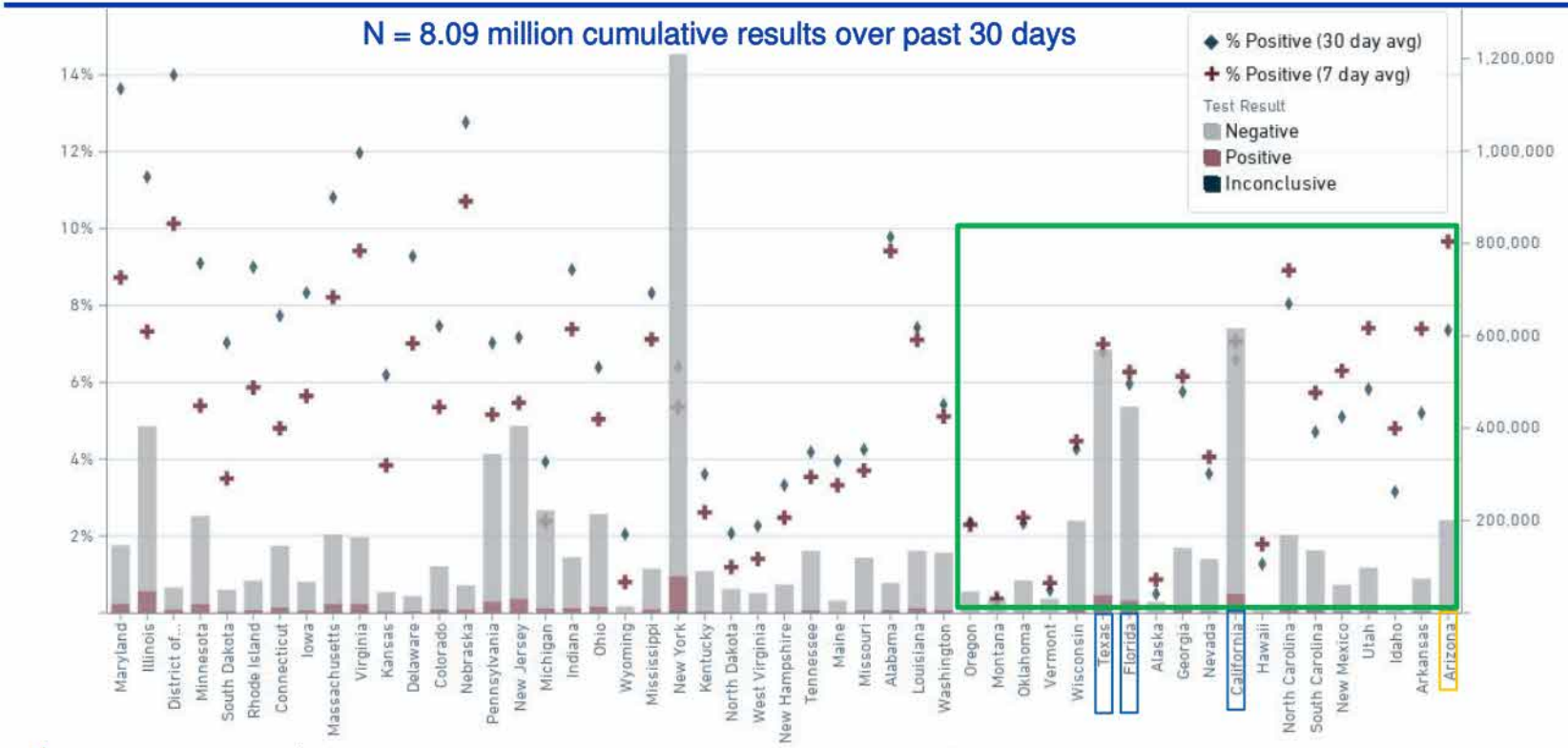
*Proportions are among cases with information on the outcome

Stokes E, Zambrano L, et al. Coronavirus Disease 2019 (COVID-19) — United States, January 22–May 30, 2020 (pending publication)

Analytics

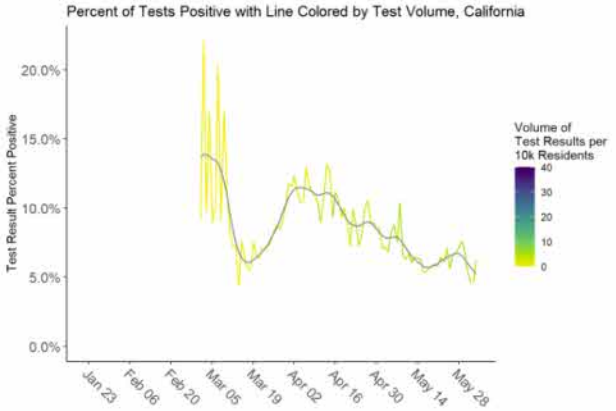
Molecular Test Results and Percent Positivity

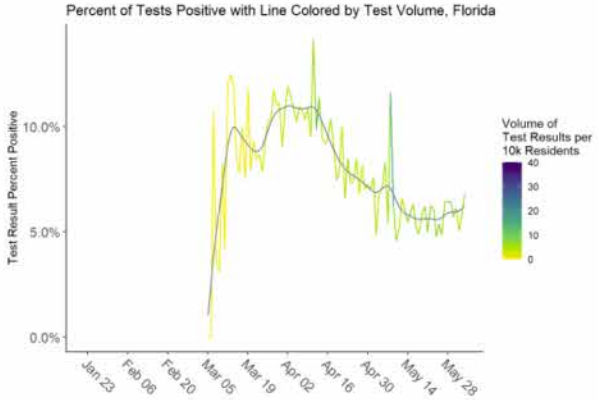
By state, ordered by 30 day vs 7 day % positive; Data through June 5, 2020*

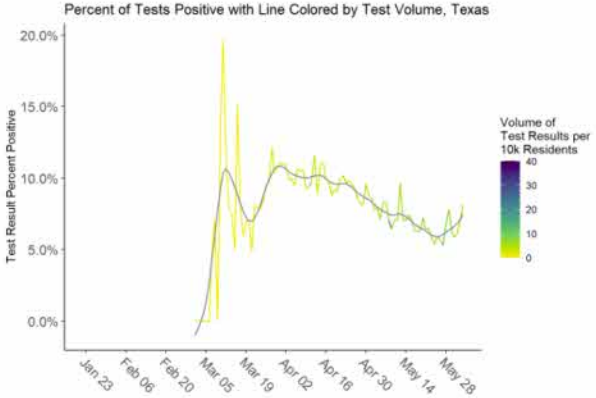


* Data from commercial/reference, state public health, and hospital laboratories data feeds

Molecular Test Results Volume and Percent Positivity





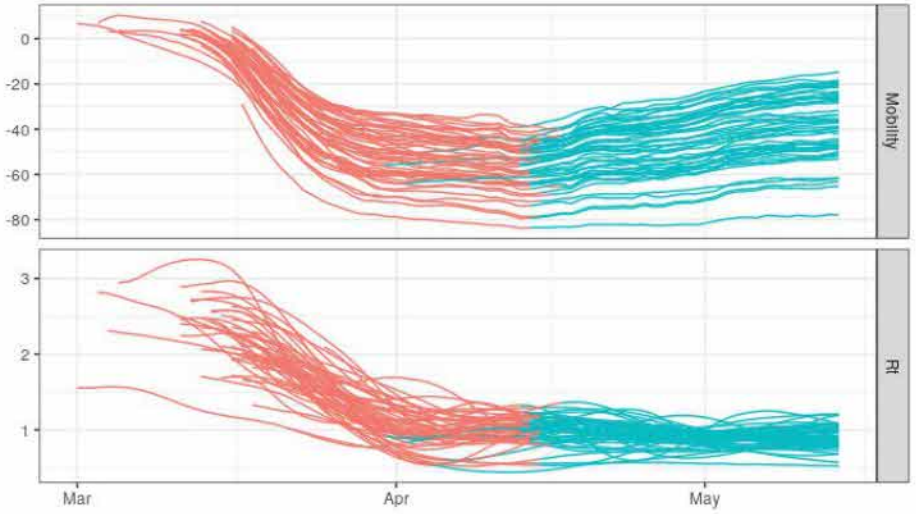


* Data from commercial/reference, state public health, and hospital laboratories data feeds

Modeling

Changing Relationship Between Time Varying Reproductive Number R(t) and Mobility Data

- There was a strong relationship between Rt and mobility as mobility decreased
- There is little to no relationship as mobility has increased
- Hypotheses
  - Impact of social distancing?
  - Impact of cloth face coverings?
  - Are the highest risk individuals maintaining lower mobility?
- How much of a mobility reduction is required to keep Rt < 1?



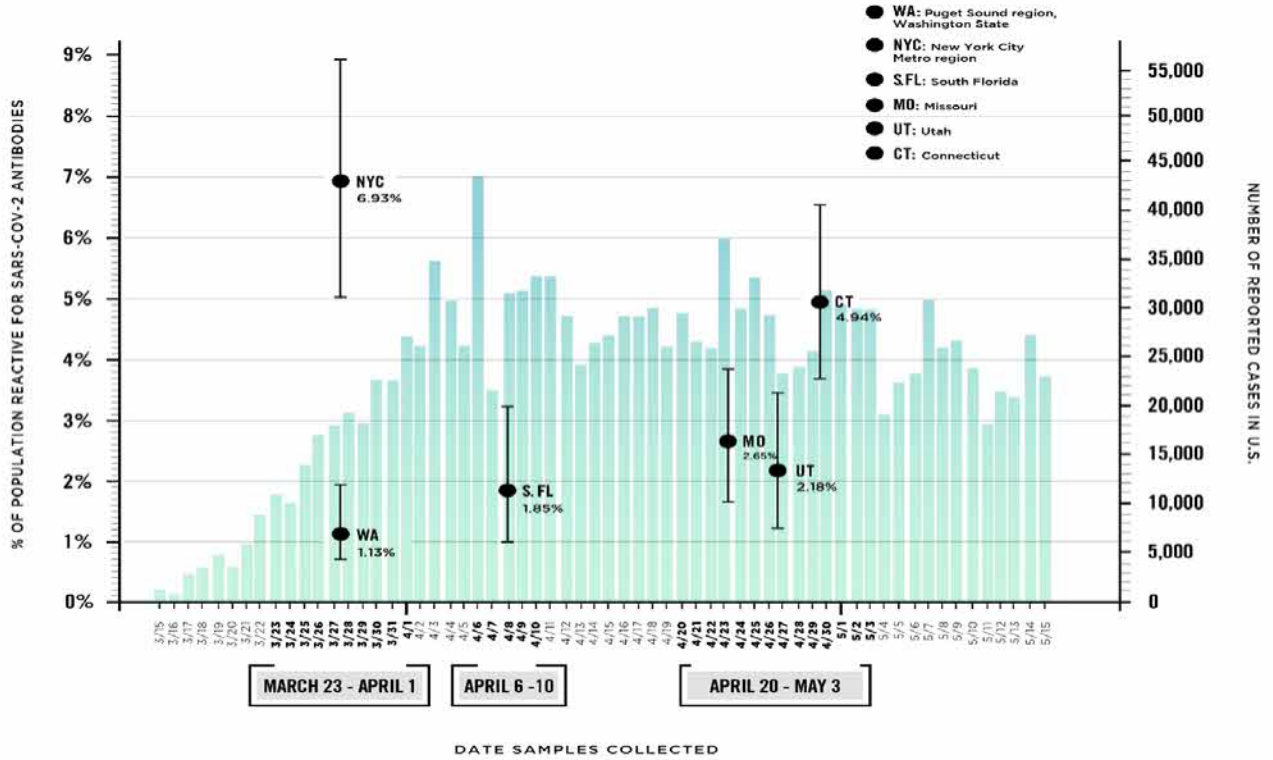
Epidemiology

SARS-Cov-2 Reactivity in Residual Sera from Commercial Labs by Age and Sex, 6 US Sites, March 23-May 3

	% Reactive (95% Confidence Interval)[a]					
	Western WA 3/23-4/1	NYC Metro 3/23-4/1	South FL 4/6-4/10	MO 4/20-4/26	UT 4/20-5/3	CT 4/26-5/3
Sex						
Male	1.41 (0.76,2.36)	5.85 (4.46,7.55)	2.20 (1.09,3.55)	3.14 (1.83,4.56)	2.17 (0.85,3.94)	5.65 (3.80,7.60)
Female	1.16 (0.67,1.91)	5.67 (4.20,7.03)	2.20 (1.23,3.42)	2.57 (1.48,3.74)	2.54 (1.21,4.10)	4.12 (2.55,5.91)
Age group, y						
0-18	0.66 (0.0,2.52)[c]	2.74 (0.9,5.03)[c]	2.41 (0.00,7.79)	1.36 (0.00,4.14)	n/a[d]	0.81 (0.00,2.89)
19-49	1.32 (0.65,2.27)[c]	8.26 (6.18, 10.17)[c]	0.87 (0.19,2.22)	3.36 (1.42,5.53)	1.82 (0.61,3.52)	6.08 (3.14,9.29)
50-64	0.85 (0.26,1.94)	6.52 (4.34,9.61)	1.95 (0.32,4.00)	1.96 (0.51,3.76)	2.89 (0.93,5.21)	8.11 (4.79,11.64)
65+	1.66 (0.85,2.74)	3.66 (2.19,5.19)	3.04 (1.74,4.45)	3.23 (1.92,4.58)	2.70 (0.89,5.04)	4.15 (2.31,6.04)
All ages, age-standardized [b]	**1.13 (0.70, 1.94)[e]**	**6.93 (5.02, 8.92)[e]**	**1.85 (1.00, 3.23)[e]**	**2.65 (1.65, 3.86)[f]**	**2.18 (1.21, 3.43)[f]**	**4.94 (3.61, 6.52)[f]**

[a] A specimen was considered reactive if it had a signal to threshold ratio of >1. [b] All estimates are adjusted for test performance characteristics (specificity 99.3% (Confidence Interval (CI) 98.32 – 99.88%); sensitivity 96.0% (CI 89.98 – 98.89%). [c] A subset of samples did not have age by year available and were classified as age 5-17, 18-49, 50-64 and 65+ years. The 5-17 and 19-49 age groups were combined with those 5-18 and 19-49 years, respectively. [d] The number of specimens for persons aged 0-18 years was inadequate, and those <18 years were excluded from the analysis. [e] Standardized to the age and sex distribution of the counties in each region from which most specimens originated, and adjusted for test performance characteristics as described above. [f] Standardized to the age and sex distribution of the state, and adjusted for test performance characteristics as described above.

SARS-CoV-2 Reactivity in Residual Sera from Commercial Labs in 6 US Sites and Reported US Cases, March 23-May 3



SUPERNOVA (VA) Network for COVID-19

- Components
  - Inpatient, laboratory-based surveillance at 5 Veterans Affairs Hospitals
  - National, electronic medical record- based surveillance at 170 VA hospitals

- Ongoing analyses
  - Incidence of COVID-19 among Veterans
  - Risk factors for severe outcomes

VA Hospital surveillance at 5 sites serving >370,000 patients/year

National, VA Hospital electronic-based surveillance at 170 sites serving >6.4 million enrollees/year

National VA Electronic Cohort Analysis of Severe Outcomes

2,098 Veterans hospitalized with COVID-19 from February 1-May 4, 2020

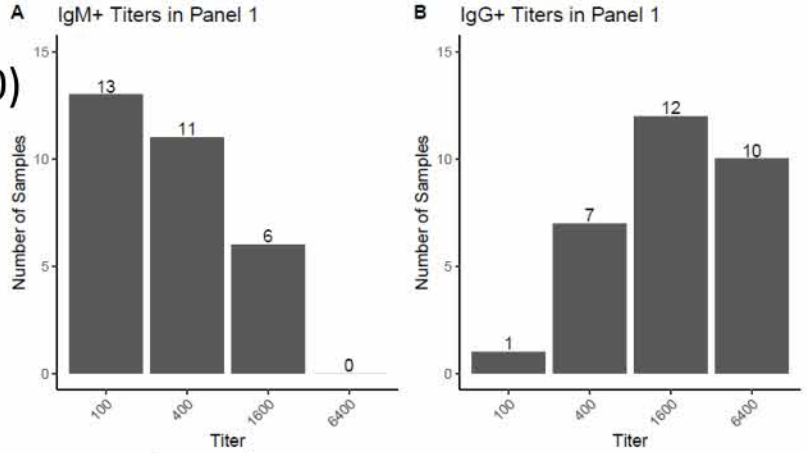
Characteristics and outcomes of cohort	N=2,098 n (%)
Male	1,987 (95%)
Age groups	
18-24	10 (0.5%)
25-44	123 (6%)
45-64	634 (30%)
65-84	1,111 (53%)
85+	220 (10%)
ICU admission	818 (39%)
Death	402 (19%)

- Other severe outcomes and complications being assessed: mechanical ventilation, MI, CVA, PE, ARF, ARDS, myocarditis
- Risk factors: demographics, urban/rural residence, underlying medical conditions, smoking, medications prior to and during hospitalization

Laboratory

Independent Evaluation of Serology Tests

- Panel Composition
  - SARS-CoV-2 Ab-positive serum samples (n=30)
  - Frozen Ab-negative serum samples (n=80)
    - Clinically agnostic, included banked HIV+ serum (n=10)
    - negative 1:100 dilution on the CDC Pan-Ig assay
- Panel Assessment
  - CDC Pan-Ig, IgM, and IgG ELISA
  - Confirmed at NCI using CDC's ELISAs (pan-Ig, IgG, and IgM)
  - Mount Sinai IgG Receptor Binding Domain (RBD) ELISA developed by the Krammer Laboratory at the Icahn School of Medicine
- Standard to Achieve
  - Sensitivity of 90% and specificity of 95% for IgG and IgM antibodies (ref. EUA)



Summary of Results - Acceptance

- **Euroimmun SARS-COV-2 ELISA (IgG)**
  - EUA authorized
  - Microplate ELISA

Measure	Estimate	Confidence Interval
IgG Sensitivity	90.0% (27/30)	(74.4%; 96.5%)
IgG Specificity	100% (80/80)	(95.4%; 100%)
Combined Sensitivity	90.0% (27/30)	(74.4%; 96.5%)
Combined Specificity	100% (80/80)	(95.4%; 100%)
Combined PPV for prevalence = 5.0%	100%	(46.1%; 100%)
Combined NPV for prevalence = 5.0%	99.5%	(98.6%; 99.8%)
Cross-reactivity with HIV+	0.0% (0/10), not detected	

- **Healgen COVID-19 IgG/IgM Rapid Test Cassette**
  - EUA authorized
  - Lateral flow assay

Measure	Estimate	Confidence Interval
IgM Sensitivity	100% (30/30)	(88.7%; 100%)
IgM Specificity	100% (80/80)	(95.4%; 100%)
IgG Sensitivity	96.7% (29/30)	(83.3%; 99.4%)
IgG Specificity	97.5% (78/80)	(91.3%; 99.3%)
Combined Sensitivity	100% (30/30)	(88.7%; 100%)
Combined Specificity	97.5% (78/80)	(91.3%; 99.3%)
Combined PPV for prevalence = 5.0%	67.8%	(35%; 88.4%)
Combined NPV for prevalence = 5.0%	100%	(99.4%; 100%)
Cross-reactivity with HIV+	0.0% (0/10), not detected	

Data from https://open.fda.gov/apis/device/covid19serology/

Summary of Results – Withdrawn/Removed

- **Biomedomics COVID-19 IgM-IgG Rapid Test kit**
  - Voluntarily withdrawn
  - POC Fingerstick

Measure	Estimate	Confidence Interval
IgM Sensitivity	86.7% (26/30)	(70.3%; 94.7%)
IgM Specificity	97.1% (68/70)	(90.2%; 99.2%)
IgG Sensitivity	73.3% (22/30)	(55.6%; 85.8%)
IgG Specificity	100% (70/70)	(94.8%; 100%)
Combined Sensitivity	96.7% (29/30)	(83.3%; 99.4%)
Combined Specificity	97.1% (68/70)	(90.2%; 99.2%)

- **Phamatech COVID19 RAPID TEST**
  - Voluntarily withdrawn
  - POC Fingerstick

Measure	Estimate	Confidence Interval
IgM Sensitivity	26.7% (8/30)	(14.2%; 44.4%)
IgM Specificity	97.5% (78/80)	(91.3%; 99.3%)
IgG Sensitivity	86.7% (26/30)	(70.3%; 94.7%)
IgG Specificity	96.2% (77/80)	(89.5%; 98.7%)
Combined Sensitivity	86.7% (26/30)	(70.3%; 94.7%)
Combined Specificity	93.8% (75/80)	(86.2%; 97.3%)

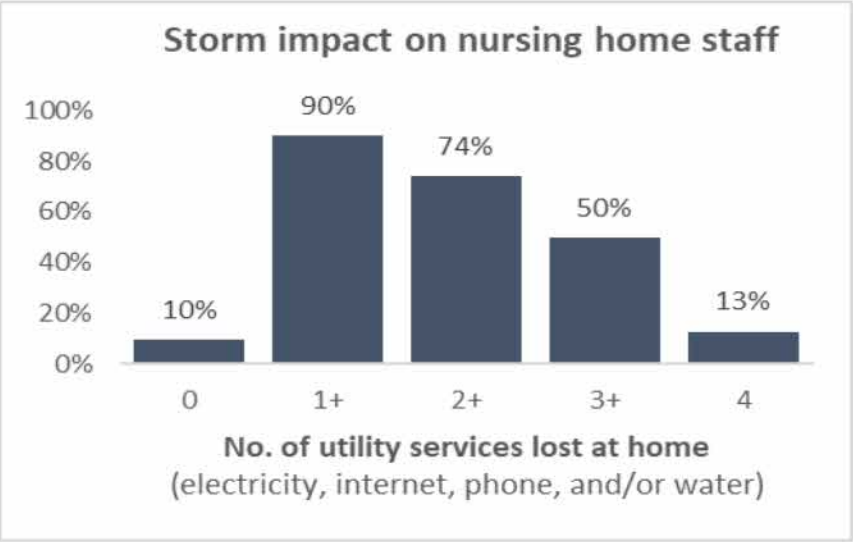
- **Tianjin Beroni Biotechnology Co., Ltd. SARS-COV-2 IgG/IgM Antibody Kit**
  - Removed
  - POC Fingerstick

Measure	Estimate	Confidence Interval
IgM Sensitivity	83.3% (25/30)	(66.4%; 92.7%)
IgM Specificity	100% (70/70)	(94.8%; 100%)
IgG Sensitivity	30.0% (9/30)	(16.7%; 47.9%)
IgG Specificity	100% (70/70)	(94.8%; 100%)
Combined Sensitivity	90.0% (27/30)	(74.4%; 96.5%)
Combined Specificity	100% (70/70)	(94.8%; 100%)

Health Department Task Force

Major Storm Impacts COVID-19 Response in KY

- Major storm in Eastern Kentucky knocks out power and water, impacting 7-county COVID-19 EOC, regional medical center, and nursing home



"Preparedness and resiliency were key to the local health department's response to this storm . They didn't miss a beat ."
-John Oeltmann, CDC Team Lead, KY

Y

*EVALI During COVID-19 Response

Background

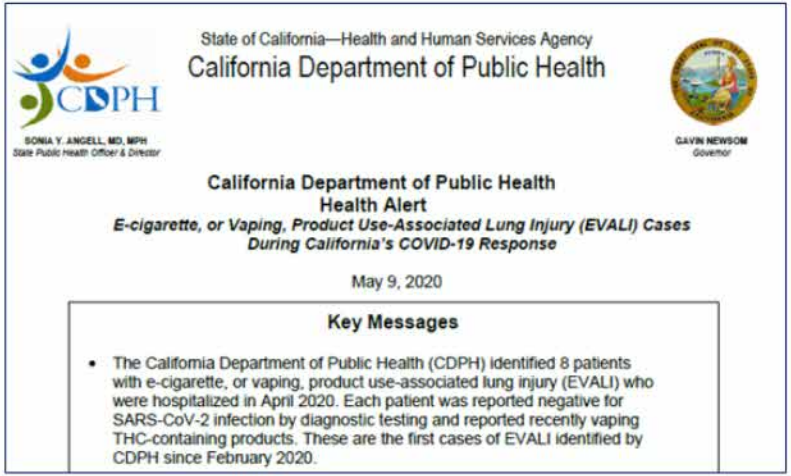
- **2019-2020:** EVALI cases peaked September 2019 and fell to nearly zero by February 2020
- **February 2020:** CDC stopped collecting case reports and CA discontinued active surveillance

Update

- **April 2020:** 8 patients with EVALI were hospitalized in CA
  - 2 required mechanical ventilation
  - 6/8 reported vaping cannabis products
  - No connections between cases identified
- **EVALI clinical presentation mimics COVID-19**

Response

- **May 9:** Health Alert issued by CA Dept. of Public Health
- **Modified EVALI case definition:** negative SARS-CoV-2 PCR
- Submitted MMWR into clearance



State of California—Health and Human Services Agency
California Department of Public Health

CDPH

SONIA Y. ANGELL, MD, MPH
State Public Health Officer & Director

GAVIN NEWSOM
Governor

California Department of Public Health
Health Alert
E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) Cases During California's COVID-19 Response

May 9, 2020

Key Messages

- The California Department of Public Health (CDPH) identified 8 patients with e-cigarette, or vaping, product use-associated lung injury (EVALI) who were hospitalized in April 2020. Each patient was reported negative for SARS-CoV-2 infection by diagnostic testing and reported recently vaping THC-containing products. These are the first cases of EVALI identified by CDPH since February 2020.

* E-Cigarette, or vaping, product use-associated with lung injury

COVID-19 County Hot Spot Drivers

Summary of Recent County Alerts

- May 30 - June 5
  - 107 counties with emerging increasing incidence identified in 31 states
  - 45 counties were on list 3 consecutive days at some point in the week
  - In the last 30 days, CDC field teams deployed to 21 of these 31 states with identified hot spots

Primary Driver	Number (%)
Long-term care facilities	29/107 (27%)
Corrections/detention	16/107 (15%)
Food processing or agricultural workplace	22/107 (21%)
Increased testing (primary driver only)	26/107 (24%)
Community transmission	67/107 (63%)
Other workplace	3/107 (3%)
Unclear/unknown	3/107 (3%)

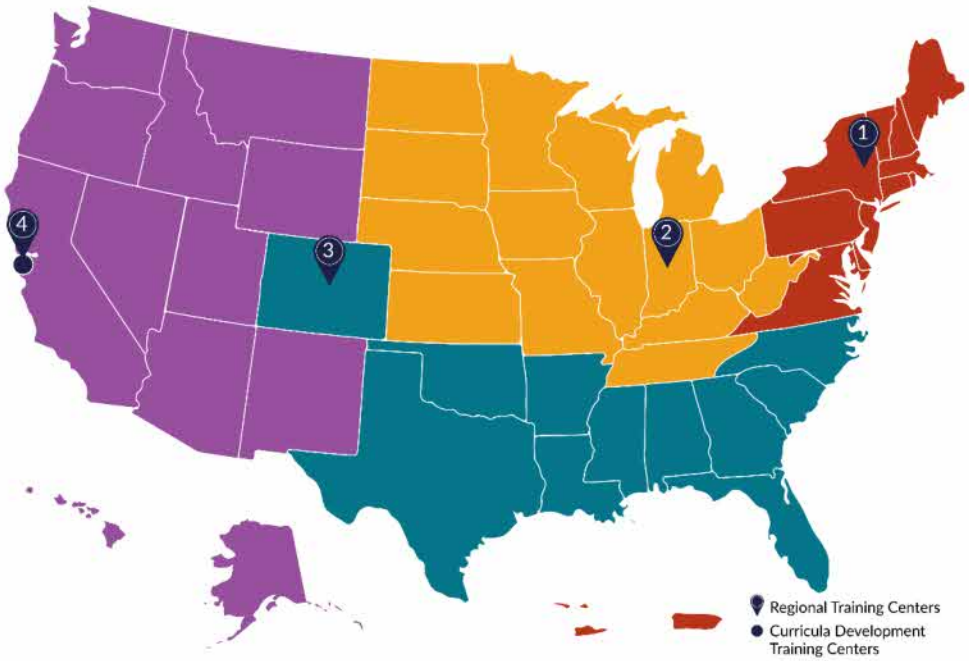
Workforce Development and Innovation

G

Newly Funded COAGs for Disease Intervention Training Centers to Conduct Contact Tracing Training

Support to existing training centers to enhance skills-based training for COVID-19 case investigators, contact tracers, and managers

- Region 1: Albany, NY
- Region 2: Indianapolis, IN
- Region 3: Denver, CO
- Region 4: San Francisco, CA
- Curriculum Development Center (San Francisco)



G

Contact Tracing Center Goals

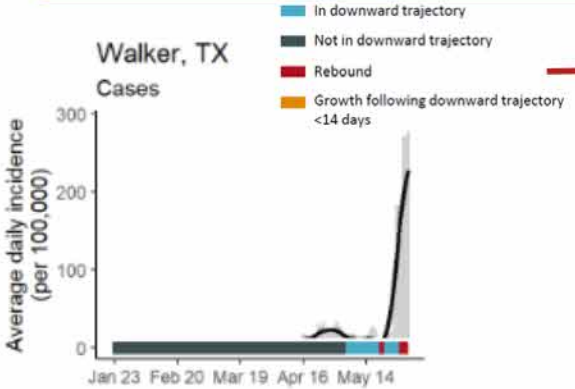
- Training Methods
  - E-Learning; self-study
  - Virtual instructor-led trainings
  - On the job training with supervisor feedback

Sample Training Targets
Train 2,000 Case investigators
Train 10,000 Contact tracers
Train 200 Managers
Develop Training of Trainers (TOT) for ~100 trainers and experienced Disease Intervention Specialists

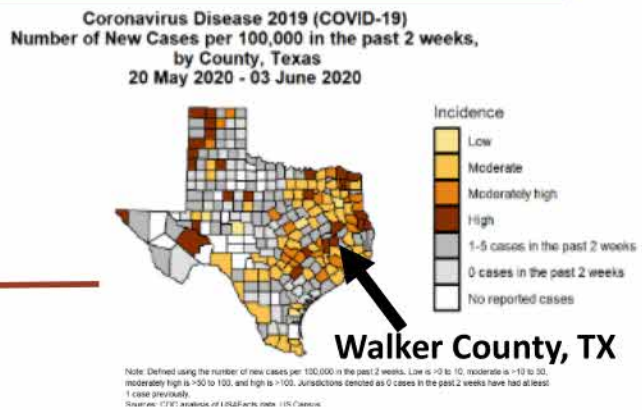
Healthcare Systems and Worker Safety

Case Surveillance & Hospital Capacity Data, Walker County, TX as of 6/5/20

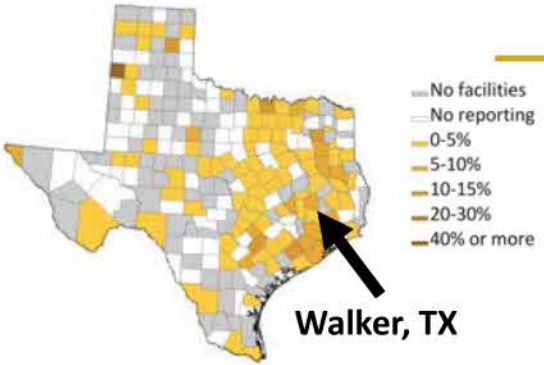
Average Daily Incidence

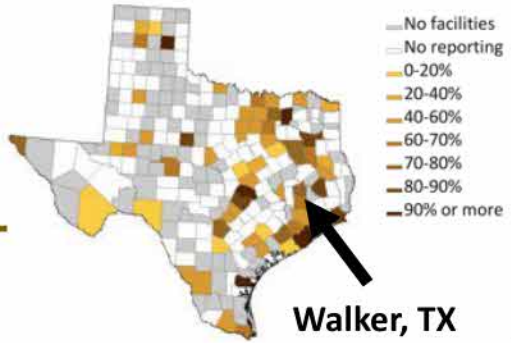


Number of New Cases per 100,000 (past 2 weeks)



9.5% of Inpatient Beds Occupied by COIVD-19 Patients

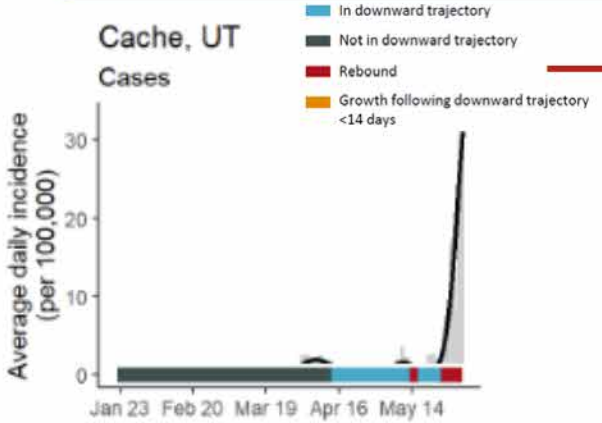




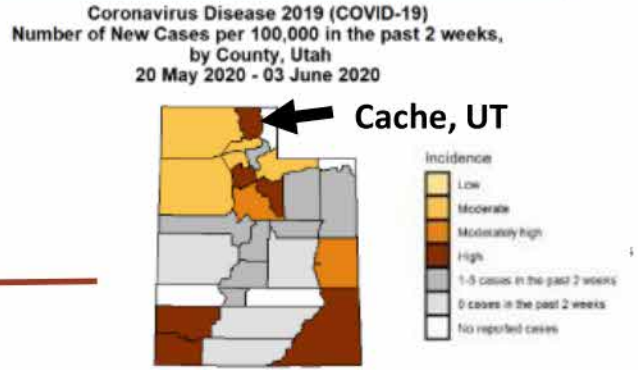
Send questions to eocmcctfhome@cdc.gov

Case Surveillance & Hospital Capacity Data, Cache County, UT as of 6/5/20

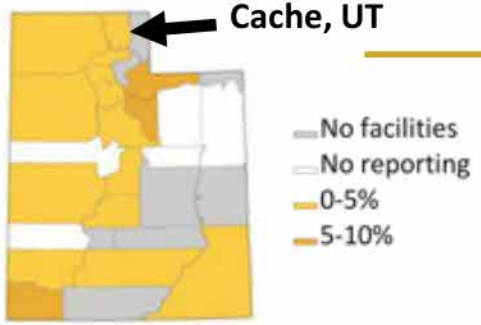
Average Daily Incidence

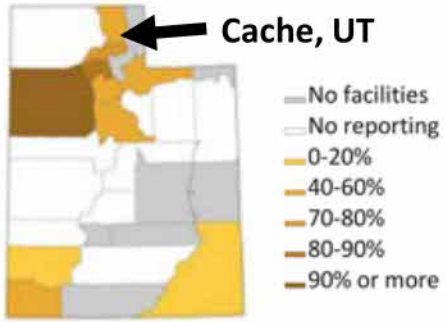


Number of New Cases per 100,000 (past 2 weeks)



2% of Inpatient Beds Occupied by COIVD-19 Patients

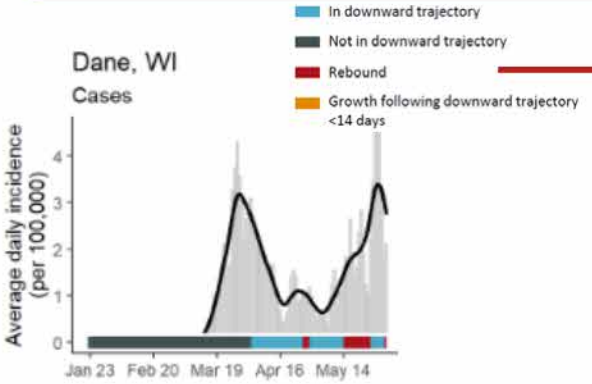




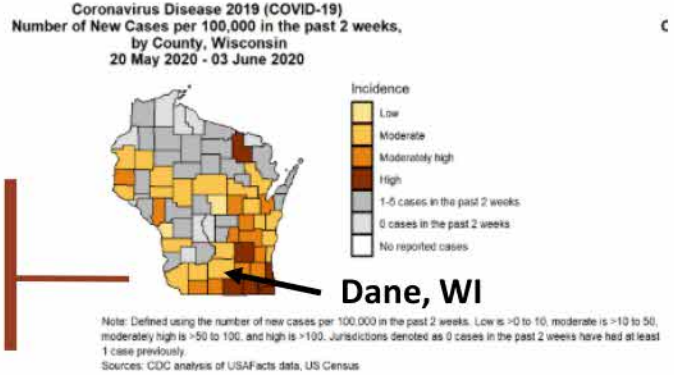
Send questions to eocmcctfhome@cdc.gov

Case Surveillance & Hospital Capacity Data, Dane County, WI as of 6/5/20

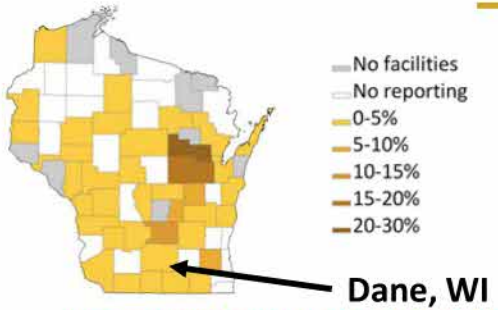
Average Daily Incidence

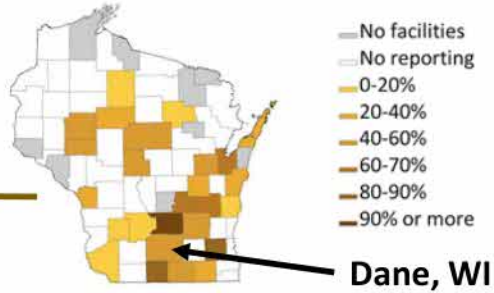


Number of New Cases per 100,000 (past 2 weeks)



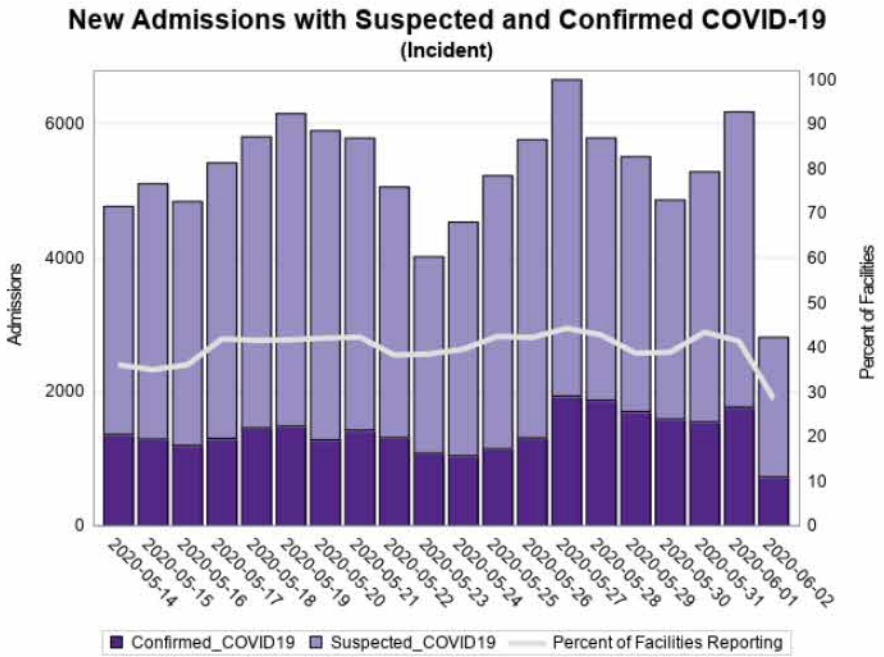
2% of Inpatient Beds Occupied by COIVD-19 Patients

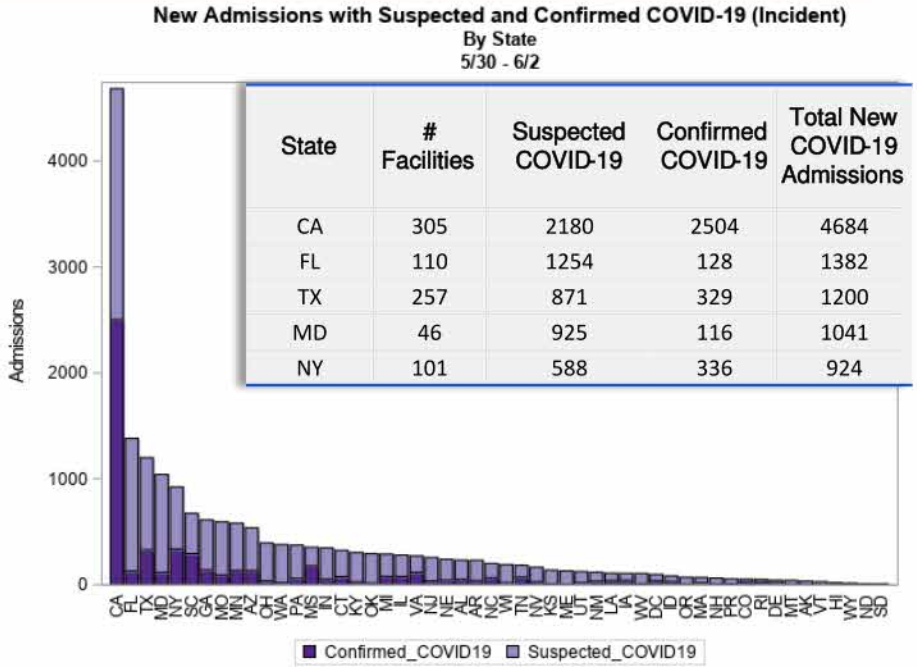




Send questions to eocmcctfhome@cdc.gov

New Admissions with COVID-19 by Day, NHSN Reporting Hospitals

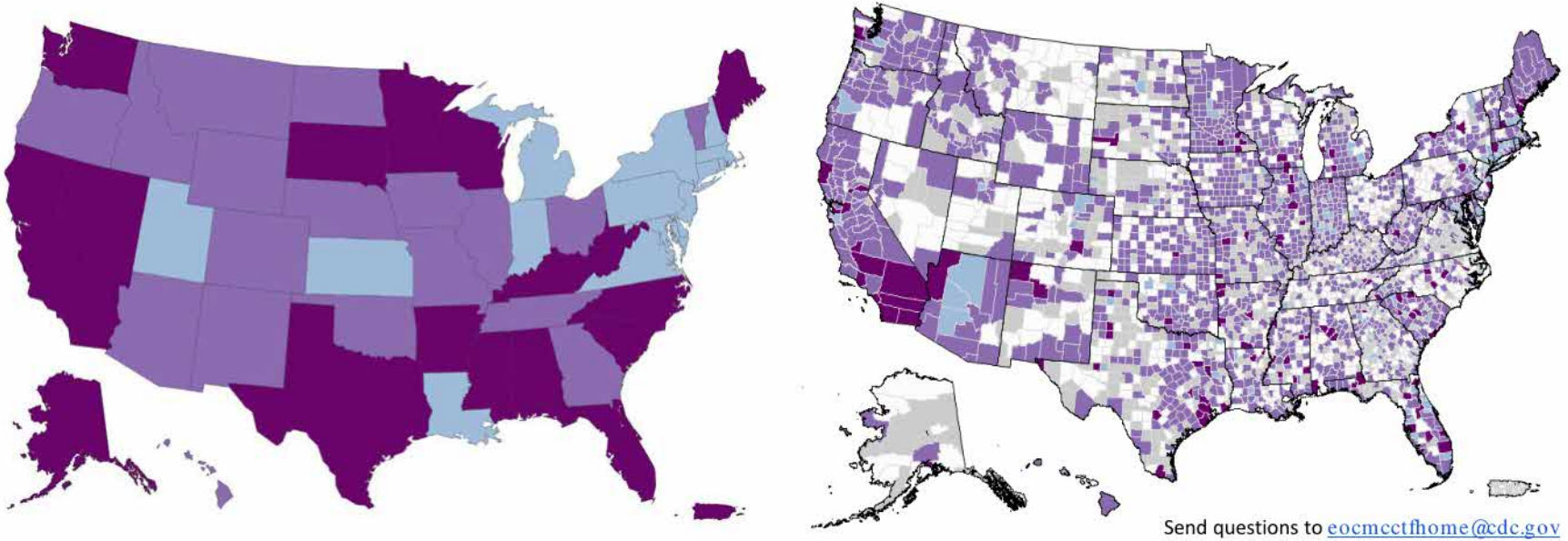




State	# Facilities	Suspected COVID-19	Confirmed COVID-19	Total New COVID-19 Admissions
CA	305	2180	2504	4684
FL	110	1254	128	1382
TX	257	871	329	1200
MD	46	925	116	1041
NY	101	588	336	924

Y

Change* in Percent of Inpatient Beds Occupied by COVID-19 Patients over 14-day Period (May 13-May 26, 2020)



Send questions to eocmcctfhome@cdc.gov

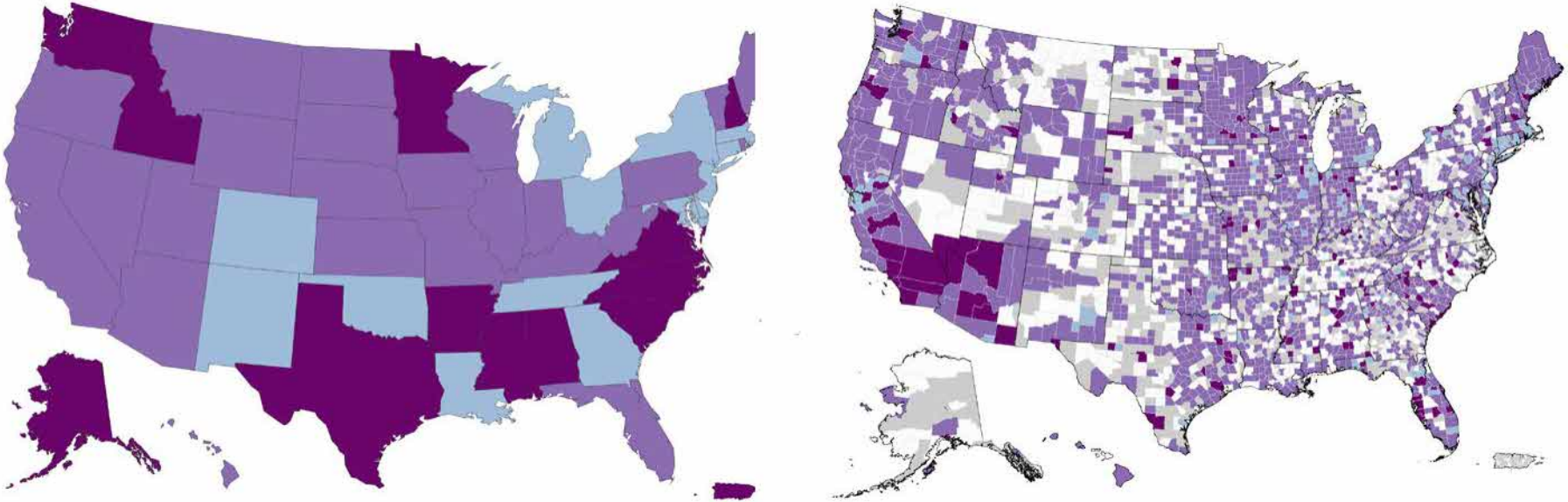
*measured as the slope of random coefficient model to 3 day-moving average of percent of inpatient beds occupied by COVID-19 patients. Model adjusted for bed size, facility type, % daily facility participation in PIHC module, and county-specific cumulative confirmed COVID-19 cases per 100,000 population (source: Johns Hopkins CSSE).

- no facilities
- facilities not reporting
- decreasing
- stable
- increasing

NHSN NATIONAL HEALTHCARE SAFETY NETWORK

Y

Change* in Percent of Inpatient Beds Occupied by COVID-19 Patients over 14-day Period (May 20-June 2, 2020)



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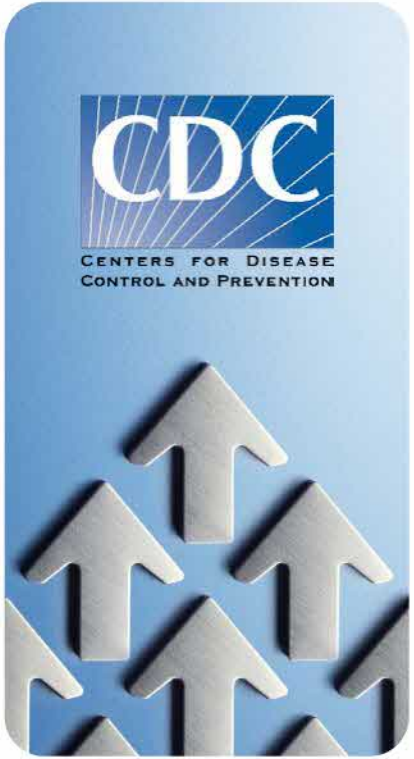
NHSN NATIONAL HEALTHCARE SAFETY NETWORK

Community and At Risk

CIARTF Priorities (June 8 – 12)



- Develop/harmonize testing strategy documents (Tiger Team)
  - homeless, corrections, schools
- Update 'At Risk for Severe Illness from COVID-19' web content
  - planning a coordinated communication roll out
- Release additional considerations documents
  - public beaches, gatherings and events, daily life
- Coordinate with the Office of the Chief Health Equity Officer
- MA EpiAid focusing on pregnant women and infants
- Advance 'unintended consequences' projects

Spotlight: New Homeless Services Support Tools

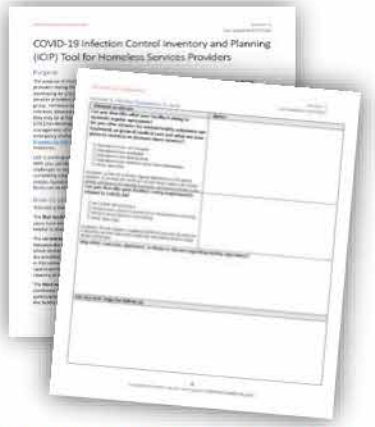
Downloadable Homeless Shelter Worker Training

- ✓ COVID-19 basics
- ✓ Infection prevention and control strategies for shelters
- ✓ Screening for symptoms of COVID-19 at shelters
- ✓ Considerations for people who are experiencing unsheltered homelessness

Now available!
Send requests to
eocevent366@cdc.gov

Infection Control Inventory and Planning (ICIP) Tool

- ✓ Modeled after tele-ICAR for nursing homes
- ✓ Piloted in Vermont and Colorado



One Health

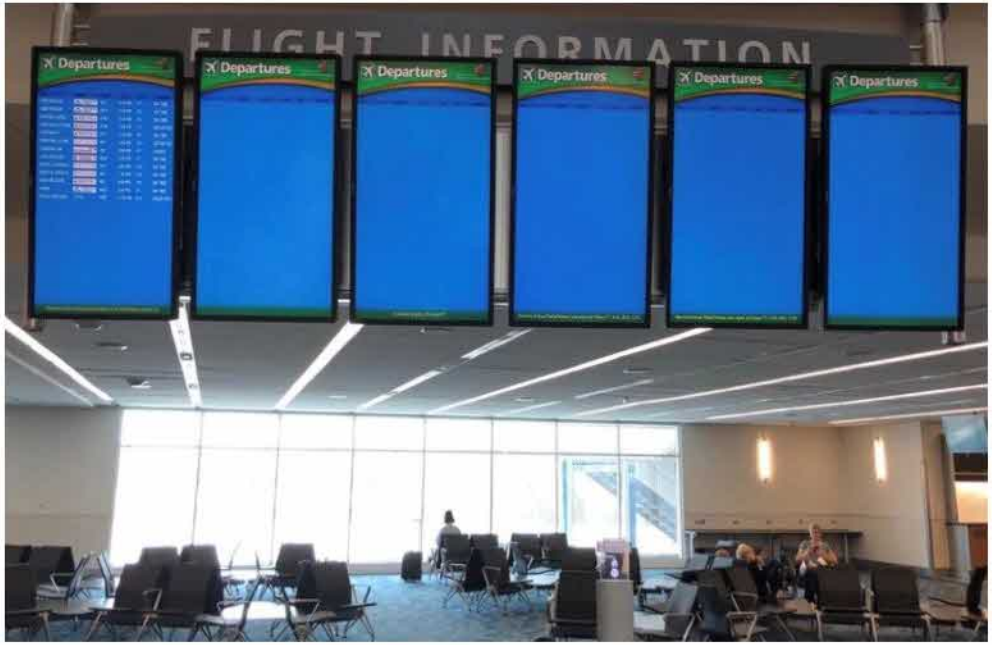
Global

R

Global Migration Task Force (GMTF)

- On June 1, SFO Quarantine Station notified of recent travel of family of 9 diagnosed with COVID-19
  - 2 intl. & 2 domestic flights taken between May 23 and May 25
- Flight manifests obtained for both domestic flights
  - Chicago – Denver: 151 pax + 5 crew; Denver – Sacramento: 157 pax + 6 crew
  - Contact info did not include mailing addresses, **thus unable to assign to states**
  - Epi-X posted for domestic flights
- Flight manifests yet to be received, but foreign PH notifications sent to countries for international flights
- (b)(5)

Global Migration Task Force (GMTF)



- During the nationwide stay home orders, domestic & intl. air travel decreased 95%
- Airlines are adding more flights to meet demand with the reopening of most states
- Though domestic travel has begun to increase, the Level 3 global travel health notice remains in effect
- Over the next few weeks, we will be looking at de-escalation criteria to be used for international travel health notices

Associate Director for Science

Y

Upcoming *MMWRs*

MMWR Title	Task Force	Release Date
First cases of SARS-CoV-2 in Companion Animals, United States, April-May, 2020	NYS Dept of PH, One Health WG	6/8/2020
COVID-19 Infections and Serologic Responses Among a Sample of US Navy Sailors - USS Theodore Roosevelt, April 2020	EPI/Lab, US Navy	6/9/2020

Chief Medical Officer

Communication

G

Joint Information Center (JIC)

MMWR Communication Surveillance Themes

- **Cleaning and Disinfecting Survey (6/5)**
  - USA Today: Americans desperate to kill virus are dangerously mixing cleaners, bleaching food
  - Yahoo News: CDC finds some Americans are still drinking and gargling bleach
  - Social Media commenter: info welcomed, helpful recs needed for supply issues (e.g. limited or no access to gloves or cleaning products)
  - *Messages with alternate guidance for times supplies are limited or unavailable*
- **Reports with continuing covered**
  - MI Child Vaccination Coverage Decline (Altmetric ↑393; total stories: 78)
  - Attack Rate at WA Choir Practice (Altmetric ↑222; total stories: 306)

Policy

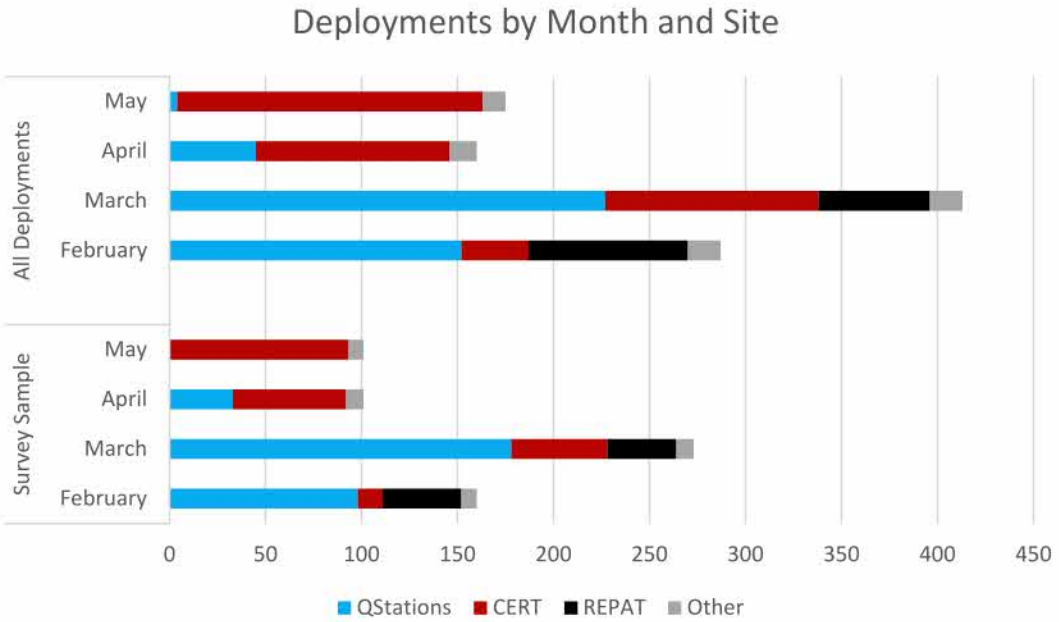
Policy

- Congressional
  - TBD – Briefing for Congressional Black Caucus, Congressional Asian Pacific American Caucus, Congressional Hispanic Caucus - Dr. Redfield, Leandris Liburd and Joe Bresee
  - 6/9 – Awareness - Senate Homeland Security and Government Affairs Committee Hearing - Evaluating the Fed Govt's Procurement & Distribution Strategies in Response to COVID-19 – Gaynor, Polowczyk, and Giroir
  - 6/10 –Four corners briefing on data modernization – Greg Armstrong, Chesley Richards
  - 6/10 – Awareness - Senate Health, Education, Labor and Pensions Hearing - COVID-19: Going Back to School Safely – Tennessee Department of Education, Nebraska Department of Education, Denver Public Schools, The Education Trust
- Partnership
  - 6/8 – Partner Call - Resuming Business Toolkit and Interim Guidance for Manufacturing Workers
  - 6/8 – PGA
  - 6/8 - Optum
  - 6/9 - Trust for America's Health
  - 6/11- Urban League of Greater Atlanta
  - 6/11 – NALEO Educational Fund
  - 6/11 – Center for Health Design
  - 6/12 – Press Ganey

Chief of Staff

Deployer Support Unit

- Survey Sample: N = 642; Response Rate: **61%**
- Debrief Participation: N = 327; Participation Rate: **26%**



Survey Highlights:

- About **1 in 4** were 1st time deployers
- **>84%** satisfaction with response support services
- Despite challenges, **95%** say they would deploy again

"I would go through all of this again. The good, bad, ugly and in between. It was extremely rewarding."

Deployer Support Unit

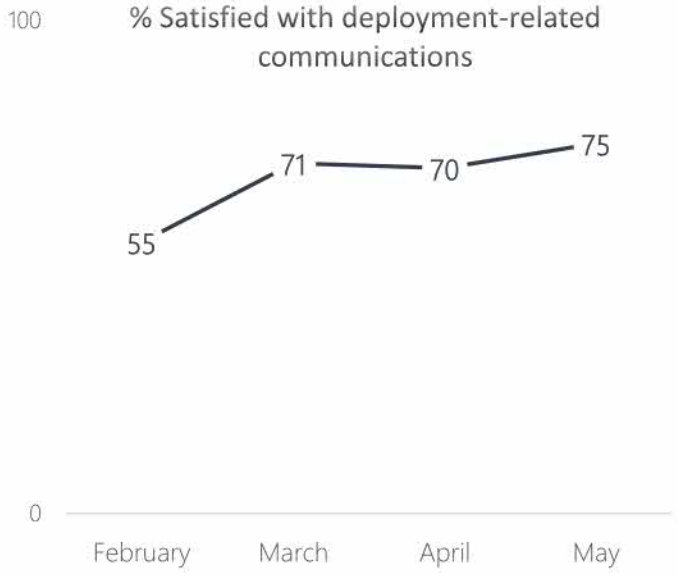
- **Most mentioned issue: Lack of clear and consistent communication**

Improvements & Solutions

- Deployer Support Unit est. in Jan
- Weekly review of Deploy.CDC.gov
- Mandatory pre-deployment briefings reflect changes in science, response priorities, processes & procedures
- PPE donning/doffing videos and instructional posters included in pre-deployment brief and material

Satisfaction with deployment-related communications **increased** from **55%** in Feb to **75%** in May

- Satisfaction highest for Deploy.CDC.gov (93%)



Deployer Support Unit

- Ways to Provide Feedback - *We want to hear from responders!*
  - COVID-19 EOC Responder Survey
  - COVID-19 Field Responder Survey

Responders should receive a unique link to the survey within a week after their deployment. If you have not received a survey, contact Deployer Support Evaluation (rmoievaluation@cdc.gov)

  - Post-Deployment Debrief

Mondays, Wednesdays, and Fridays

11:00am – 12:30pm EST (via Skype)

Returned from deployment and haven't received an invitation to a debrief?

  - Contact CDC IMS Deployer Support at eoccol3@cdc.gov

Safety Security and Asset Management

- To Date:
  - Occupational Health Clinic has processed 2133 (+98) medical clearances
  - Resilience Team has conducted mid-deployment outreach efforts to 244 (+30) deployers
  - Respiratory Protection Program has completed fit testing for 1,271 (+6) responders

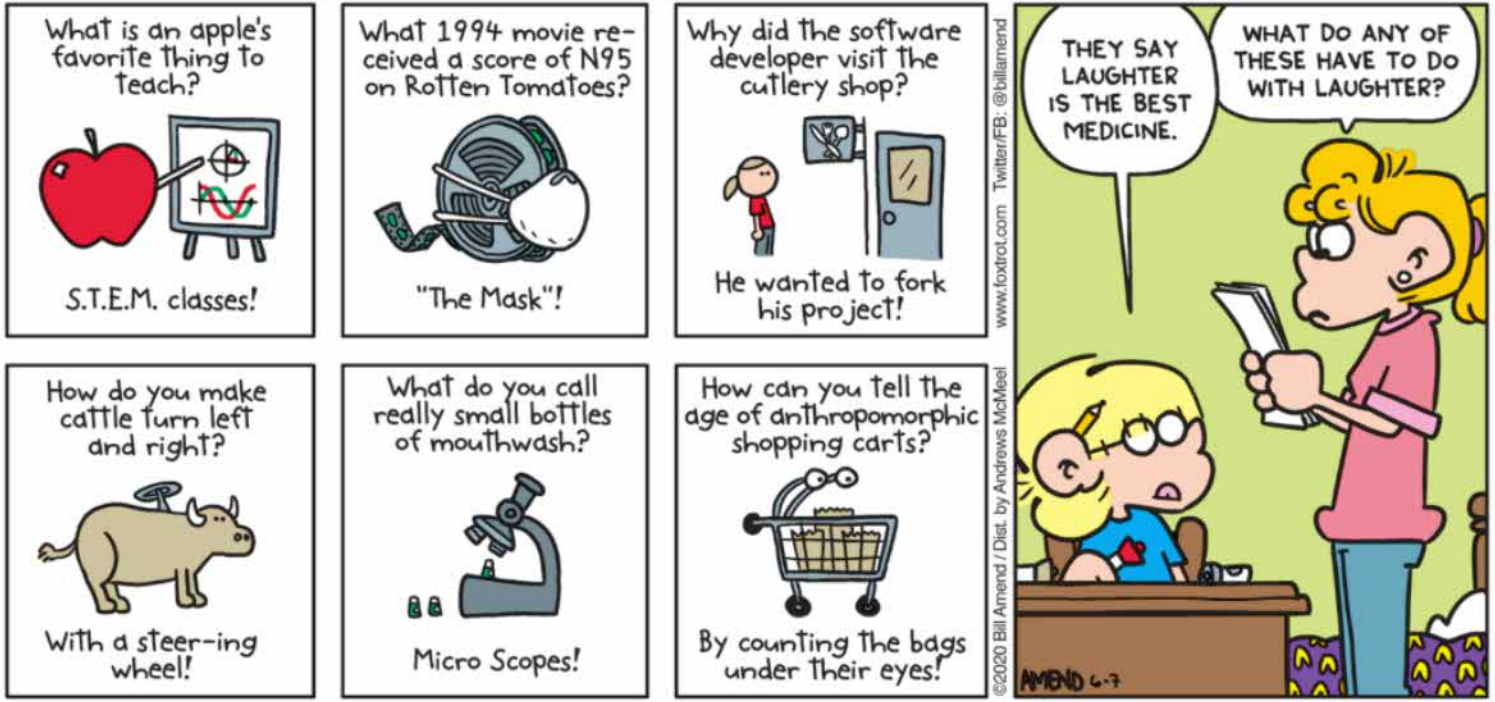
G

Comic Tributes for Sharp-Eyed Readers – June 7

Past Sunday, cartoonists paid visual tribute to first responders and other essential workers by embedding six icons into the comic strips, including – a medical **mask**, a **steering wheel** for those who drive delivery trucks, a supermarket **shopping cart**, **apples** for teachers, a **fork** to thank food service workers and a **microscope** to salute medical researchers.

G

Comic Tributes for Sharp-Eyed Readers – June 7



Laughable
Published June 7, 2020

FoxTrot by Bill Amend

Questions/Comments

For more information, contact CDC Emergency Operations Center
770-488-7100
www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Backup Slides

Incident Manager

Do Not Distribute

- These slides are for internal use only.
- All content sides are color coded to indicate sharing instructions

– **Red = internal IMS only, close hold** – e.g., Information is sensitive and should not be shared

– **Yellow = needs approval before distribution** – e.g., Mix of public and non-public info/unofficial sources; slide concept/idea is new or still forming

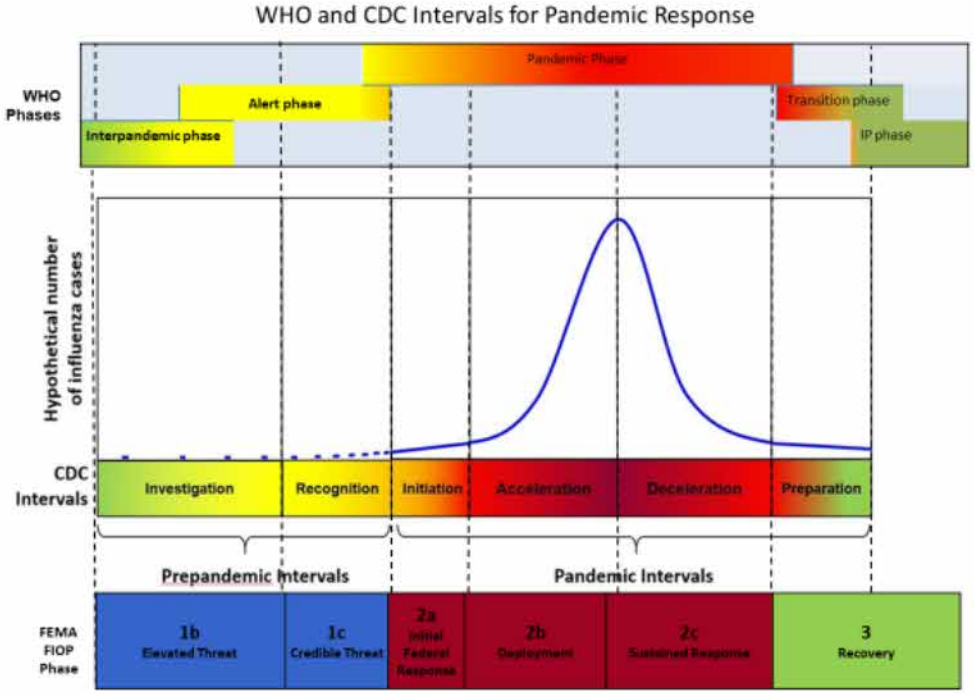
– **Green = public information/okay for wider distribution**. – e.g., All info is available on CDC website or is public

G

Agenda

- Incident Manager
- NRCC
- Case Surveillance
- Analytics
- Modeling
- Epidemiology
- Laboratory
- Health Department Support
- Food Systems
- Health Systems and Worker Safety
- Community and At Risk
- One Health
- Global
- Chief Health Equity Officer
- Associate Director for Science
- Chief Medical Officer
- Communication
- Policy
- Chief of Staff

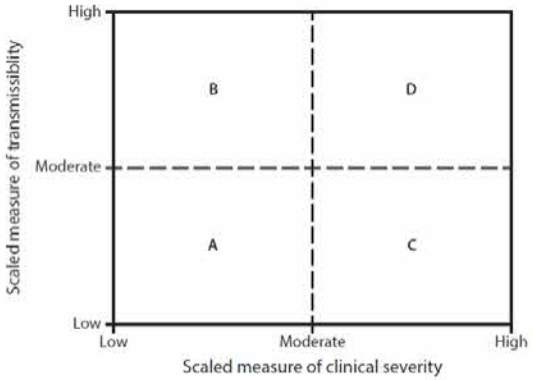
Incident Manager Priorities



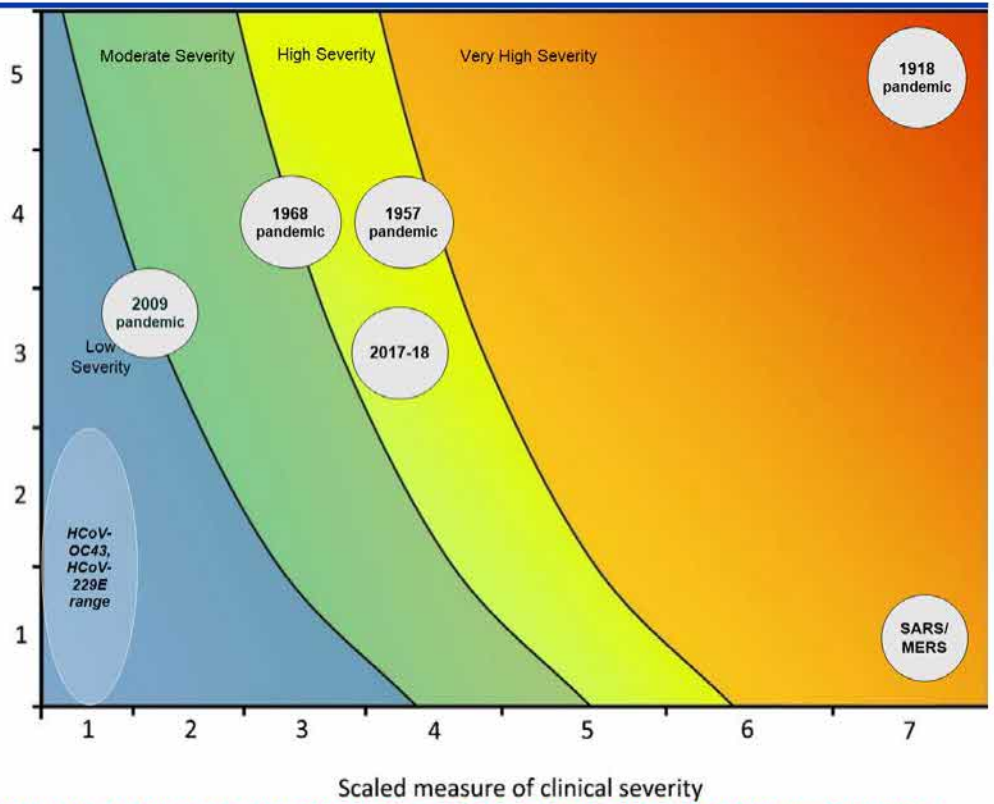
Adapted from: MMWR Recomm Rep. 2014 Sep 26;63(RR-06):1-18. **Updated preparedness and response framework for influenza pandemics.** Holloway R et al

Incident Manager Priorities

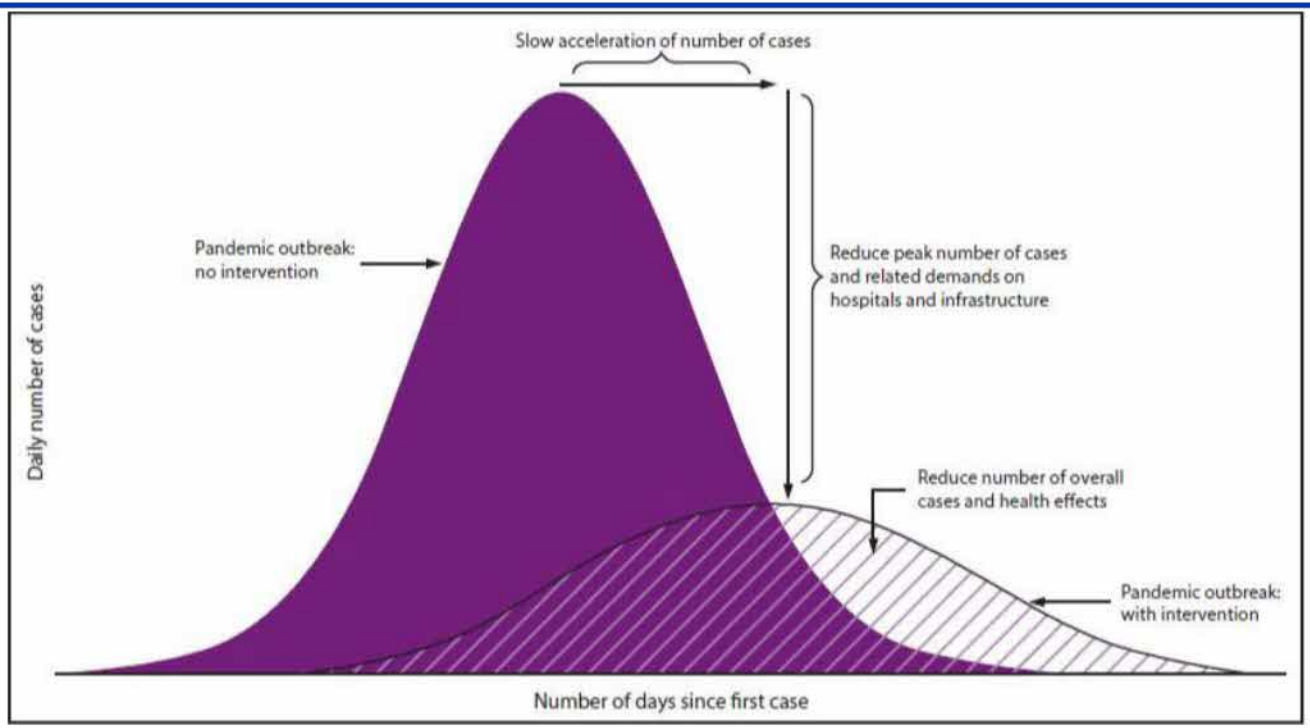
FIGURE 3. Pandemic Severity Assessment Framework for the initial assessment of the potential impact of an influenza pandemic



Source: Reed C, Biggerstaff M, Finelli L, et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 2013;19:85–91.



Incident Manager Priorities



Source: Adapted from: CDC. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States—early, targeted, layered use of nonpharmaceutical interventions. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. https://stacks.cdc.gov/view/cdc/11425.

G

CDC Response Mission Statement

- CDC will implement strategies to slow the introduction and impact of COVID-19 in the United States. CDC will coordinate with international and domestic partners to provide clinical and infection control guidance and implement other methods to mitigate the impact of this virus.

Analytics

Test Results and Percent Positivity by Day

Molecular tests: May 23–June 5, 2020*

* Data from commercial/reference, state public health, and hospital laboratories data feeds

Epidemiology

DVD Enhanced Surveillance Platforms

Platform	Population/setting	Priority study outputs	Status
NVSN	• Children <18 years of age • Outpatient/ED/inpatient at 7 sites	• Incidence (proportion positive) • Presenting symptoms, illness spectrum, risk groups • Clinical outcomes and risk factors for severe disease • Viral genomics by time, location, severity • Immune response • Multisystem inflammatory syndrome in children studies	• All sites enrolling and testing • Retrospective testing from Jan-Mar (manuscript submitted)
PREVAIL	• Maternal-child (aged 18 months-4 years) longitudinal community cohort at 1 site	• Transmission dynamics of SARS-CoV-2 • Immune response to asymptomatic and symptomatic infections • Impact of endemic coronaviruses on SAR-CoV-2 infections • Viral shedding	• Received funding week of June 1 • IRB approved
RSV SuNA	• All ages • Outpatient/inpatient at 5 Indian Health Service sites in AZ and AK	• Incidence (proportion positive) • Presenting symptoms, illness spectrum, risk groups • Clinical outcomes and risk factors for severe disease	• Received funding week of June 1 • Protocol developed and IRB approved
SUPERNOVA	• Adults ≥18 years of age • Inpatient at 5 VA hospitals • National electronic health records from 170 VA hospitals	• Incidence (proportion positive) • Presenting symptoms, illness spectrum, risk groups • Clinical outcomes and risk factors for severe disease	• 4 of 5 sites enrolling • Analysis of severe outcomes from national data