MIS-C in Children and Other Pediatric COVID-19 Considerations

Michael Kuduk, M.D.
Division of Pediatric Hospital Medicine
Joel Howard, MD
Division of Pediatric Infectious Disease

We have no conflicts of interest to disclose.

Hopefully this information will be very useful to you and your patients.

College of Medicine
Office of Medical Education

Learning objectives:

1. Compare the multiple ways COVID-19 and MIS-C can present in pediatric populations and contrast them with similar disease presentations
2. Summarize treatment modalities for both acute COVID-19 and MIS-C in pediatric patients
3. Analyze current issues related to vaccines, vaccine hesitancy, and their role in outbreak control

December 12, 2019

House Judiciary Committee Delays Votes On 2 Articles Of Impeachment Until Friday

December 12, 2019 · 5:00 AM ET

PHILIP EWING DOMENICO MONTANARO

December 12, 2019

Article

A pneumonia outbreak associated with a new coronavirus of probable bat origin

https://doi.org/10.1038/s41586-020-2012-7

Received: 20 January 2020

Accepted: 29 January 2020

Published online: 3 February 2020

Open access

Check for updates

Peng Zhou[1,5], Xing-Lou Yang[1,5], Xian-Guang Wang[2,5], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]✉

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats[1–4]. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans[5–7]. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of *SARSr-CoV*. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

Debate is ongoing about the origins of the virus.

Did it make the jump to humans in the Huanan market, or did the market simply provide an excellent medium for spread?

College of Medicine
Office of Medical Education

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*

Summary

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Methods All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

Findings By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49·0 years (IQR 41·0–58·0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median

Lancet 2020; 395: 497–506

Published Online
January 24, 2020
https://doi.org/10.1016/S0140-6736(20)30183-5

This online publication has been corrected. The corrected version first appeared at thelancet.com on January 30, 2020

See Comment pages 469 and 470

*Contributed equally

†Joint corresponding authors

Jin Yin-tan Hospital, Wuhan, China (Prof C Huang MD, Prof L Zhang MD, T Yu MD, J Xia MD, Y Wei MD, Prof W Wu MD, Prof X Xie MD); **Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for**

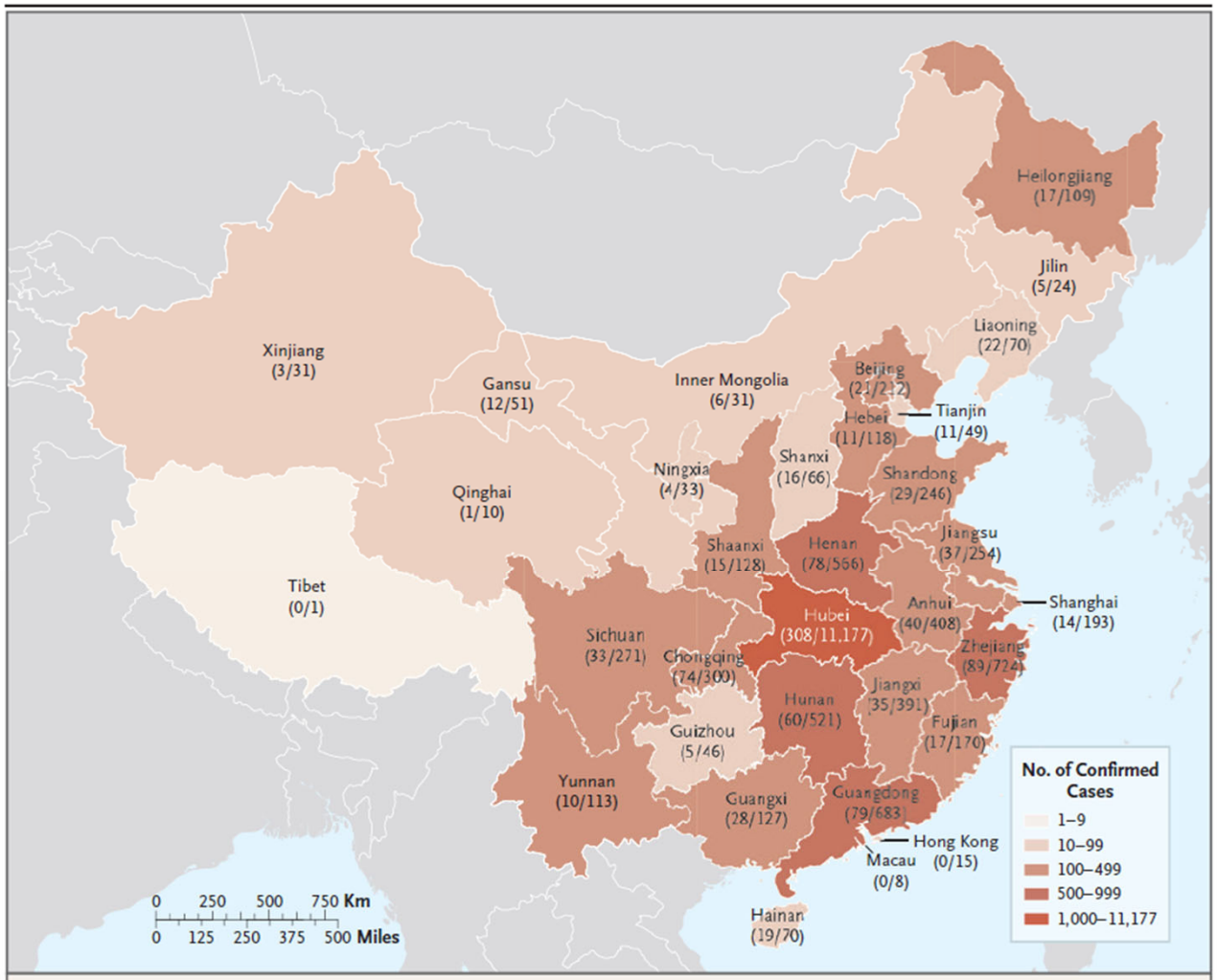
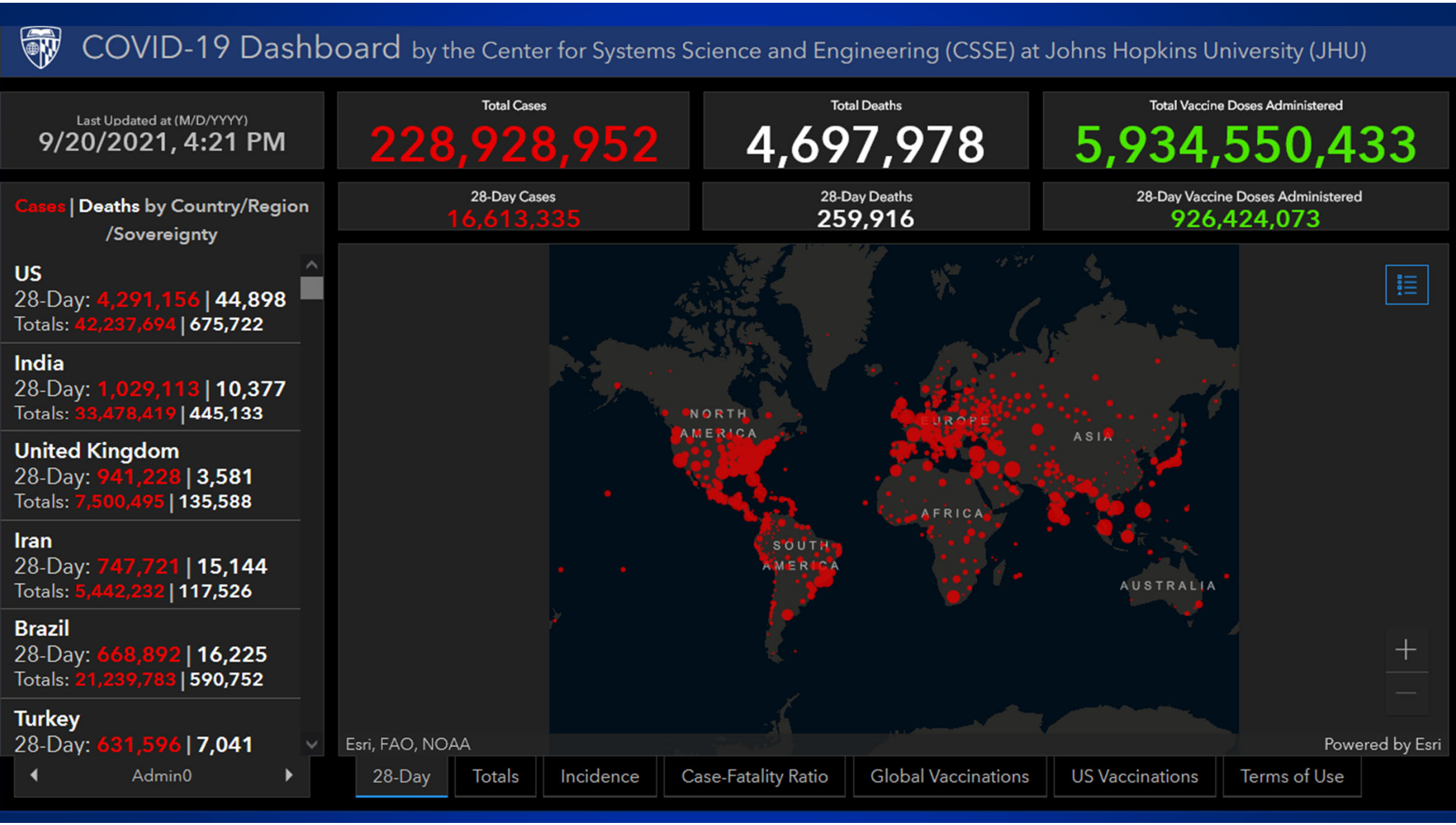


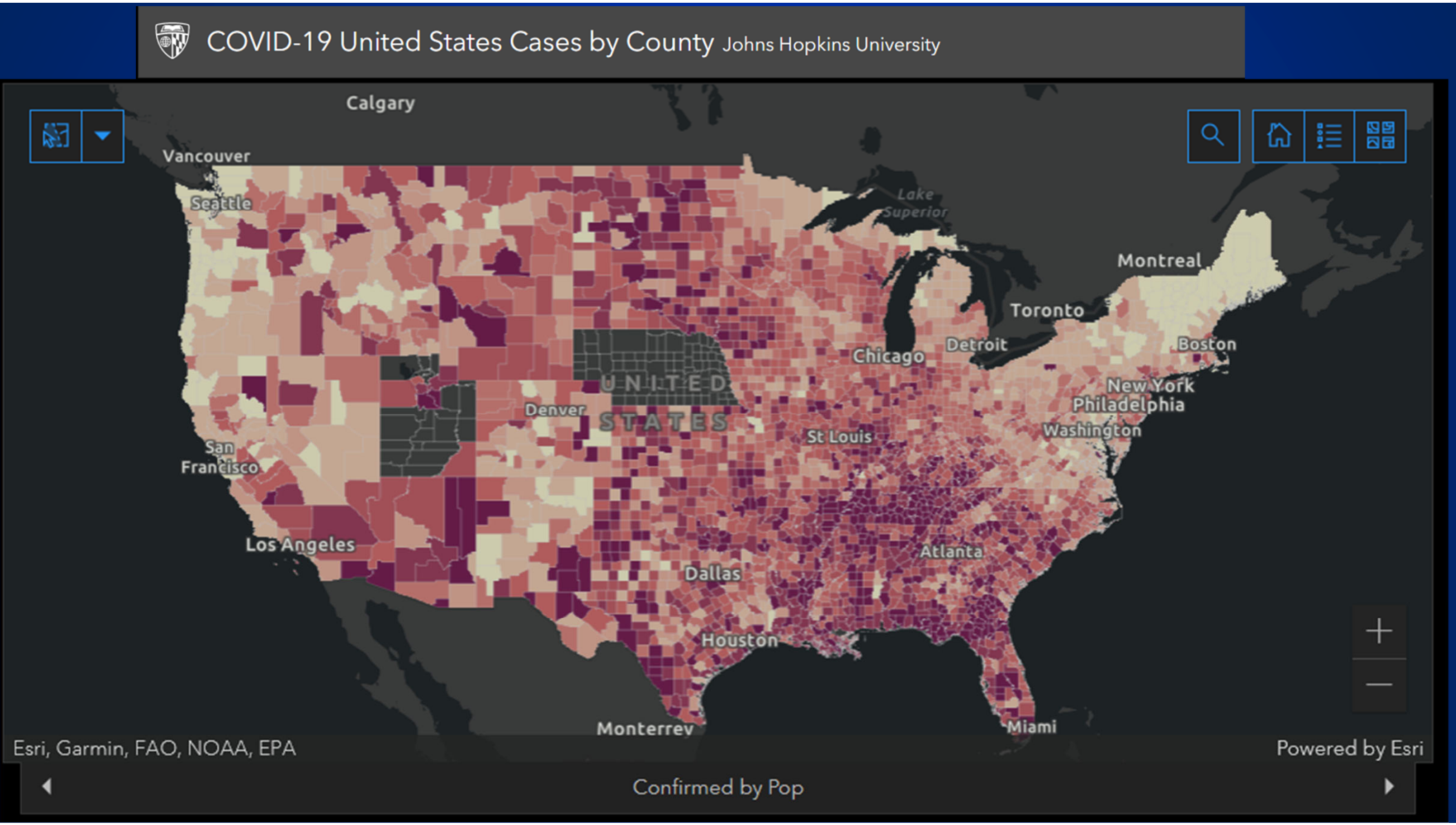
Figure 1. Distribution of Patients with Covid-19 across Mainland China.

Shown are the official statistics of all documented, laboratory-confirmed cases of coronavirus disease 2019 (Covid-19) throughout China, according to the National Health Commission as of February 4, 2020. The numerator denotes the number of patients who were included in the study cohort and the denominator denotes the number of laboratory-confirmed cases for each province, autonomous region, or provincial municipality, as reported by the National Health Commission.

Spread in China as of February 4, 2020

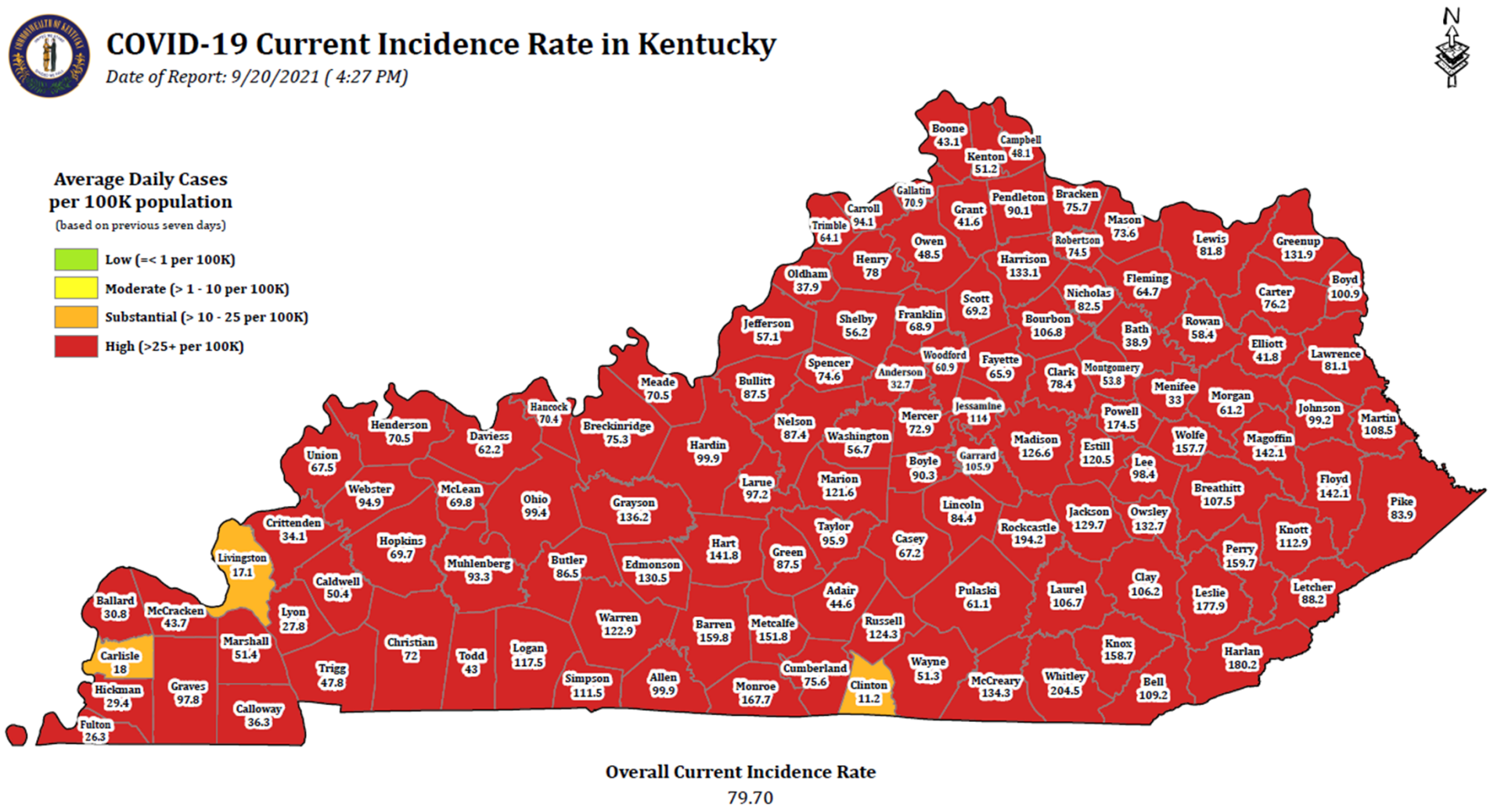
Guan et. al.
NEJM
2/28/2020


COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)
Last Updated at (M/D/YYYY)
9/20/2021, 4:21 PM
Total Cases
228,928,952
Total Deaths
4,697,978
Total Vaccine Doses Administered
5,934,550,433
28-Day Cases
16,613,335
28-Day Deaths
259,916
28-Day Vaccine Doses Administered
926,424,073
Cases | Deaths by Country/Region /Sovereignty
US
28-Day: 4,291,156 | 44,898
Totals: 42,237,694 | 675,722
India
28-Day: 1,029,113 | 10,377
Totals: 33,478,419 | 445,133
United Kingdom
28-Day: 941,228 | 3,581
Totals: 7,500,495 | 135,588
Iran
28-Day: 747,721 | 15,144
Totals: 5,442,232 | 117,526
Brazil
28-Day: 668,892 | 16,225
Totals: 21,239,783 | 590,752
Turkey
28-Day: 631,596 | 7,041
Admin0
NORTH AMERICA
EUROPE
ASIA
AFRICA
SOUTH AMERICA
AUSTRALIA
Esri, FAO, NOAA
Powered by Esri
28-Day
Totals
Incidence
Case-Fatality Ratio
Global Vaccinations
US Vaccinations
Terms of Use


COVID-19 United States Cases by County Johns Hopkins University
Calgary
Vancouver
Seattle
Lake Superior
Montreal
Toronto
Detroit
Chicago
Boston
New York
Philadelphia
Washington
UNITED STATES
Denver
St Louis
San Francisco
Los Angeles
Atlanta
Dallas
Houston
Monterrey
Miami
Esri, Garmin, FAO, NOAA, EPA
Powered by Esri
Confirmed by Pop

COVID-19 Current Incidence Rate in Kentucky

Date of Report: 9/20/2021 (4:27 PM)



Overall Current Incidence Rate

79.70

Population values from the 2019 US Census Bureau Estimates

Total number of cases used in the calculations: 658,222 Cases

Data Source: Kentucky Department for Public Health

R0 for common viral illnesses:

Measles	12-18
Varicella	10-12
COVID-19 delta (best guess)	5-7
Pertussis	5-6
Polio	5-7
RSV	3
SARS	2-3
COVID-19 alpha (Wuhan data)	2.2-5.7
Influenza (1918 pandemic)	1.5-3.0
Rhinovirus (best guess)	1.2-1.8
MERS	0.3-0.8

What does COVID-19 infection look like in children and adolescents?

College of Medicine
Office of Medical Education

Dong et. al. Pediatrics March, 2020

- Looked at characteristics of 2143 pediatric patients in Wuhan retrospectively, both confirmed and suspected cases
- Classification of illness:
  1. Asymptomatic
  2. Mild – upper respiratory or GI symptoms only; +/- fever
  3. Moderate – evidence of pneumonia but no SOA or hypoxia
  4. Severe – pneumonia with SOA and/or hypoxemia
  5. Critical – respiratory failure, ARDS

Table 1 Characteristics of Children' COVID-19 Cases in China

Characteristics	All cases	Different Category		*P* Value
		Confirmed	Suspected	
Median age (Interquartile range)	7.00 (11.0)	10.00(11.0)	6.00(10.0)	<0.001
Age group				
<1	379(17.7)	86(11.8)	293(20.8)	
1-5	493(23.0)	137(18.7)	356(25.2)	
6-10	523(24.4)	171(23.4)	352(24.9)	<0.001
11-15	413(19.3)	180(24.6)	233(16.5)	
>15	335(15.6)	157(21.5)	178(12.6)	
Gender				
Boy	1213(56.6)	420(57.5)	793(56.2)	0.567
Girl	930(43.4)	311(42.5)	619(43.8)	
Severity of illness				
Asymptomatic	94(4.4)	94(12.9)	0(0.0)	
Mild	1091(50.9)	315(43.1)	776(54.9)	
Moderate	831(38.8)	300(41.0)	531(37.6)	
Severe	112(5.2)	18(2.5)	94(6.7)	<0.001
Critical	13(0.6)	3(0.4)	10(0.7)	
Missing	2(0.1)	1(0.1)	1(0.1)	
Days from symptom onset to diagnosis				
Median days (Interquartile range)	2(4.0)	3(4.0)	2(4.0)	<0.001
Range	0-42	0-42	0-36	
Province				
Hubei	984(45.9)	229(31.3)	755(53.5)	
Surrounding areas*	397(18.5)	155(21.2)	242(17.1)	<0.001
Others	762(35.6)	347(47.5)	415(29.4)	
Total	2143	731(34.1)	1412(65.9)	

Data are presented with median (Interquartile range) and n (%).

Table 2 Different Severity of Illness by Age Group

Age group*	Asymptomatic	Mild	Moderate	Severe	Critical	Total
<1	7(7.4)	205(18.8)	127(15.3)	33(29.5)	7(53.8)	379(17.7)
1-5	15(16.0)	245(22.5)	197(23.7)	34(30.4)	2(15.4)	493(23.0)
6-10	30(31.9)	278(25.5)	191(23.0)	22(19.6)	0(0)	521(24.3)
11-15	27(28.7)	199(18.2)	170(20.5)	14(12.5)	3(23.1)	413(19.3)
>15	15(16.0)	164(15.0)	146(17.5)	9(8.0)	1(7.7)	335(15.7)
Total	94	1091	831	112	13	2141(100)

Data were presented with number and percent (%);*Two cases had missing values.

Dong et. al. Pediatrics
March, 2020

College of Medicine
Office of Medical Education

Bialek et. al. MMWR April 6, 2020

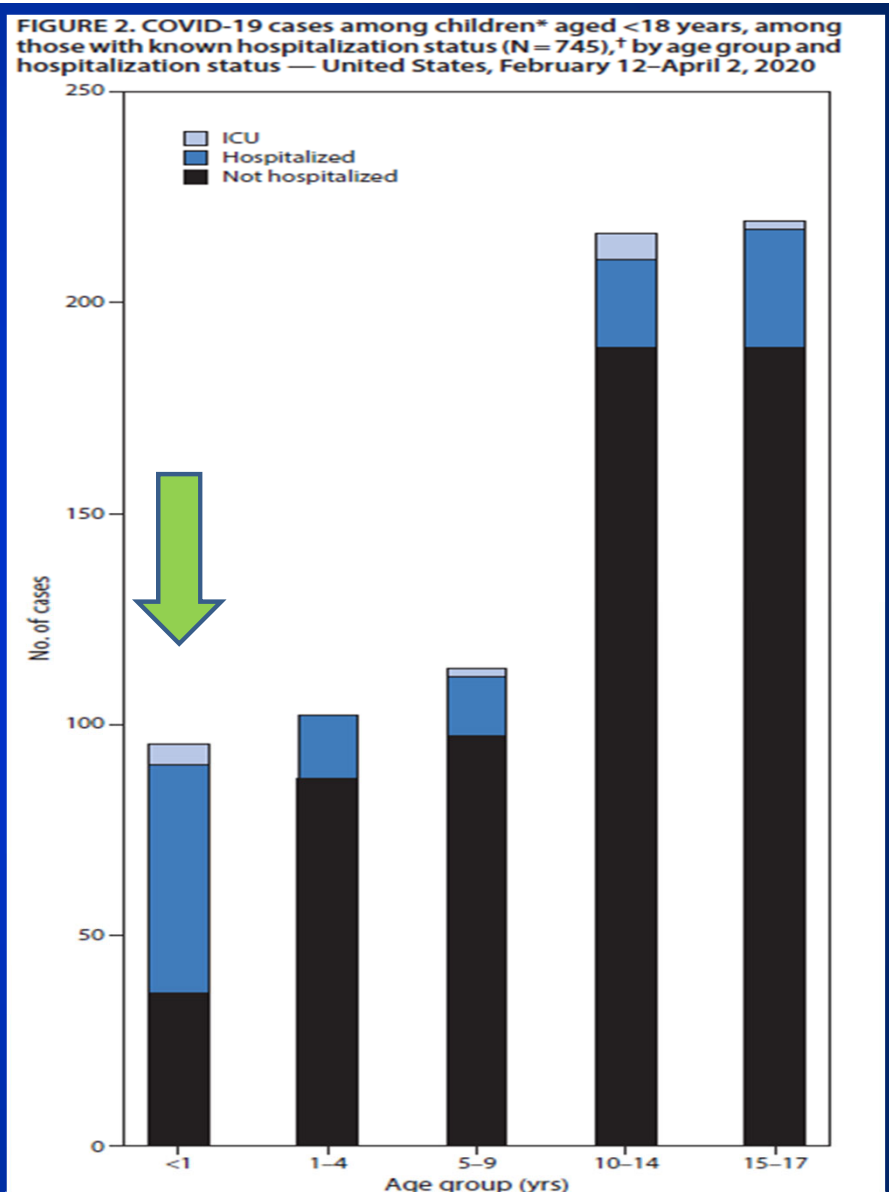
- Looked at SARS-CoV-2 disease in children in the United States from February 12 to April 2, 2020
- Generated from CDC data obtained from states and municipalities, due to workloads many cases are missing data
- 2,572 cases under age 18:
  - Able to look at symptoms (9.4%), underlying conditions (13%), and hospitalizations (30%)

TABLE. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients* with laboratory-confirmed COVID-19 — United States, February 12–April 2, 2020

Sign/Symptom	No. (%) with sign/symptom	
	Pediatric	Adult
Fever, cough, or shortness of breath†	213 (73)	10,167 (93)
Fever§	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose¶	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain¶	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

* Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
† Includes all cases with one or more of these symptoms.
§ Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.
¶ Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.

Bialek et. al. MMWR April 6, 2020

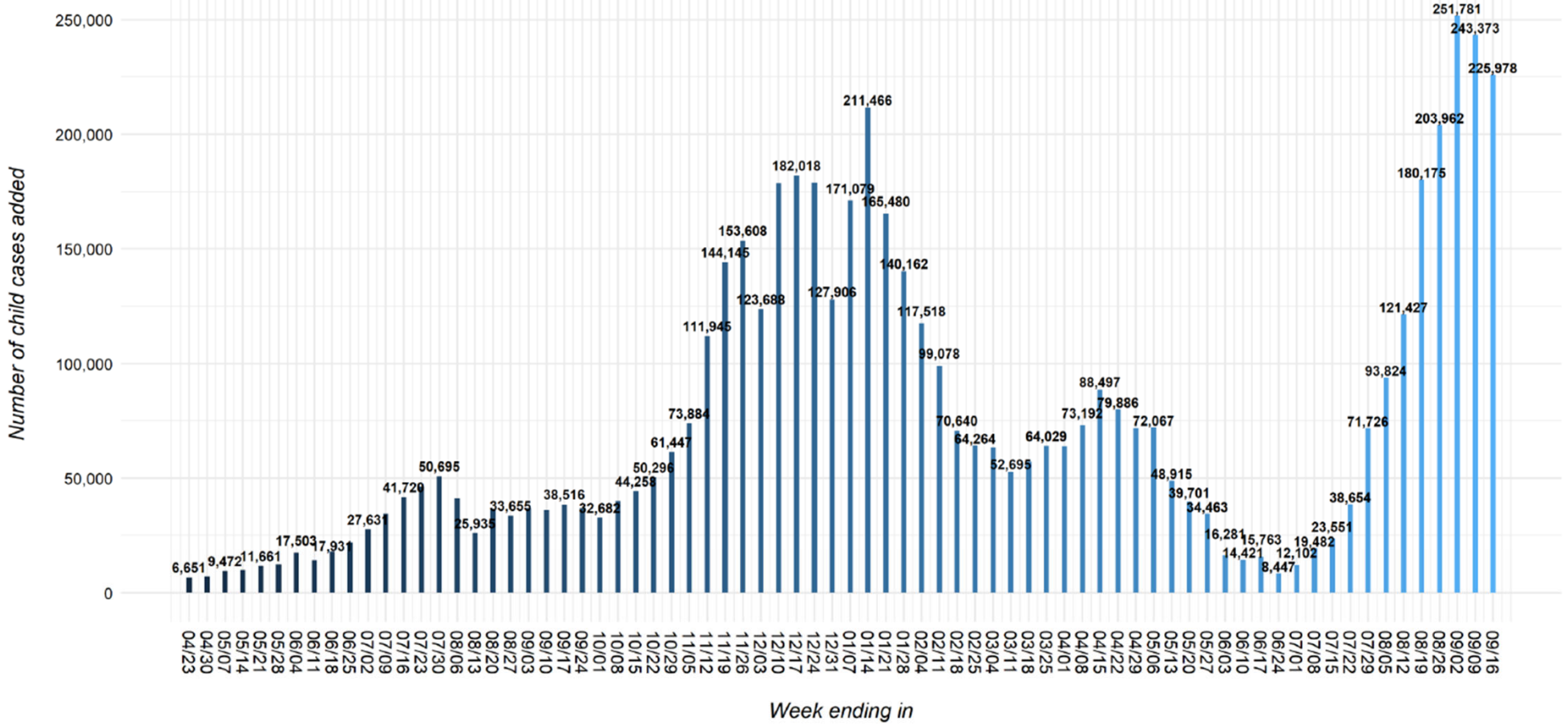


COVID-19, the original:

- Initially, we expected to see a fair number of ill neonates and infants – we did not
- Most children with acute COVID-19 were adolescents and were few and far between

That all changed a few months ago…..

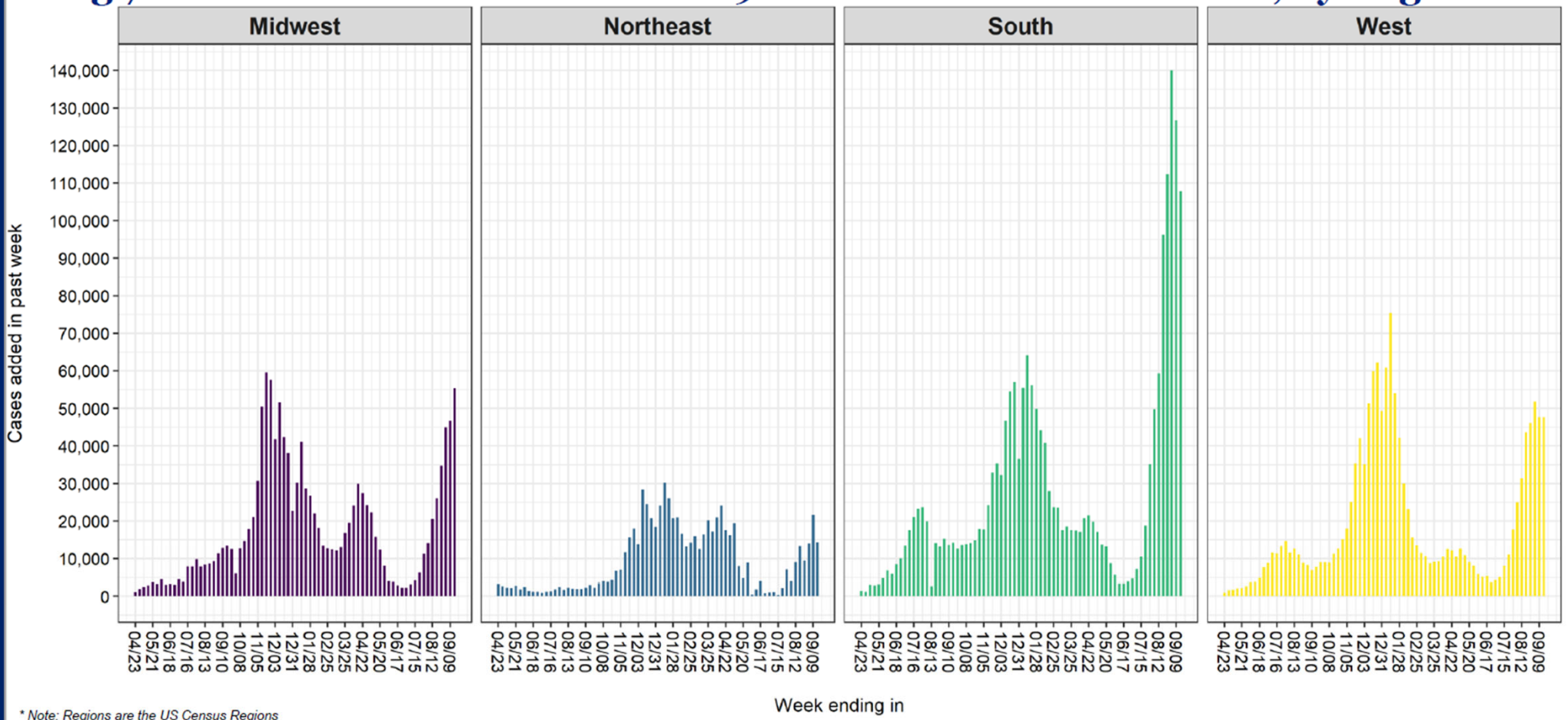
Fig 6. United States: Number of Child COVID-19 Cases Added in Past Week*



** Note: 5 states changed their definition of child cases: AL as of 8/13/20, HI as of 8/27/20, RI as of 9/10/20, MO as of 10/1/20, WV as of 8/12/21*
TX reported age for only a small proportion of total cases each week (eg, 3-20%); TX cumulative cases through 8/26/21
As of 6/30/21, NE COVID-19 dashboard is no longer available; NE cumulative cases through 6/24/21
Due to available data and changes made to dashboard, AL cumulative cases through 7/29/21
Due to available data and calculations required to obtain MA child cases, weekly estimates fluctuate (eg, on 9/16/21 there were 184 fewer cumulative child cases)
See detail in Appendix: Data from 49 states, NYC, DC, PR and GU
All data reported by state/local health departments are preliminary and subject to change; Analysis by American Academy of Pediatrics and Children's Hospital Association

CHILDREN'S HOSPITAL ASSOCIATION
American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Fig 7. United States: Child COVID-19 Cases Added in Past Week, by Region*



** Note: Regions are the US Census Regions*

5 states changed their definition of child cases: AL as of 8/13/20, HI as of 8/27/20, RI as of 9/10/20, MO as of 10/1/20, WV as of 8/12/21;
TX reported age for only a small proportion of total cases each week (eg, 3-20%); TX cumulative cases through 8/26/21
As of 6/30/21, NE COVID-19 dashboard is no longer available; NE cumulative cases through 6/24/21
Due to available data and changes made to dashboard, AL cumulative cases through 7/29/21
Due to available data and calculations required to obtain MA child cases, weekly estimates fluctuate (eg, on 9/16/21 there were 184 fewer cumulative child cases)
See detail in Appendix: Data from 49 states, NYC, DC, PR and GU
All data reported by state/local health departments are preliminary and subject to change; Analysis by American Academy of Pediatrics and Children's Hospital Association

CHILDREN'S HOSPITAL ASSOCIATION

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

UK's current experience:

- Neonates can present with high fever with little to distinguish COVID-19 from other illnesses
  - Some sepsis workups in less than 28 day olds are COVID-19 positive
- We are now seeing a bronchiolitis/viral pneumonia type picture in infants, especially those patients with underlying pulmonary disease (e.g. chronic lung disease of prematurity)
- Both neonates and infants can present with high fever and are often dehydrated

UK’s current experience:

- Toddlers and school age children will present with fever or a viral picture which is difficult to distinguish from other viral illnesses
- Diagnosis is becoming more difficult as the volume of non-COVID-19 infections continues to rise in all age groups
- Like adults, adolescents are presenting with fever, shortness of breath, and hypoxia

Questions?

College of Medicine
Office of Medical Education

What exactly is MIS-C?

College of Medicine
Office of Medical Education

Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval to 2 million children in South East England. During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,[1] or toxic shock syndrome (typical number is one or two children per week). This case cluster formed the basis of a national alert.

All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile

Published Online
May 6, 2020
https://doi.org/10.1016/
S0140-6736(20)31094-1

Riphagen et. al. Lancet May 23, 2020

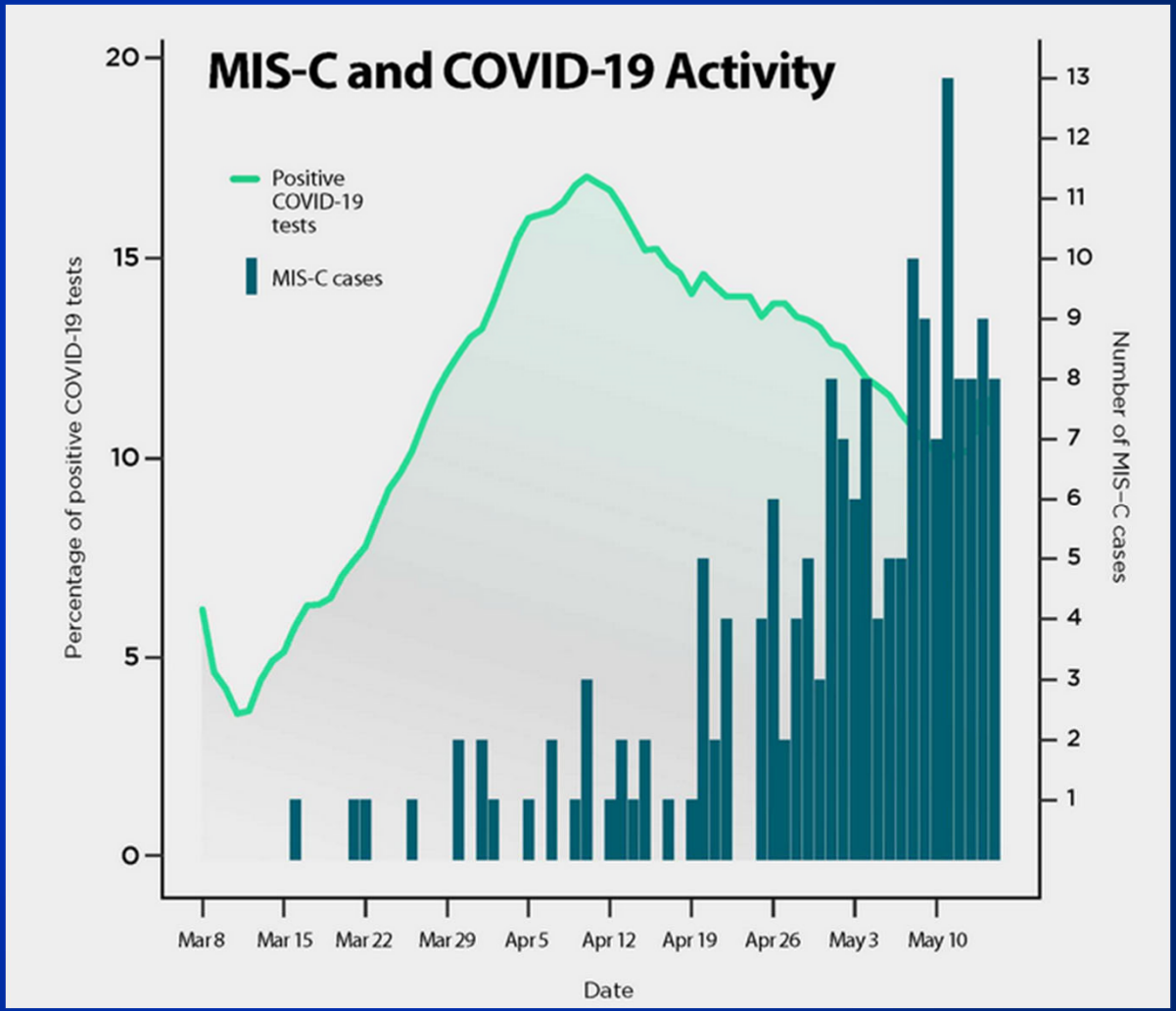
Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

Distributed via the CDC Health Alert Network
May 14, 2020, 4:45 PM ET
CDCHAN-00432

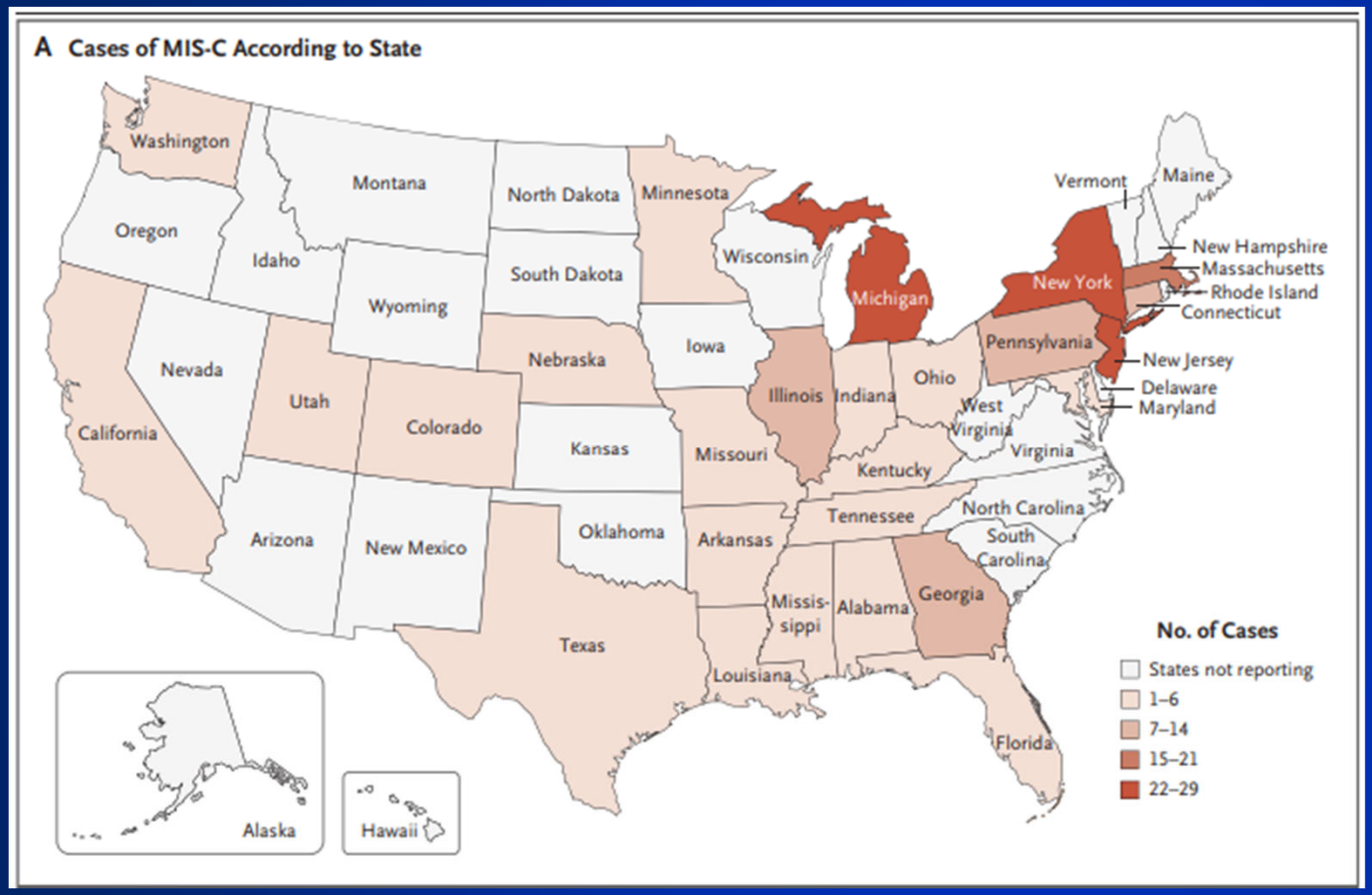
Summary

The Centers for Disease Control and Prevention (CDC) is providing 1) background information on several cases of a recently reported multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19); and 2) a case definition for this syndrome. CDC recommends healthcare providers report any patient who meets the case definition to local, state, and territorial health departments to enhance knowledge of risk factors, pathogenesis, clinical course, and treatment of this syndrome.

Source: CDC data



College of Medicine
Office of Medical Education



MIS-C cases
from March 15
to May 15, 2020

Feldstein et. al.
NEJM July 23, 2020

MIS-C (Multisystem Inflammatory Syndrome in children):

- Originally thought to be a variant of Kawasaki Disease due to some similarities in presentation, now known to be different
- Follows acute COVID-19 infection by 4 to 6 weeks
  - The initial infection is often asymptomatic
  - Immediate family members often show symptoms
- Children are acutely ill and have high fever at initial presentation

MIS-C symptoms:

- All have fever
- Most look systemically ill
- Physical findings:
  - Rash (variable, not vesicular)
  - GI symptoms (common – V/D/abdominal pain)
  - Swelling of hands/feet
  - Oral mucus membrane changes (red lips, strawberry tongue)
  - Conjunctivitis
  - Lymphadenopathy

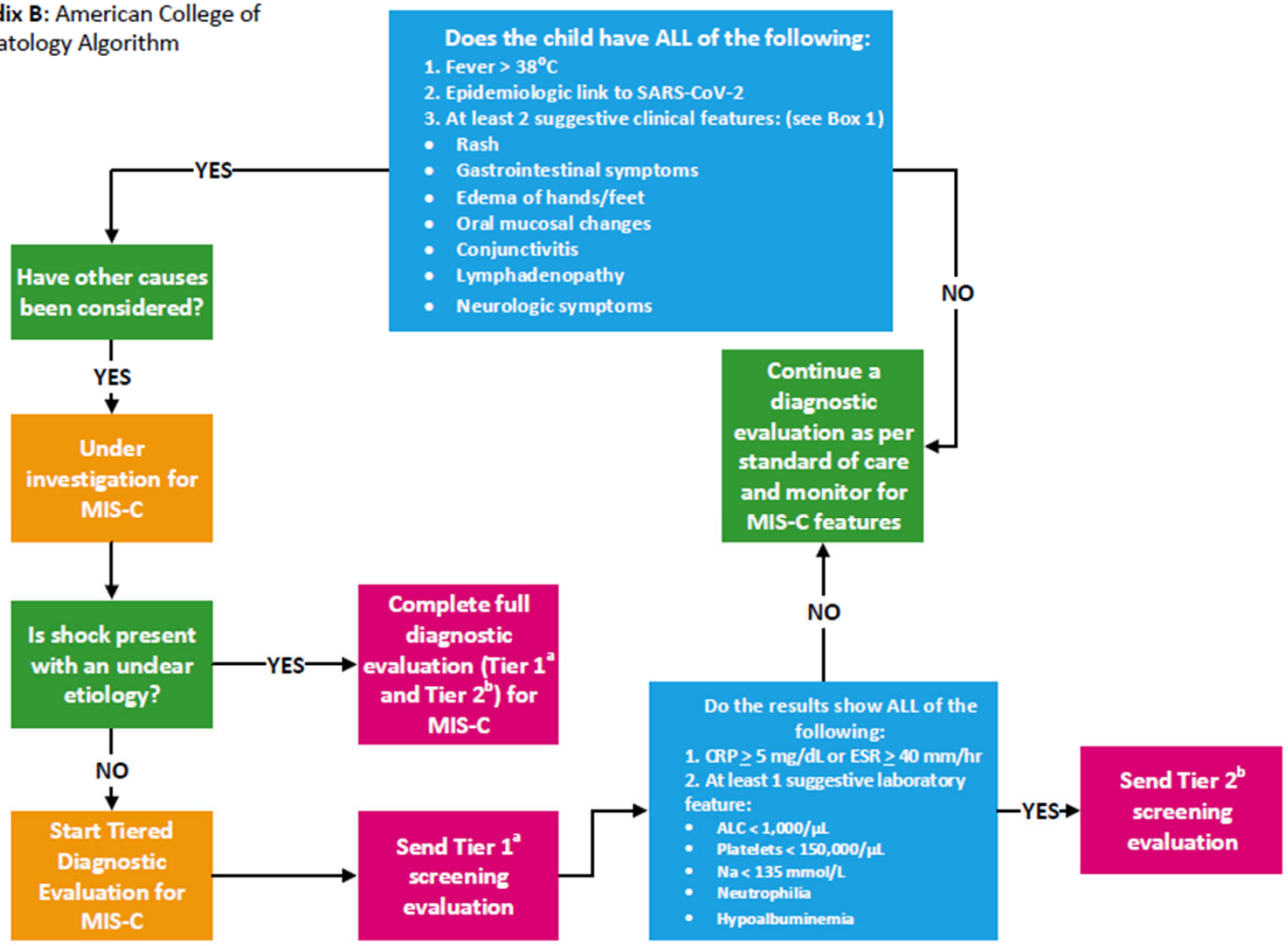
MIS-C differential diagnosis:

- Kawasaki disease
- Sepsis
- Juvenile idiopathic arthritis, systemic onset
- Viral infection, especially adenovirus or mononucleosis
- Malignancy
- Myocarditis

MIS-C lab results:

- Seen in nearly all patients:
  - Markedly elevated CRP
  - Decreased lymphocyte count
  - Decreased platelet count
- Also common:
  - Low sodium
  - Increased neutrophils
  - Low serum albumin
  - Increased alphaBNP

Appendix B: American College of Rheumatology Algorithm



[a]Tier 1: CBC, CMP, ESR, CRP, SARS-CoV-2 PCR and/or serology, nasopharyngeal respiratory PCR
[b]Tier 2: BNP, tropinin T, procalcitonin, ferritin, PT, PTT, D-dimer, fibrinogen, LDH, UA, triglycerides, SARS-CoV-2 serology, ECG, ECHO
Obtain Cytokine Panel per Consult Service Recommendation Only

12

Tier 1 labs help with differential diagnosis

Tier 2 labs confirm MIS-C

Questions?

College of Medicine
Office of Medical Education

Real Case Presentations

College of Medicine
Office of Medical Education

MIS-C Mimicker

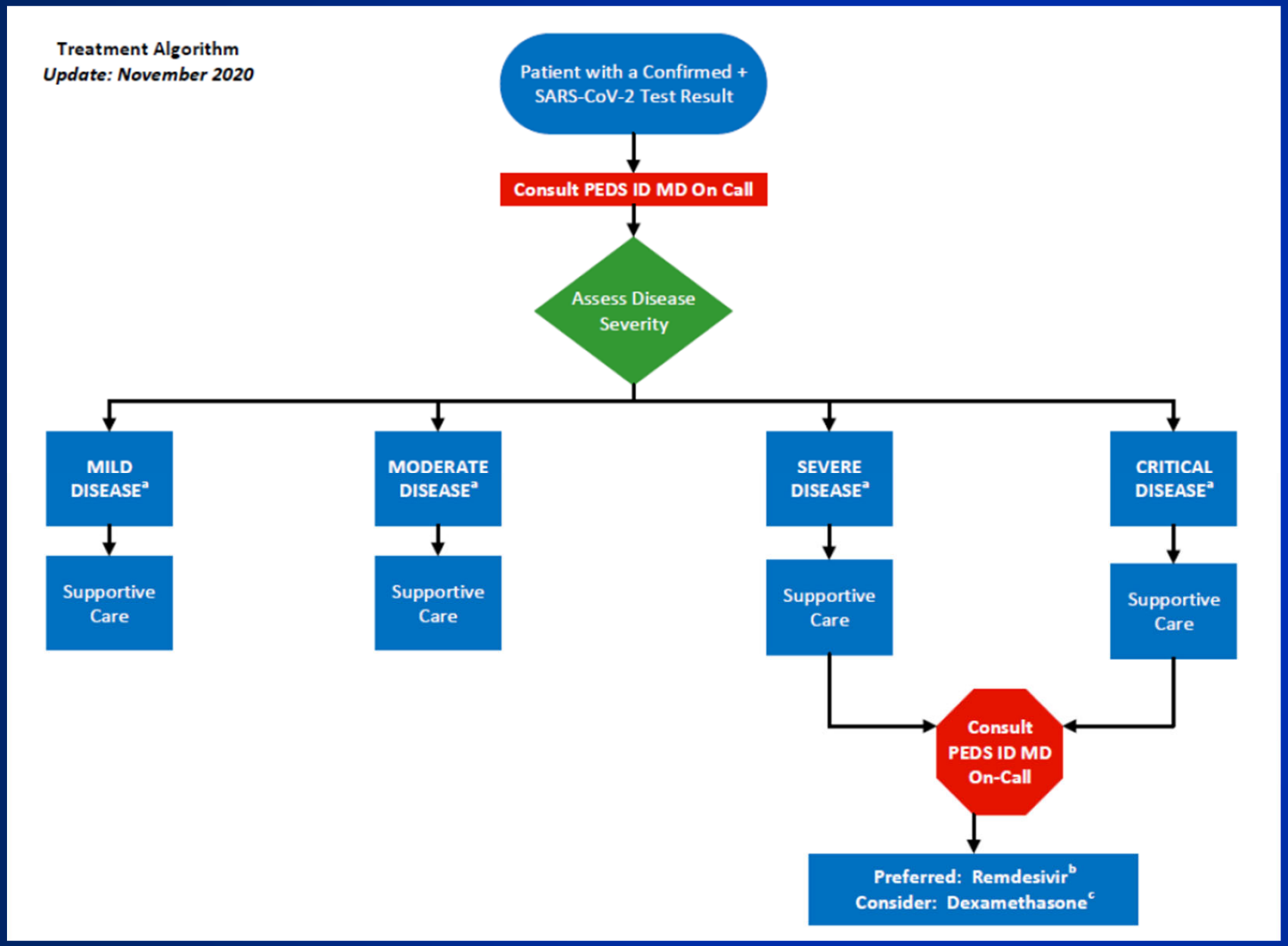
- Previously healthy 15 yo female presents with 2 days of fever, severe myalgias, vomiting, and diarrhea. Found to be in shock and had tampon in place. Started on pressors; IV vanc, Zosyn, and clinda. No rash. 2nd dose of Pfizer 12 days prior to symptom onset. SARS CoV2 PCR positive. ALC 280. Plts 142. CRP 49. No epi link but worked at McDonalds.

Broad MIS-C criteria

- Previously healthy ~2 yo M presents with 4 days of fever, abdominal pain, and vomiting. Ultrasound negative for intussusception or appendicitis. COVID PCR and serology positive. CRP 283. ALC 1140. Had a non-specific febrile illness 5 weeks prior. Responded to MIS-C treatment and was discharged. Represented with persistent fever and new cough 1 week later, found to have RML pulmonary abscess.

How is acute COVID-19 treated?

College of Medicine
Office of Medical Education



Current UK pediatric recommendations

Mild – upper respiratory only

Moderate – chest disease, No O2 requirement

Severe – Sustained SpO2 < 94% on room air, increase in baseline O2 requirement

Critical – Invasive/Non-invasive mechanical ventilation or rapid worsening

Remdesivir

Dosing:

Remdesivir Loading Dose[a]	Remdesivir Maintenance Dose[a] (duration based on disease severity)
5 mg/kg (maximum 200 mg) IV on day 1	Severe Disease: 2.5 mg/kg (maximum 100 mg) IV on days 2 through 5[b,c]
	Critical Disease: 2.5 mg/kg (maximum 100 mg) IV on days 2 through 10[c]

[a] For patients < 12 years OR between 3.5 and < 40 kg, see **Appendix B** regarding EUA requirements
[b] May extend treatment for up to 5 additional days in patients not demonstrating clinical improvement
[c] Complete full course of therapy or until hospital discharge, whichever comes first

Monitoring Needs:

- Baseline: CMP and Prothrombin Time
- Daily: CMP and Prothrombin time

For patients < 12 years of age OR 3.5 to < 40 kg you must complete the following per EUA requirements:

- Documentation in the electronic medical record by **attending** as outlined in **Appendix B**
- Provide patient/caregiver with fact sheet: https://www.fda.gov/media/137565/download
- Ongoing review for adverse drug reactions and adhere to monitoring plan outlined above

Dexamethasone

Dosing:

- Dexamethasone 0.15 mg/kg (maximum 6 mg) IV or PO once daily
  - Duration: up to 10 days or until hospital discharge, whichever comes first
    - Consideration of a shorter duration may be considered in patients that are improving rapidly
  - A corticosteroid taper may be considered based on patient response and duration of therapy

Alternatives Corticosteroids: to be considered if dexamethasone is not available

- Prednisone/Prednisolone 1 mg/kg (maximum 40 mg) PO once daily
- Methylprednisolone 0.8 mg/kg (maximum 32 mg) IV/PO once daily

For Additional Information Regarding COVID-19 at UK HealthCare Visit:

https://covid-19.ukhc.org/

Casirivimab/Imdevimab (REGEN-COV)

Inclusion Criteria:

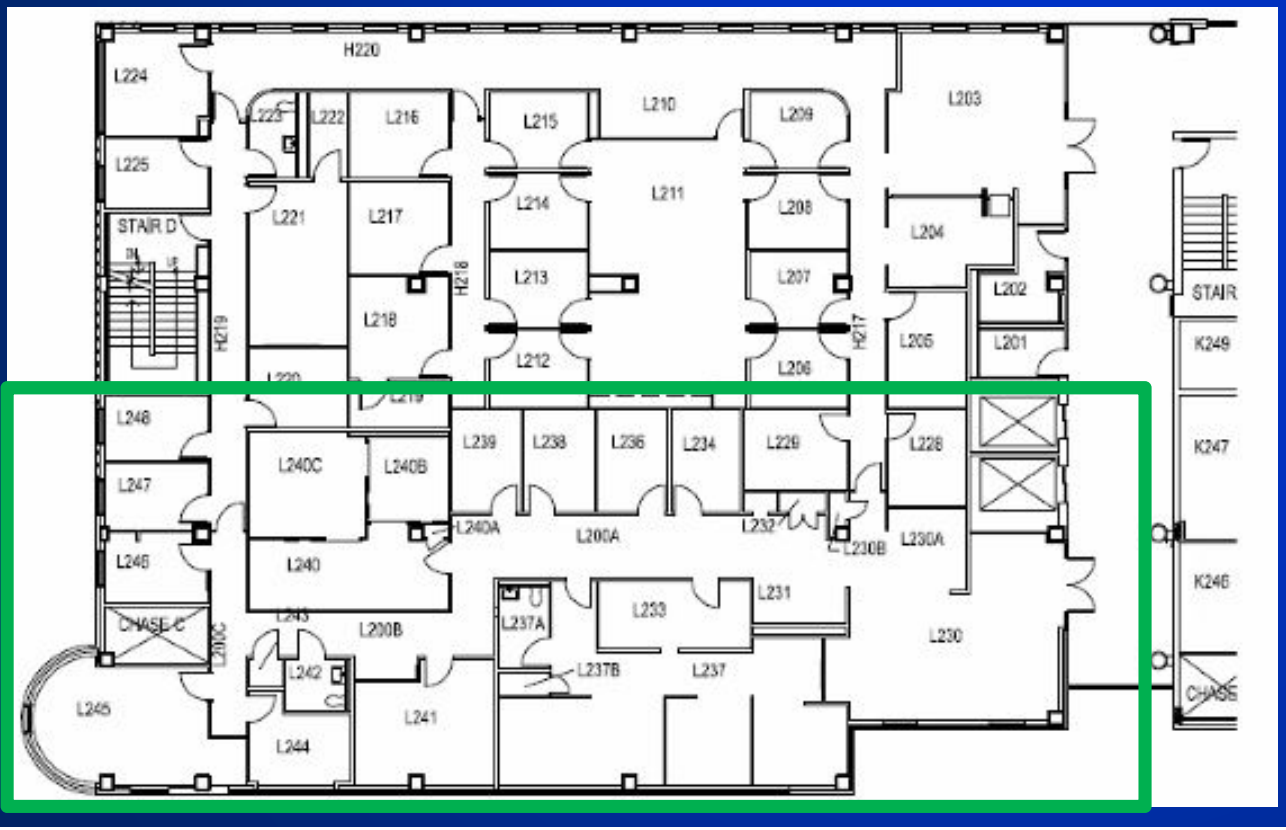
- Pediatric patients 12 to < 18 years of age **AND** weighing at least 40 kg meeting high risk criteria (below) for developing a severe COVID-19 infection and are currently outpatient and **not** hospitalized for COVID-19 (as listed per exclusion criteria below)

Treatment	Post-Exposure Prophylaxis
Mild-to-moderate COVID-19 infection with positive results of direct SARS-CoV-2 viral testing (PCR or antigen) with the following: • Symptomatic (at least 2 of the following: fever, cough, sore throat, malaise, headache, myalgias, gastrointestinal symptoms, shortness of breath) • Within 10 days of symptom onset	Not fully vaccinated OR who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination **AND** • Have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC **or** • Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of an occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting

High risk Criteria:

- BMI ≥ 85% for age/gender
- Congenital Heart Disease
- Chronic Lung Disease/Tracheostomy and ventilator dependence
- Sickle cell disease
- Pregnancy
- Immunocompromised
- Diabetes
- CKD
- Neurodevelopmental disorders
- “Other”

NEW LOCATION!



- Hours: 3-9 pm M - F
- Previous Pediatric Hematology/Oncology Clinic
- Increased capacity
  - Individual Rooms
  - Sibling Rooms
- Initial Plans:
  - 9 infusion per day
  - Ability to expand

HealthCare
KENTUCKY CHILDREN'S HOSPITAL

Patient Information:
Name: _____
DOB: _____

Pediatric COVID-19 Monoclonal Antibody Referral Form

This form must be completed by the referring provider and will be uploaded as a PDF to the patient's chart in EPIC via Media Manager functio
*Complete the required fields (annotated by *) and submit this referral form along with the order form (page 2) to ###-####*

Indication*: *patient must meet both of the below criteria in addition to others listed below*
This patient is:
- ☐ 12 years of age or older
- ☐ At least 40 kg (documented weight: ____ kg (date obtained: _____ (MM/DD/YYYY))

☐ **Treatment** *(if selected, complete the below fields)*
1. ☐ Mild to moderate COVID-19 infection with positive results of direct SARS-CoV-2 viral testing (PCR or antigen):
   - Date of SARS-CoV-2 Test: _____ (MM/DD/YYYY)
   - Date of Symptom Onset: _____ (MM/DD/YYYY)

   AND
2. ☐ At least two of the following symptoms: *select all that apply*
   - ☐ Fever ☐ Cough ☐ Sore Throat
   - ☐ Malaise ☐ Headache ☐ Myalgias
   - ☐ Gastrointestinal Symptoms
   - ☐ Shortness of Breath ☐ Other: _____

☐ **Post-Exposure Prophylaxis** *(if selected, complete the below fields)*
1. ☐ Not fully vaccinated OR
   ☐ Not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination

   AND
2. ☐ Have been exposed to an individual infected with SARS CoV-2 consistent with close contact criteria per CDC OR
   ☐ Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of an occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting

Select the Patient's High Risk Criteria* outlined in the EUA include the following:
- ☐ Obesity or being overweight (BMI ≥ 85% for their age and gender on CDC growth charts)
- ☐ Chronic kidney disease
- ☐ Diabetes
- ☐ Immunosuppressive disease or immunosuppressive treatment
- ☐ Cardiovascular disease (including congenital heart disease)
- ☐ Sickle cell disease
- ☐ Pregnant
- ☐ Chronic lung disease (moderate to severe asthma, interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- ☐ Neurodevelopmental disorders or other conditions that confer medical complexity (i.e., cerebral palsy, genetic/metabolic syndromes, severe congenital anomalies)
- ☐ Medical-related technological dependent (i.e., tracheostomy, gastrostomy, positive pressure ventilation not related to COVID-19)
- ☐ Other medical conditions/factors associated with increased risk for progression to severe COVID, per CDC website
  If other, please specify: _____

☐ **I have provided the patient's legal guardian with a copy of the Fact Sheet for Parents and Caregivers (English; Spanish)***

Legal Attestation*:

_____ (Last Name, First Name) is a _____ (age) year old _____ (gender) under my care for COVID-19. I have assessed my patient as eligible to receive casirivimab and imdevimab under the FDA Emergency Use Authorization (EUA). I have reviewed the mandatory requirements for drug use within the Fact Sheet for Health Care Providers and obtained approval for use according to institutional policy. I have provided information consistent with the Fact Sheet for Patients and Parents/Caregivers EUA of casirivimab and imdevimab and given the patient/legal representative a copy. The patient/legal representative was informed of the potential risks and benefits of casirivimab and imdevimab, alternatives to casirivimab and imdevimab, and that casirivimab and imdevimab is an unapproved drug that is authorized for use under EUA. The patient or patient's legal representative has expressly agreed to this treatment.

Signature, Referring Provider	Date (MM/DD/YYYY)	Contact Information

Updated: 09/15/2021

HealthCare
KENTUCKY CHILDREN'S HOSPITAL

Pediatric COVID-19 Monoclonal Antibody Order Form

*Complete the required fields (annotated by *) and submit this order form along with the referral form (page 1) to ###-####*

Patient Name*: _____ Date of Birth*: _____

Legal Guardian Name*: _____ Phone Number*: _____

Allergies*: _____
☐ No Known Drug Allergies

Indication*:
☐ Treatment
☐ Post-Exposure Prophylaxis

https://covid-19.ukhc.org/documents/

Casirivimab/Imdevimab Order:

Intravenous Administration
☒ casirivimab 600 mg, imdevimab 600 mg in sodium chloride 0.9% 100 mL IV piggyback administered over 30 minutes

If intravenous access cannot be obtained the subcutaneous order will be activated for use as selected below

Subcutaneous Administration
☒ casirivimab 300 mg (2.5 mL) subcutaneous every 5 minutes for 2 doses as needed for intravenous access difficulty

AND

☒ imdevimab 300 mg (2.5 mL) subcutaneous every 5 minutes for 2 doses as needed for intravenous access difficulty

Additional Drug Therapy Orders:
☒ lidocaine (Anecream) 1 application topically as needed for line insertion OR
☒ lidocaine (Anecream) 4 applications topically as needed for subcutaneous injections

Nursing Orders:
☒ Insert peripheral IV
☒ Clinically monitor patient during administration and observe patient for at least 1 hour after administration is complete; monitor vital signs at baseline, at end of the administration and 1 hour after administration is completed

Hypersensitivity Orders:
☒ Hypersensitivity Management per University of Kentucky HealthCare Protocol
☒ hydrocortisone _____ *mg (2 mg/kg (max: 100 mg)) intravenous as needed for Grade 2, 3 or 4 infusion reactions
☒ diphenhydramine _____ *mg (1 mg/kg (max: 50 mg)) intravenous as needed for Grade 2, 3 or 4 infusion reactions
☒ famotidine 20 mg (0.5 mg/kg (max: 20 mg)) intravenous as needed for Grade 2, 3 or 4 infusion reactions
☒ albuterol 108 (90 base) mcg/act inhaler 4 puffs as needed for Grade 3 or 4 infusion reactions
☒ epinephrine 0.3 mg intramuscular as needed for Grade 4 infusion reactions

Signature, Referring Provider	Date (MM/DD/YYYY)	Contact Information
Printed Name, Referring Provider	Credentials	License Number

Updated: 09/15/2021

Therapy	Pediatric Infectious Diseases Society Panel Recommendation
Antiviral	
Hydroxychloroquine (or Chloroquine)	• The panel recommends against the use of hydroxychloroquine, alone or in combination with azithromycin, for the treatment of COVID-19, outside of a clinical trial
Lopinavir-Ritonavir	• The panel recommends against the use of lopinavir-ritonavir, along or in combination with ribavirin, except as part of a clinical trial
Immunomodulatory	
General Statement:	*Suggest that immunomodulatory therapy only be used for pediatric patients in the setting of confirmed critical COVID-19* ***with*** *evidence of hyperinflammation. There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients, therefore no guidance can be provided to support the use of one immunomodulatory therapy over another*
Convalescent Plasma	• Use of convalescent plasma in pediatric COVID-19 may be considered as part of the established FDA emergency investigational new drug program
IVIG	• Do not recommend the use of IVIG for treatment of acute COVID-19 in pediatric patients
Tocilizumab (IL-6)	• IL-6 inhibition may be considered in the care of pediatric patients with critical COVID-19, with priority given to clinical trial enrollment if available
Anakinra (IL-1)	• IL-1 inhibition may be considered in the care of pediatric patients with critical COVID-19, with priority given to clinical trial enrollment if available
Interferons	• Type I or Type III interferon should not be used for pediatric COVID-19 patients outside of clinical trials

How is MIS-C treated?

College of Medicine
Office of Medical Education

IVIG

Mild, Moderate or Severe Disease
2 g/kg[a,b] IV (maximum: 100 grams; round to nearest 5 gram vial)
Administration: Infuse over 10 to 12 hours. Adjust titration instructions to ensure appropriate infusion time
Pre-medications (given 30 minutes prior to IVIG) • Acetaminophen 15 mg/kg x 1 (maximum dose: 1000 mg) • Diphenhydramine 0.5 mg/kg x 1 (maximum dose: 50 mg) **Caution:** Due to the risk of infusion related reactions, order IVIG via the order set to ensure a hypersensitivity kit available during administration **Prior to IVIG Administration:** Send serum for freeze and hold for additional testing needs, including serum for Ig Profile
Repeat dose is not recommended due to risk of fluid overload and hemolytic anemia associated with large doses of IVIG.

Methylprednisolone

Mild or Moderate Disease	Severe Disease and/or Refractory to IVIG
Methylprednisolone 2mg/kg (maximum: 80mg) every 24 hours followed by steroid taper over 2 to 3 weeks	Methylprednisolone 30 mg/kg (maximum: 1,000 mg) every 24 hours followed by a steroid taper over 2-3 weeks

Aspirin

Indication	Dose	Contraindications	Duration
• Confirmed MIS-C	Low-Dose: 3 to 5 mg/kg/day (maximum: 81 mg)	• Platelets < 80,000/µL • Actively bleeding or at high risk for bleeding	• Continued until platelet count normalizes and normal coronary arteries are confirmed at ≥ 4 weeks after diagnosis

For patients that do not meet the above criteria, antiplatelet therapy should be tailored to the patient's risk of thrombosis

Anticoagulation *(The use of mechanical VTE prophylaxis is recommended in all MIS-C patients)*

Indication	Agent and Dose	Therapeutic Drug Monitoring	Duration
Prophylaxis: • D-dimer ≥ 5 times the upper limit of normal **OR** • One or more HA-VTE risk factors (see **Appendix C**) **HOLD** anticoagulation if platelet count < 50,000/µL	Enoxaparin: • < 2 months: 0.75 mg/kg SC every 12 hours • ≥ 2 months of age: 0.5 mg/kg SC every 12 hours Heparin: *in setting of renal dysfunction (estimated GFR < 30 mL/min/1.73 m²)* • > 60 kg: 5000 mg SC every 8 to 12 hours • BMI ≥ 40: 7500 mg SC every 8 hours	Anti-Xa 4 hours after the second dose (enoxaparin only) (goal anti-Xa 0.2 to < 0.5 U/mL)	• Discharge prophylactic anticoagulation may be required, if[a]: ○ D-dimer is ≥ 5 times the upper limit (ULN) of normal, within 24 to 36 hours of anticipated discharge **AND** ○ One or more VTE risk factors (see **Appendix D**) • Discharge prophylactic anticoagulation is NOT required, if: ○ D-dimer is < 5 times the ULN, within 24 to 36 hours of anticipated discharge **OR** ○ D-dimer is ≥ 5 times the ULN, within 24 to 36 hours of anticipated discharge AND no VTE risk factors (see **Appendix D**)
Therapeutic: • CAAs present with Z-Score ≥ 10 OR absolute dimension of ≥ 8 mm (+ low dose aspirin) **OR** • Moderate to severe left ventricular (LV) dysfunction (LVEF ≤ 35%) **OR** • Documented thrombosis Modify anticoagulation plan based on platelet count (see **Appendix E**)	Enoxaparin: • < 2 months: 1.5 mg/kg SC every 12 hours • ≥ 2 months of age: 1 mg/kg SC every 12 hours Heparin: *in setting of renal dysfunction (estimated GFR < 30 mL/min/1.73 m²)* • Initiate heparin continuous infusion per institutional protocol	Anti-Xa 4 hours after the second dose (enoxaparin only) (goal anti-Xa 0.5 to 1 U/mL)	• At least 2 weeks post-discharge • Longer duration may be considered in patients with: ○ CAAs with Z-Score > 10 ○ Documented thrombosis ○ Ongoing moderate to severe LV dysfunction

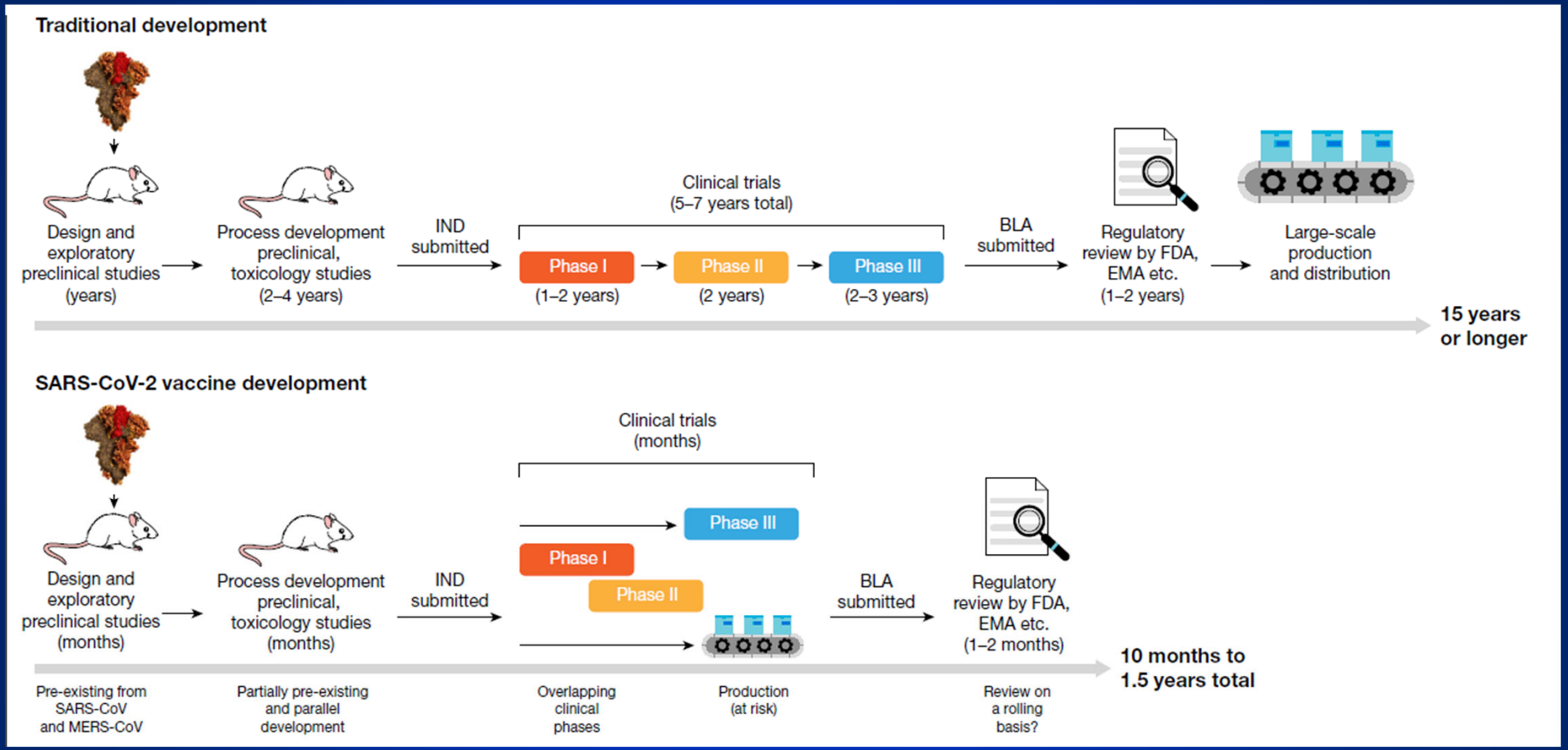
For patients that do not meet the above criteria, anticoagulation therapy should be tailored to the patient's risk of thrombosis

MIS-C Disposition

- Suspicion for MIS-C:
  - Admission/observation for lab and fever trending, echocardiography
    - Ideally to a unit with telemetry
    - Airborne isolation typically not indicated
  - Ideally obtain all tier 1 and 2 labs prior to admission (except echo)
  - Inpatient team to arrange rheumatology and cardiology follow up
- Less suspicion for MIS-C:
  - Return precautions: persistent fever beyond 5 days, new symptoms, worsening of previous symptoms
  - PCP follow up within 48 hours is reasonable

Vaccines: Need to Know

College of Medicine
Office of Medical Education



Krammer, Nature October 22, 2020

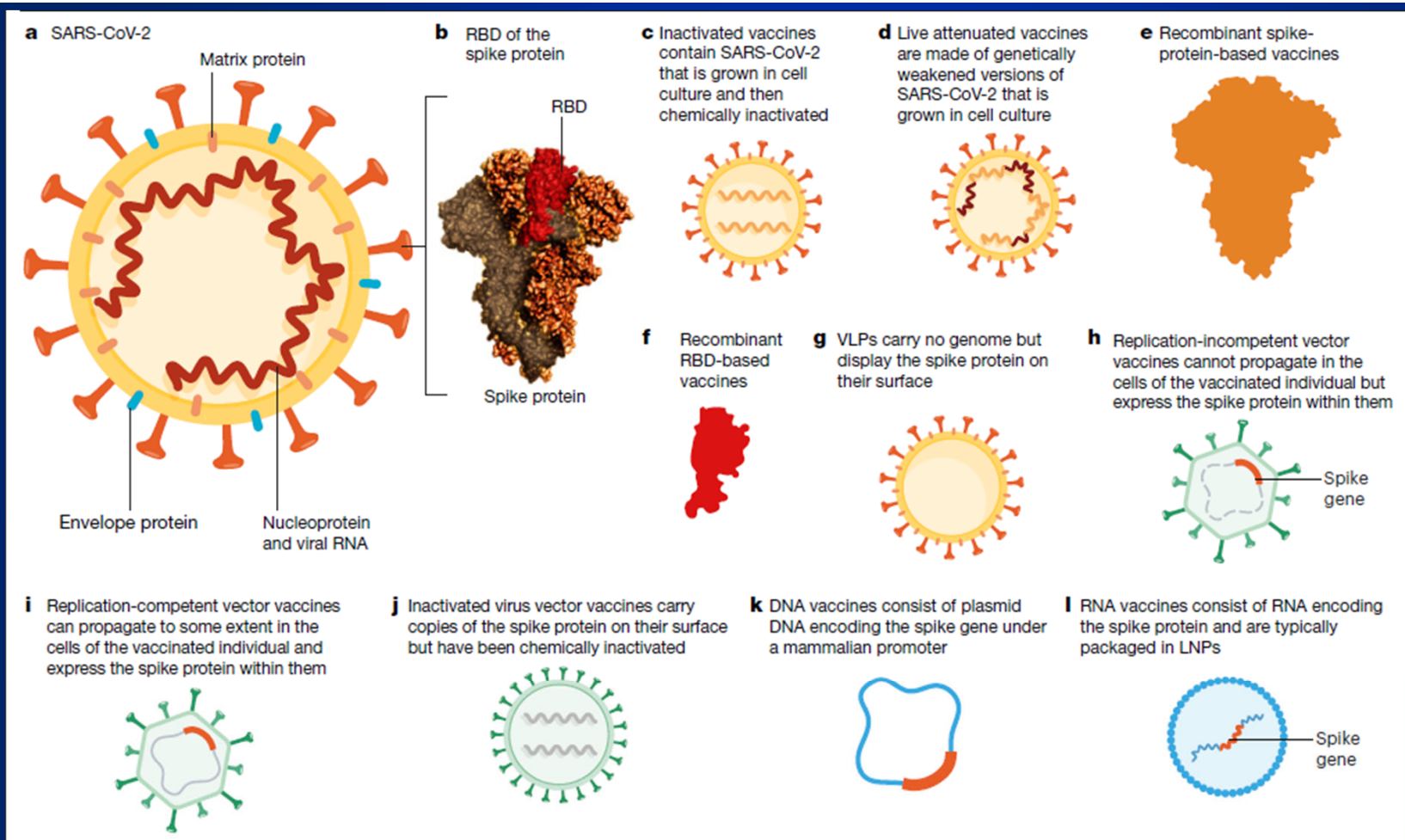


Fig. 3 | Vaccine platforms used for SARS-CoV-2 vaccine development. **a**, A schematic of the structural proteins of the SARS-CoV-2 virion, including the lipid membrane, the genomic RNA covered by the nucleoprotein on the inside, the envelope and matrix proteins within the membrane, and the spike protein on the surface of the virus. **b**, The structure of the spike protein; one monomer is highlighted in dark brown and the RBD is shown in red. **c**–**l**, Current SARS-CoV-2 vaccine candidates include inactivated virus vaccines (**c**), live attenuated vaccines (**d**), recombinant protein vaccines based on the spike protein (**e**), the RBD (**f**) or on virus-like particles (**g**), replication-incompetent vector vaccines (**h**), replication-competent vector vaccines (**i**), inactivated virus vector vaccines that display the spike protein on their surface (**j**), DNA vaccines (**k**) and RNA vaccines (**l**).

Krammer, Nature October 22, 2020

Pfizer Pediatric Timeline

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
>55 years	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7).

Complications of Pfizer vaccination

- Myocarditis and Pericarditis
  - Symptoms: Chest pain, shortness of air, fast-beating/fluttering heart
  - Within several days of vaccination
  - More common in males (Incidence 1 in 5,000 in 16-17 yo males)
  - More common after second dose
  - Not seen in children under 12 so far (Smaller numbers)
  - Suspected cases should be reported to VAERs
  - Inpatient management and follow up per cardiology
  - Most cases respond quickly to therapy. Long term outcomes pending.

Vaccine Hesitancy in the ED

- Up 1/3 of non-COVID ED patients report vaccine hesitancy
- Highest vaccine hesitancy rates in Black race and young age (18-24)
  - Prompt: “I like to give all my patient’s the opportunity to ask questions about COVID vaccination, do you have any?”
  - Response:
    - “I hope that you trust me when I say that I care about you. I trust the vaccine is effective and the review process was enough, and it is my personal and professional medical opinion that the benefits of the vaccine outweigh the risk for you” (~15 seconds)
    - “I have gotten the vaccine for myself and I will get it for my children when it’s available to them.” (~5 seconds)

Questions?

College of Medicine
Office of Medical Education

Michael Brook

Passed away on
April 2, 2020 from COVID-19

Dr. John Reed

Passed away on
November 22, 2020 from COVID-19