

Prevention SIG Webinar Series

Welcome! We will begin shortly.

“Update 2022: COVID-19, Multisystem Inflammatory Syndrome in Children, and the Heart”



Jane W. Newburger, M.D., M.P.H.

Associate Cardiologist-in-Chief for Academic Affairs, Boston Children's Hospital;
Commonwealth Professor of Pediatrics, Harvard Medical School

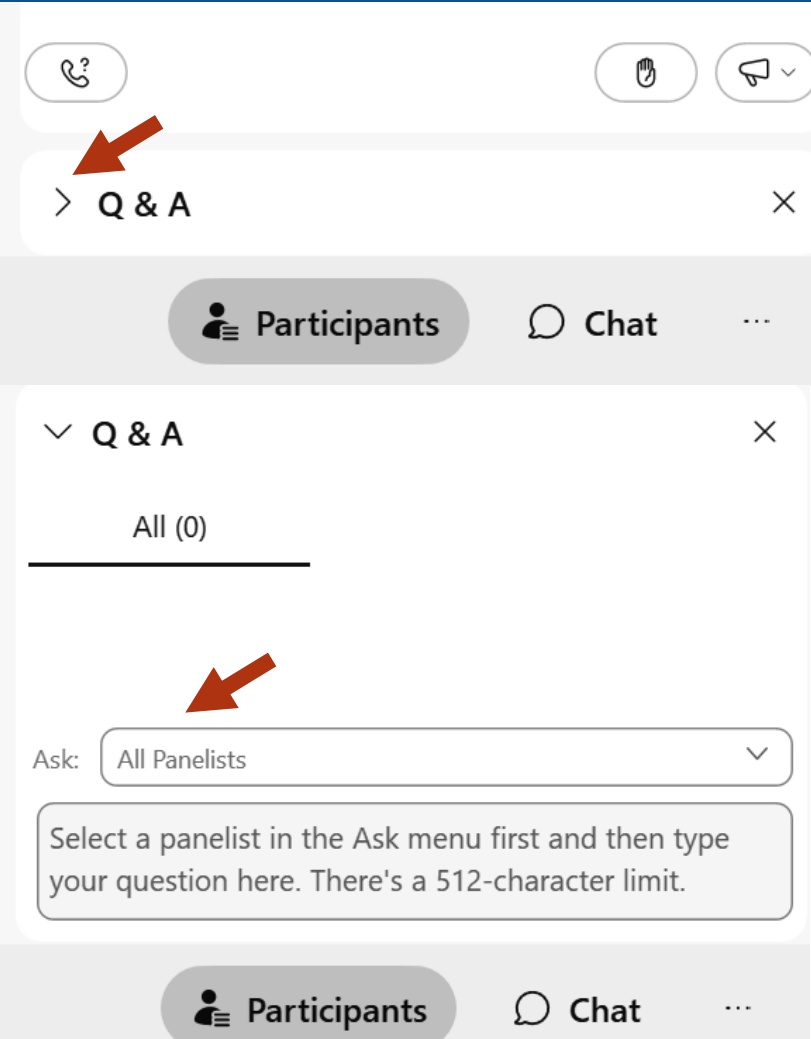


Dongngan Truong, M.D., M.S.

Associate Professor of Pediatrics, The University of Utah and Primary Children's Hospital

Introduction by Victoria Pemberton, M.S., RNS, CCRC, Program Officer, NHLBI/PHN

Prevention SIG Webinar Series



Upcoming Q & A Session

Please send us your questions via the
Q & A pod directed to All Panelists

You may use the Chat pod for general commentary or to
request technical assistance

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“Update 2022: COVID-19, Multisystem Inflammatory Syndrome in Children, and the Heart”



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Prevention SIG Webinar Series
January 26, 2022

Update 2022: COVID-19, the Multisystem Inflammatory Syndrome in Children, and the Heart

Jane W. Newburger, M.D., M.P.H.

Boston Children's Hospital

Dongngan T. Truong, M.D., M.S.C.I.

University of Utah and Primary Children's Hospital

Disclosures and Conflicts of Interest (COI)

- Jane Newburger:
 - Grant Support: NIH, CDC
 - Co-PI for Planned NHLBI Pediatric Heart Network-Pfizer Partnership to Study Vaccine-Associated Myocarditis after COVID-19 Vaccine
 - Chair, Independent Events Adjudication Committees for trials sponsored by Bristol-Myers Squibb, Pfizer, Novartis
 - Member, Steering Committee, Enoble Trial (sponsor: Daiichi Sankyo)
- Dongngan Truong:
 - Grant Support: NIH
 - Co-PI for Planned NHLBI Pediatric Heart Network-Pfizer Partnership to Study Vaccine-Associated Myocarditis after COVID-19 Vaccine

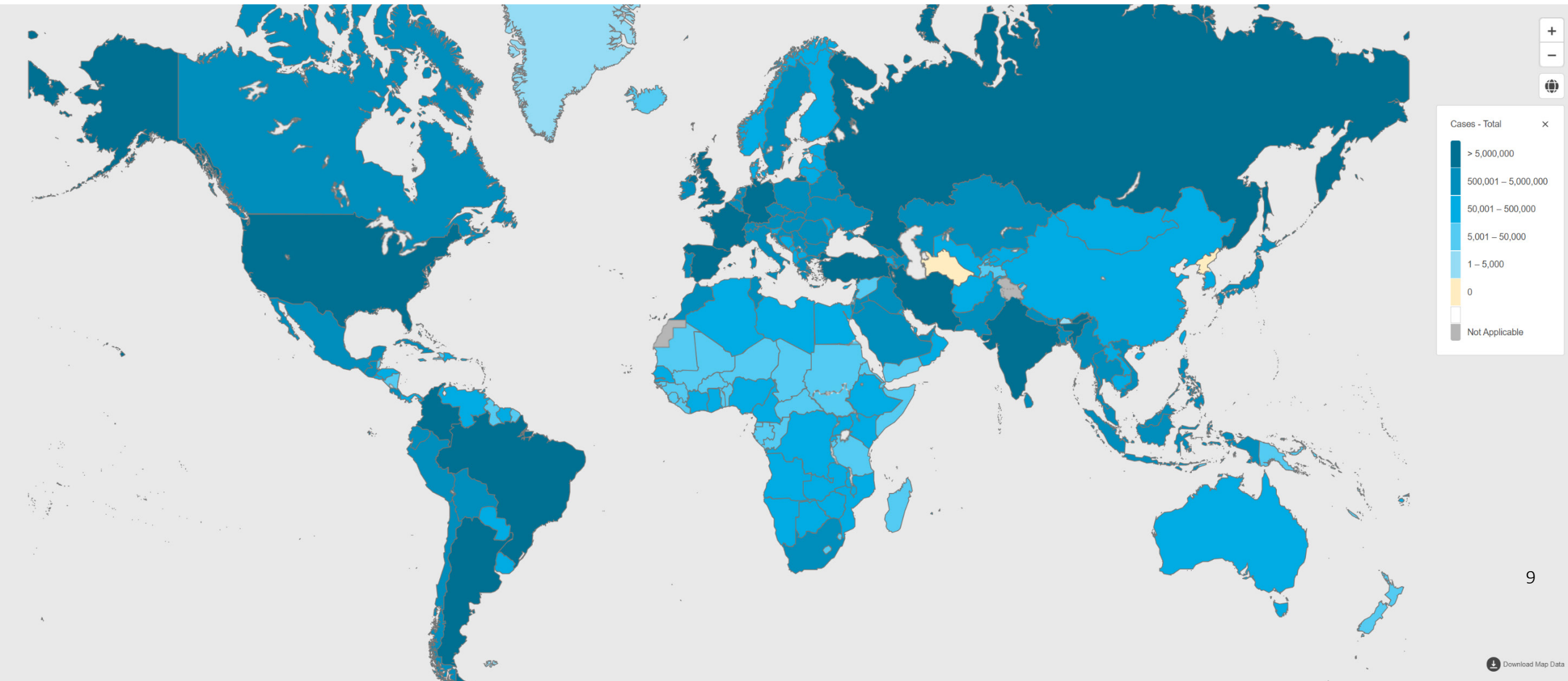
Learning Objectives

- Review the epidemiology of COVID-19 and MIS-C in children.
- Identify the cardiovascular manifestations and management of MIS-C.
- Review the NHLBI MUSIC study.
- Review the current understanding of myocarditis temporally related to COVID-19 vaccination

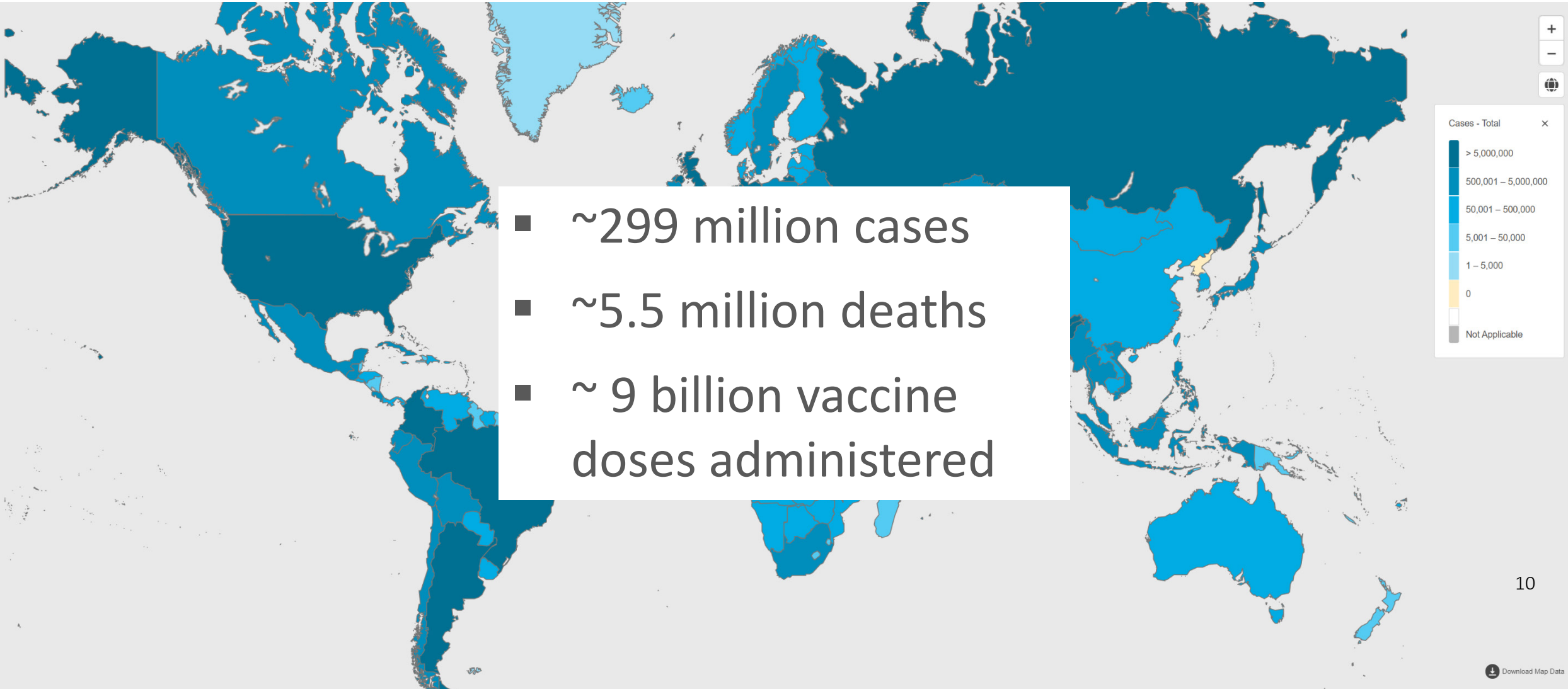




WHO MAP JAN 7, 2022

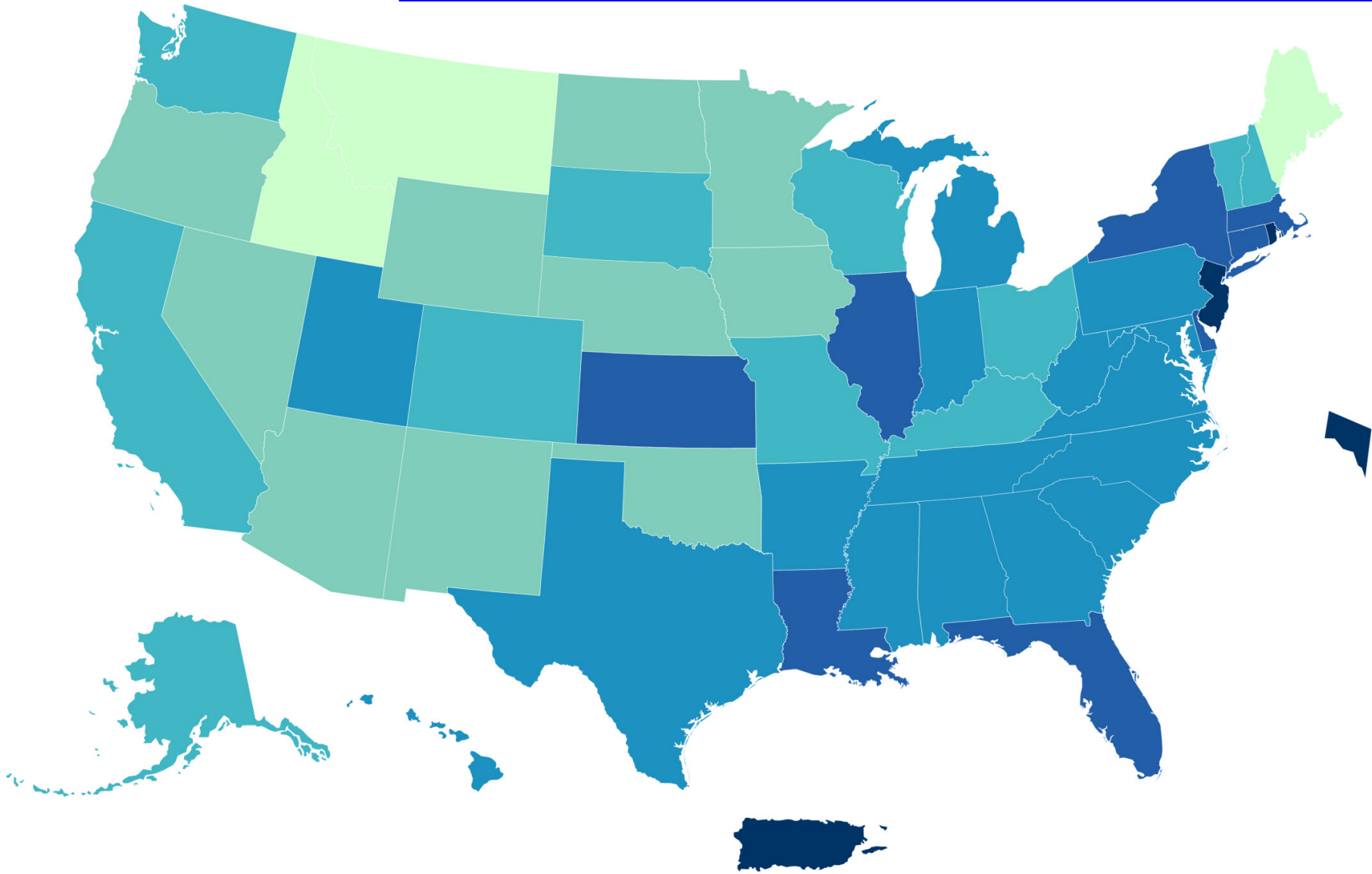


WHO MAP JAN 7, 2022



Burden of COVID-19 Among Children (12/30/21)

- Positive US cases in children: **~7.9 million**
- COVID-19 is much milder in children than adults:
 - **17%** of confirmed cases since pandemic onset
 - **18%** of confirmed cases in last week.
 - **10,484 cases per 100,000** children in the population
 - **0.1% - 1.6%** of children with COVID-19 are hospitalized
- Mortality rate in children 0.00% to < 0.02% in state reporting



7-Day Case Rate per 100,000

0 - 490.9 635.1 - 965.7 1.0k - 1.2k 1.2k - 1.5k 1.6k - 2.0k 2.2k - 3.2k



Original Investigation | Pediatrics

Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children

Lyudmyla Kompaniyets, PhD; Nickolas T. Agathis, MD; Jennifer M. Nelson, MD; Leigh Ellyn Preston, DrPH; Jean Y. Ko, PhD; Brook Belay, MD; Audrey F. Pennington, PhD; Melissa L. Danielson, MSPH; Carla L. DeSisto, PhD; Jennifer R. Chevinsky, MD; Lyna Z. Schieber, DPhil, MD; Hussain Yusuf, MD; James Baggs, PhD; William R. Mac Kenzie, MD; Karen K. Wong, MD; Tegan K. Boehmer, PhD; Adi V. Gundlapalli, MD, PhD; Alyson B. Goodman, MD

Abstract

IMPORTANCE Information on underlying conditions and severe COVID-19 illness among children is limited.

OBJECTIVE To examine the risk of severe COVID-19 illness among children associated with underlying medical conditions and medical complexity.

Key Points

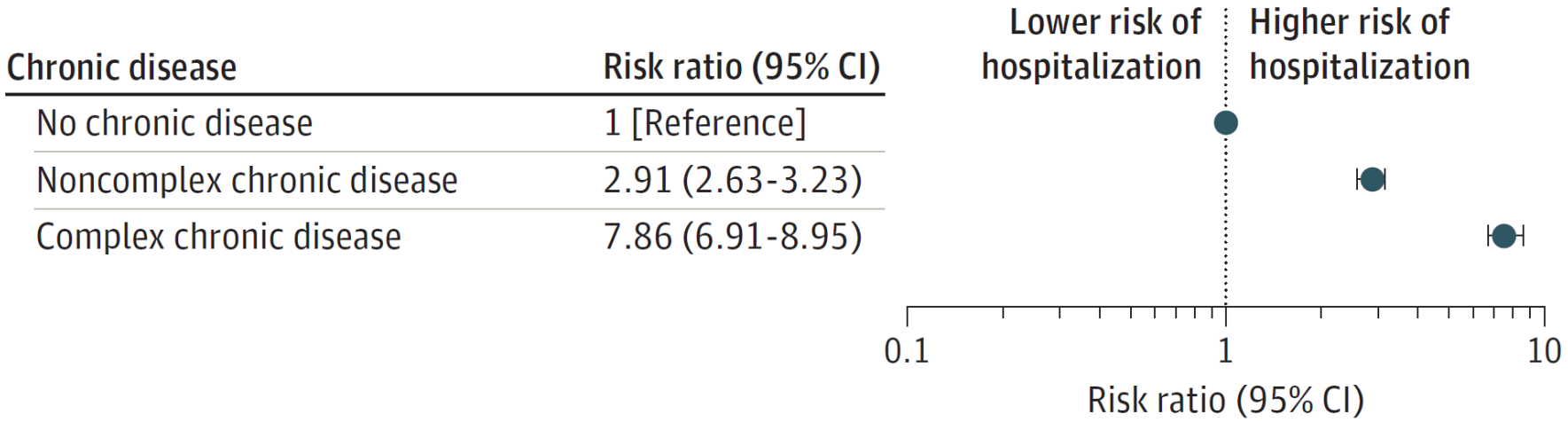
Question Among children with a COVID-19 diagnosis, what conditions are common, and which are associated with severe COVID-19 illness?

13

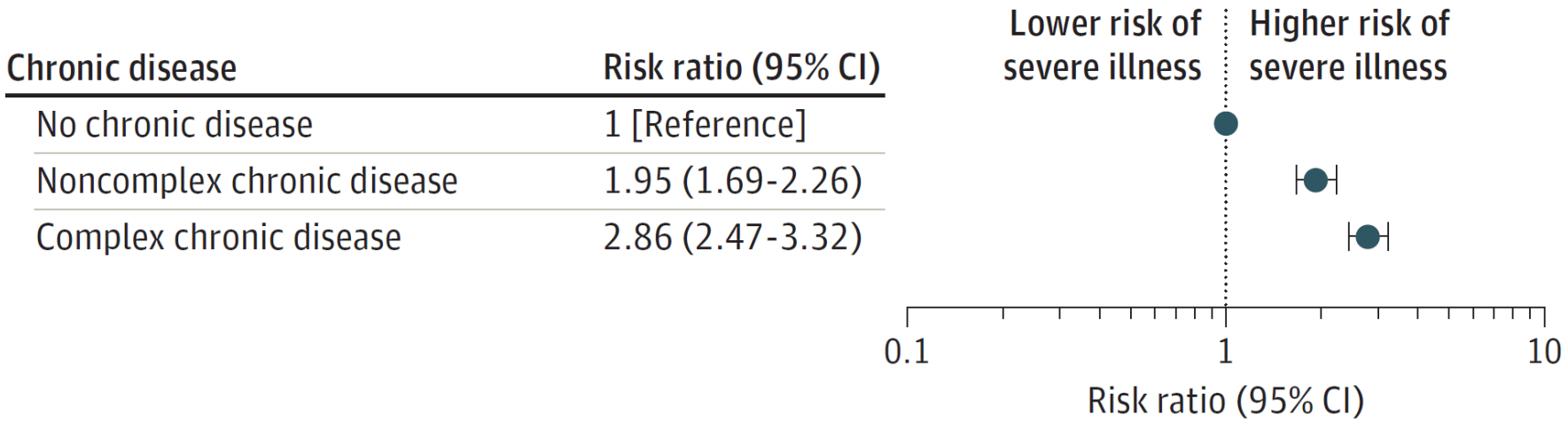
Findings In this cross-sectional study of 42 465 patients aged 18 years or

Figure 2. Association Between Medical Complexity and Risk of Hospitalization or Severe Illness When Hospitalized in the Sample
Kompaniyets et al, JAMA Open, 2021

A Hospitalization



B Severe illness when hospitalized

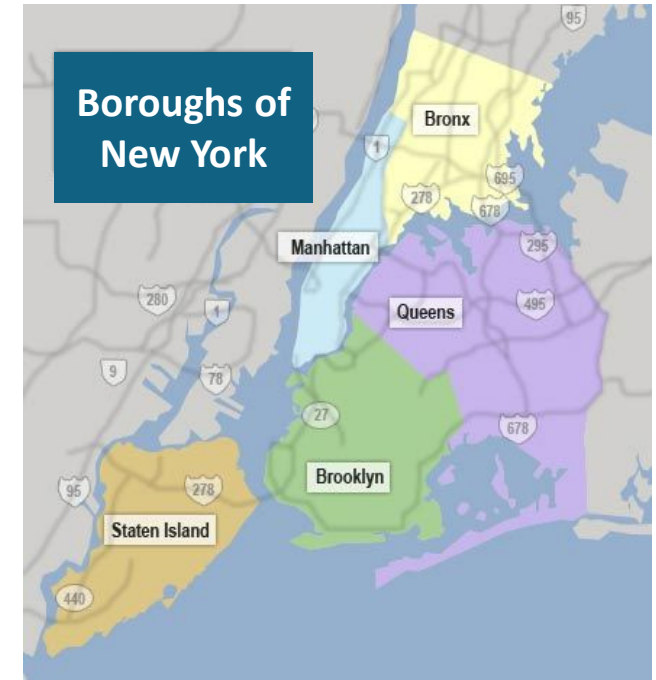


The Emergence of a New Syndrome in Children

April-May 2020 – Worldwide Alert



March 2020

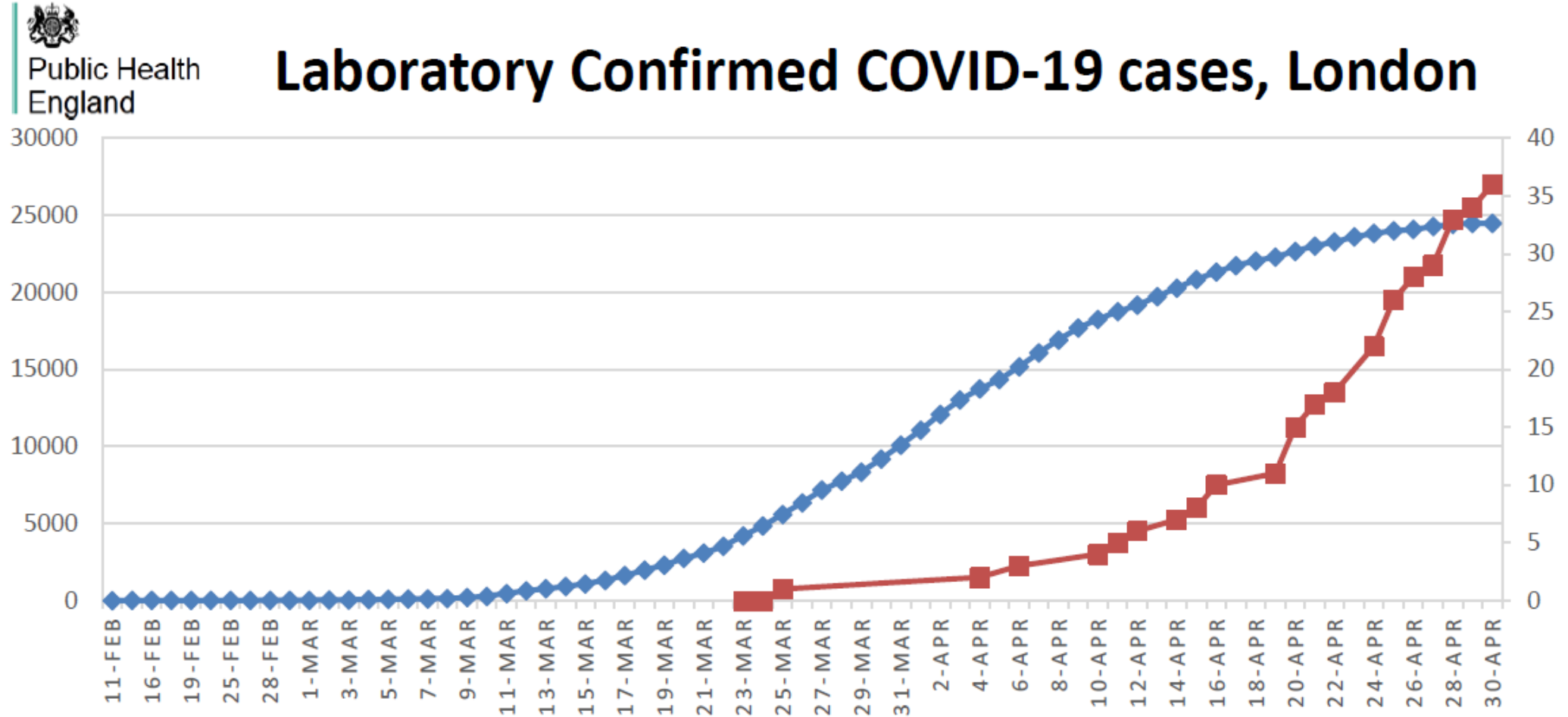


April 2020

CDC Case Definition for Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (MIS-C)

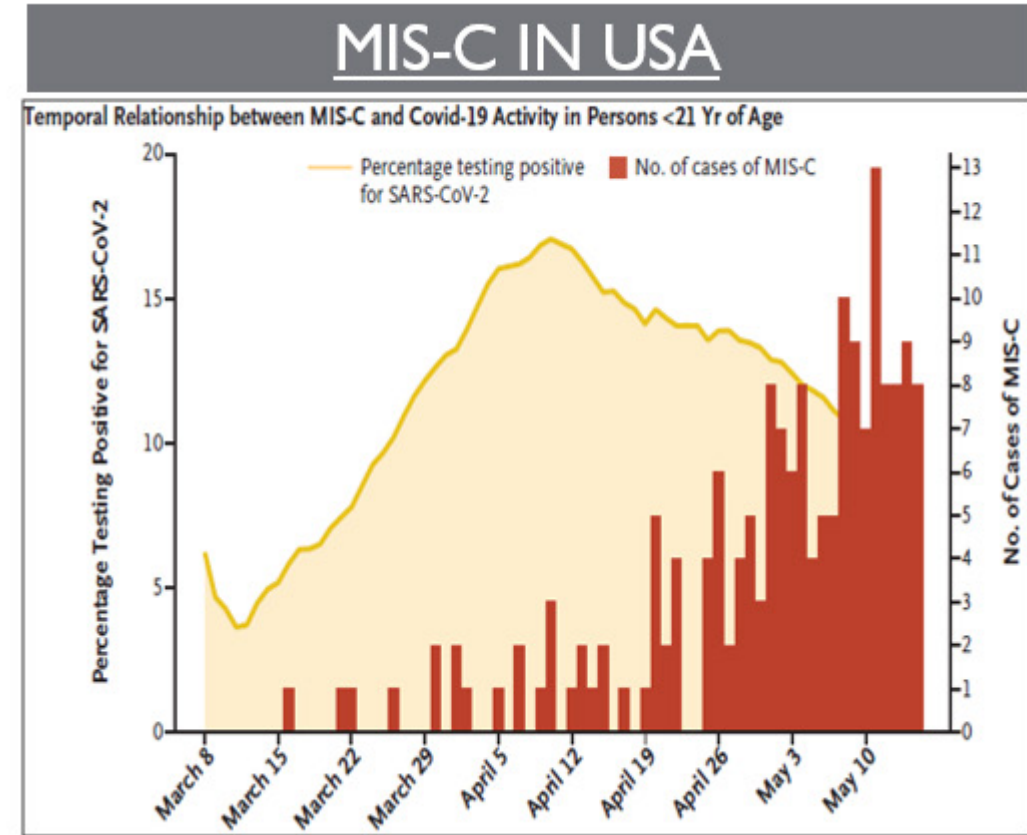
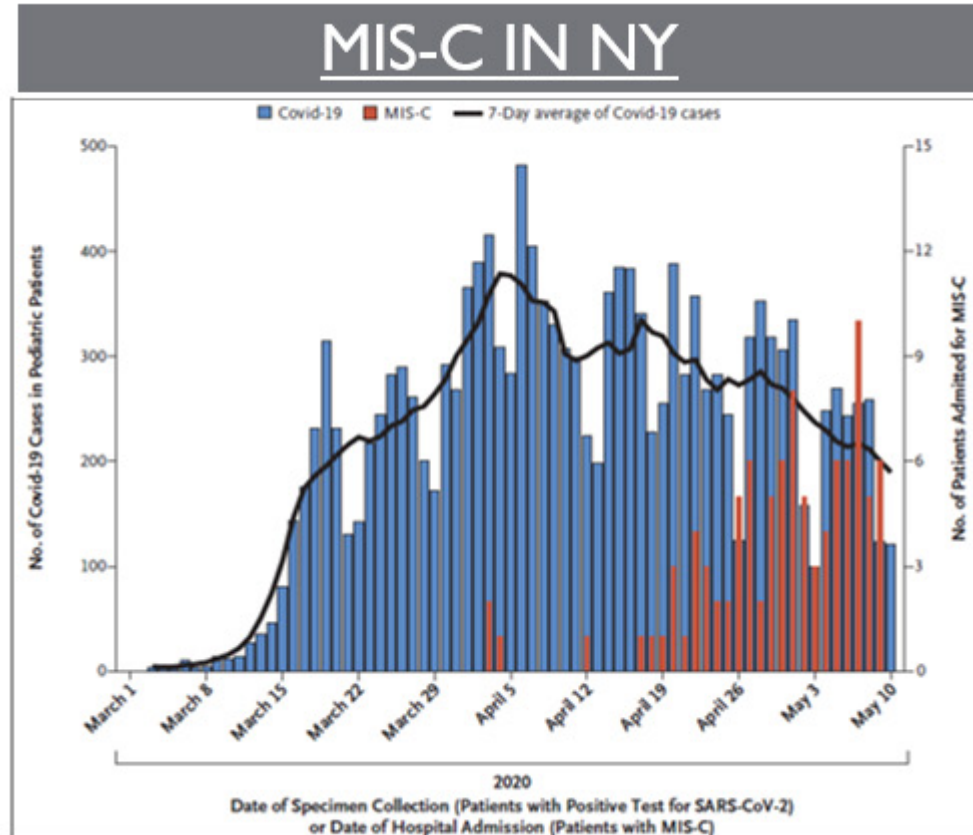
- Age **<21 years**
- **Fever** $\geq 38^{\circ}$ C for ≥ 24 hours
- Laboratory evidence of **inflammation**
- Evidence of clinically severe illness requiring **hospitalization**, with **multisystem (≥ 2) organ involvement** based on clinical judgment from record review, discharge dx, lab or diagnostic tests.
- Positive for **current or recent SARS-CoV-2 infection** by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms
- No plausible alternative explanation.

TIMING OF MIS-C IN RELATION TO COVID-19



Dr. Mike Levin, Imperial College London

TIMING OF MIS-C IN RELATION TO COVID-19



MIS-C

CDC Update, 01/03/22

- Number of cases: 6,431
- Total deaths: 55 (0.9%)
- Percent male: 61%
- + test for SARS-CoV-2: 98%
- Half between ages 5 -13 years

Race/Ethnicity	%
Hispanic/Latino	27.4%
Black Non-Hispanic	31.9%
White Non-Hispanic	32.5%
Other Non-Hispanic	3.5%
Asian Non-Hispanic	2.6%
Multiple Races, Non-Hispanic	<1.0%
American Indian/Alaskan Native	<1.0%
Native Hawaiian/Pacific Islander	<1.0%



Original Investigation | Public Health

Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2

Amanda B. Payne, PhD, MPH; Zunera Gilani, PhD, MPH; Shana Godfred-Cato, DO; Ermias D. Belay, MD; Leora R. Feldstein, PhD; Manish M. Patel, MD;

- Population incidence: 5.1 per 1 million person-months
- Compared with White persons, higher rate in
 - Black persons: aIRR = 9.26
 - Hispanic/Latino: aIRR = 8.92
 - Asian/Pacific Islander: aIRR = 2.94



Original Investigation | Public Health

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 - Black persons: aIRR = 9.26
 - Hispanic/Latino: aIRR = 8.92
 - Asian/Pacific Islander: aIRR = 2.94
- MIS-C incidence: 316 per million SARS-CoV-2 infections
- Compared with White persons, higher rate in
 - Black persons: aIRR = 5.62
 - Hispanic/Latino: aIRR = 4.26
 - Asian/Pacific Islander: aIRR = 2.88

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

Published online June 29, 2020

186 Cases Reported to CDC, March 15 – May 20, 2020

OVERCOMING
COVID-19

Treatment

Intravenous Immunoglobulin (IVIg)	77%
Second dose IVIg	21%
Systemic Steroids	49%
IL-6 Inhibitors (tocilizumab and siltuximab)	8%
IL-1Ra Inhibitor (anakinra)	13%
Systemic Anticoagulation	47%

Highest Level of Care

Ward	20%
Intensive Care Unit	80%
Intensive Care Interventions	
ECMO ⁹	4%
Mechanical Ventilation	20%
Vasoactive Support	48%

Outcomes

Median Hospitalization	7 days
Still Hospitalized May 20, 2020	28%
Discharged Alive	70%
Died	2%

Symptoms Vary According to Age Group

Symptom Category	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Dermatologic or mucocutaneous	87.1	78.6	61.5
Gastrointestinal	74.2	83.3	80.8
KD or atypical KD	48.4	42.9	11.5
Myocarditis	38.7	50.0	73.1
Neurologic	12.9	38.1	38.5

Percent of Patients

0 to 38.4 38.5 to 46.2 46.3 to 66.1 66.2 to 79.0 79.1 to 100

Symptoms Vary According to Age Group

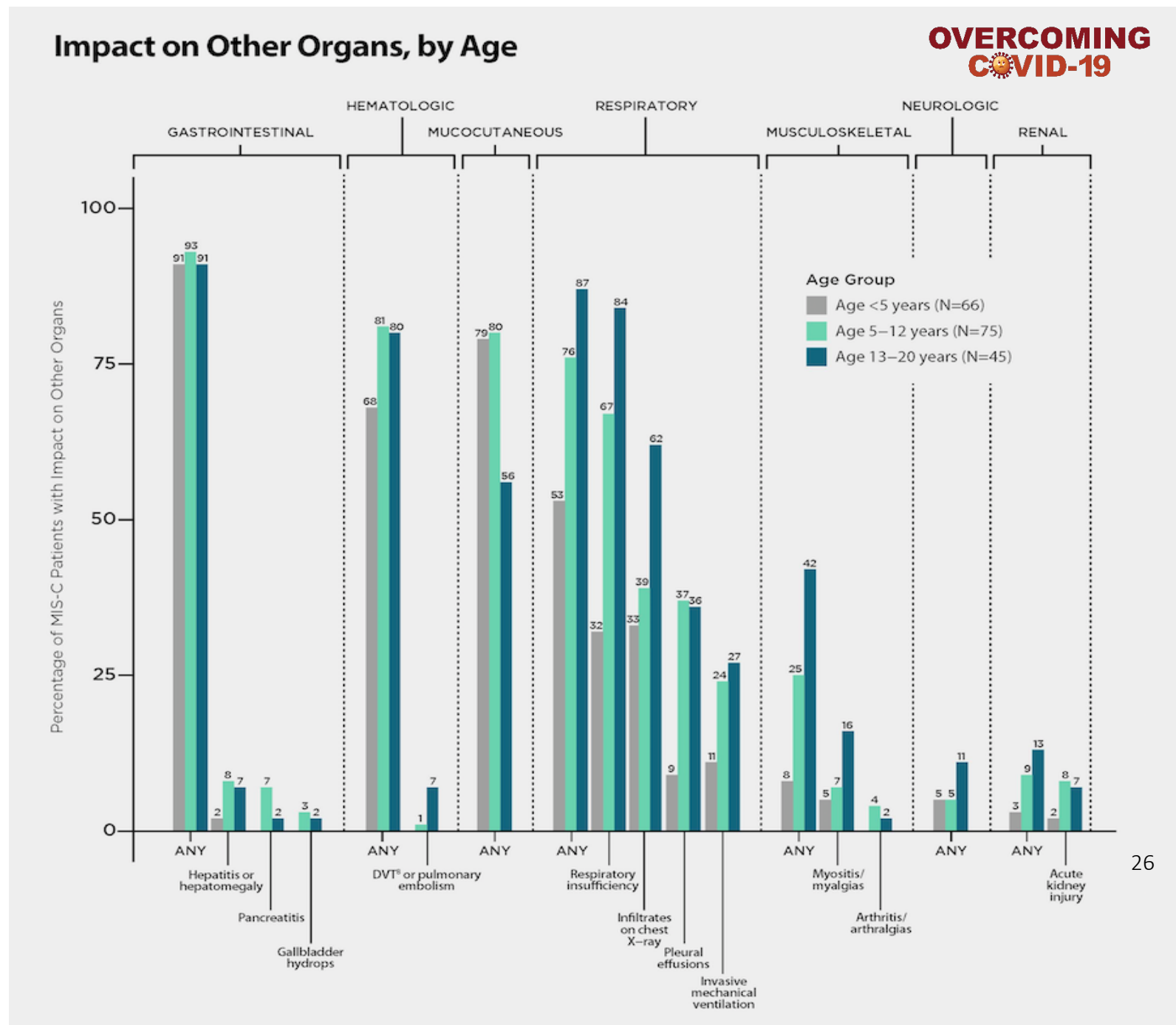
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Percent of Patients

0 to 38.4 38.5 to 46.2 46.3 to 66.1 66.2 to 79.0 79.1 to 100

Non-Cardiovascular Involvement

- Gastrointestinal symptoms
- Hematologic symptoms
- Coagulopathy
- DVT/PE
- Mucocutaneous
- Respiratory symptoms
- Musculoskeletal
- Neurologic complications
- Guillain Barré
- ADEM

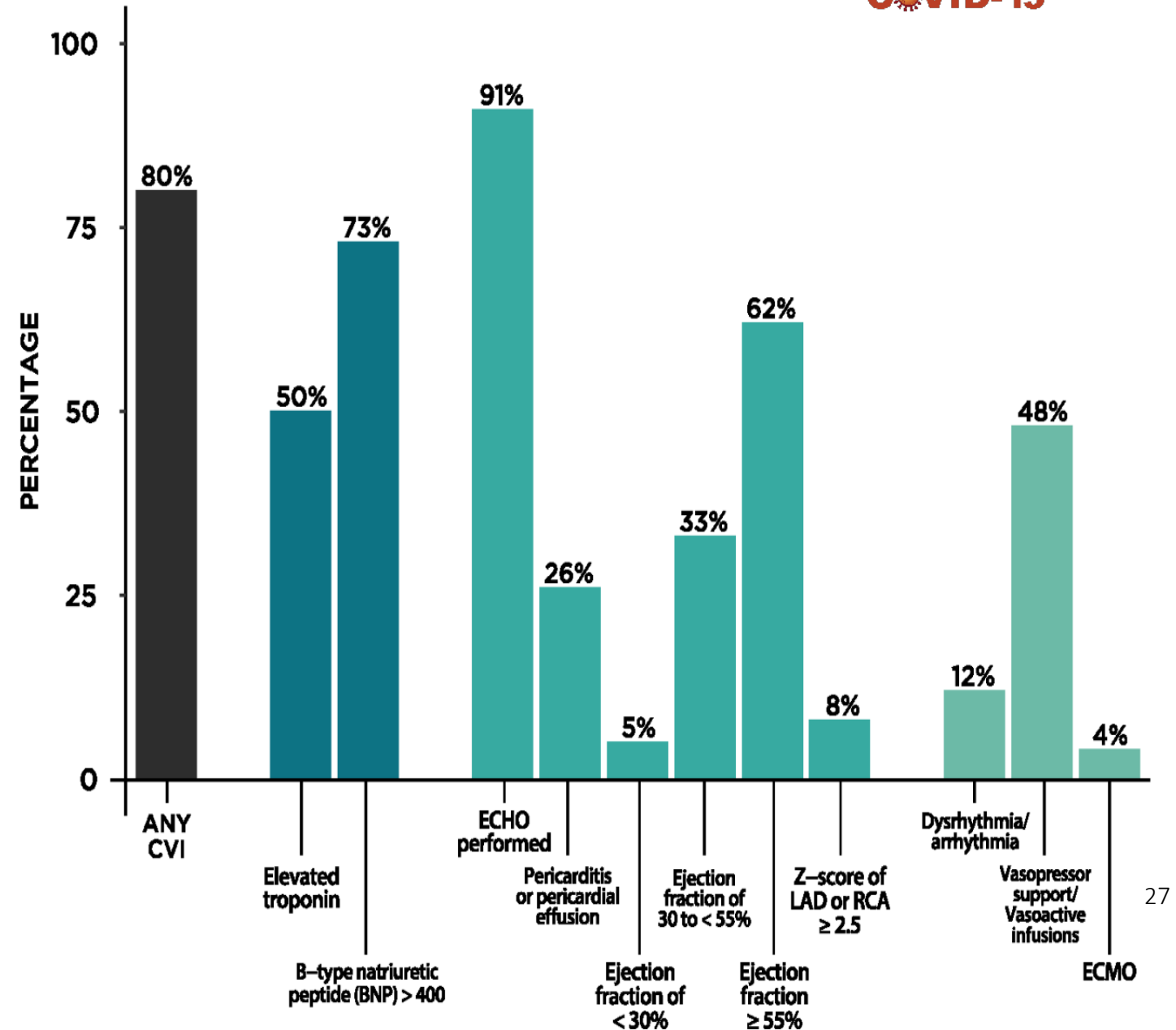


Cardiovascular Involvement

- Any cardiovascular involvement: 80%
- Elevated troponin: 50%
- BNP > 400: 73%
- LV ejection fraction < 55%: 38%
- Coronary aneurysms ≥ 2.5 : 8%
- ECMO: 4%

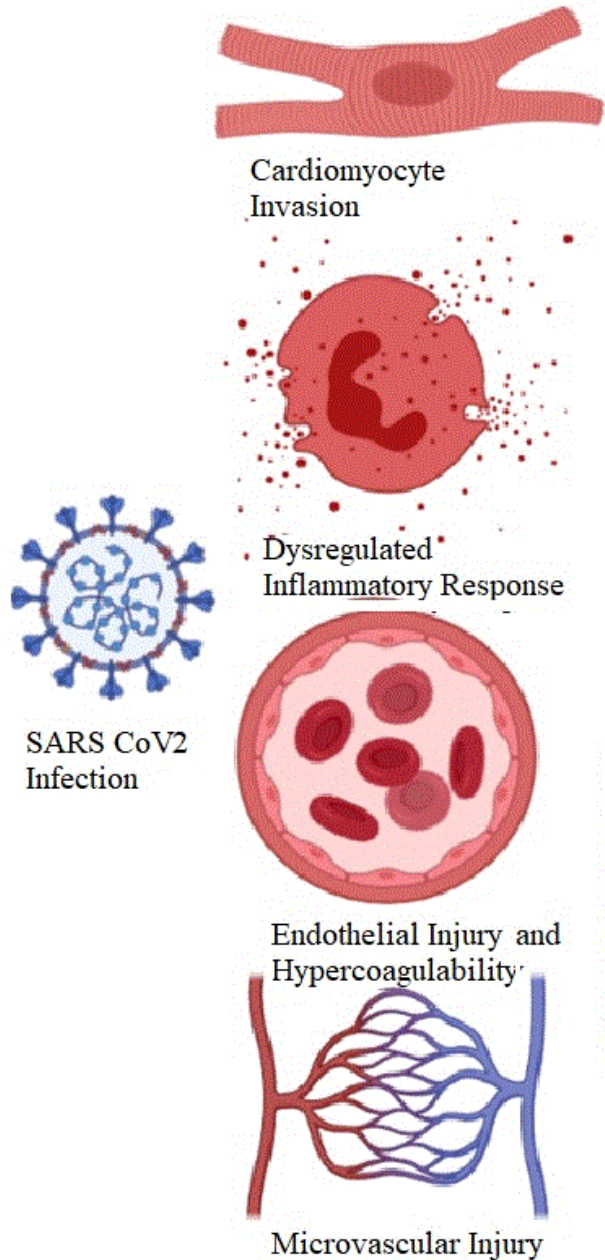
Feldstein LR, NEJM, 2020

OVERCOMING
COVID-19

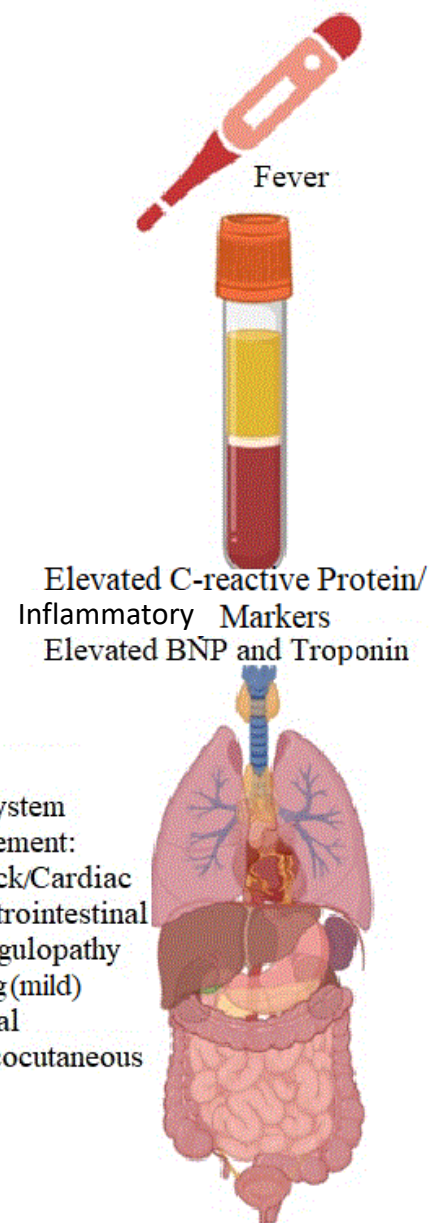


Multisystemic Inflammatory Syndrome in Children

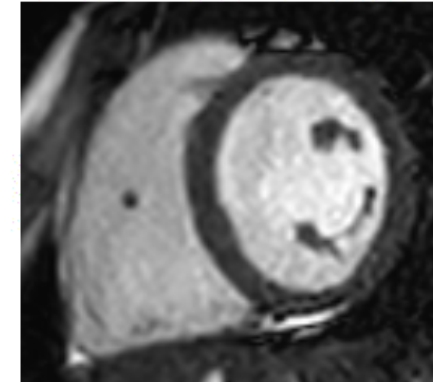
Pathophysiology



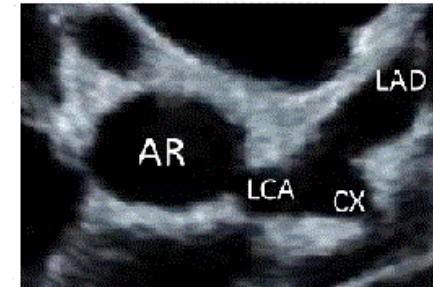
Clinical Manifestation



Cardiac Manifestation



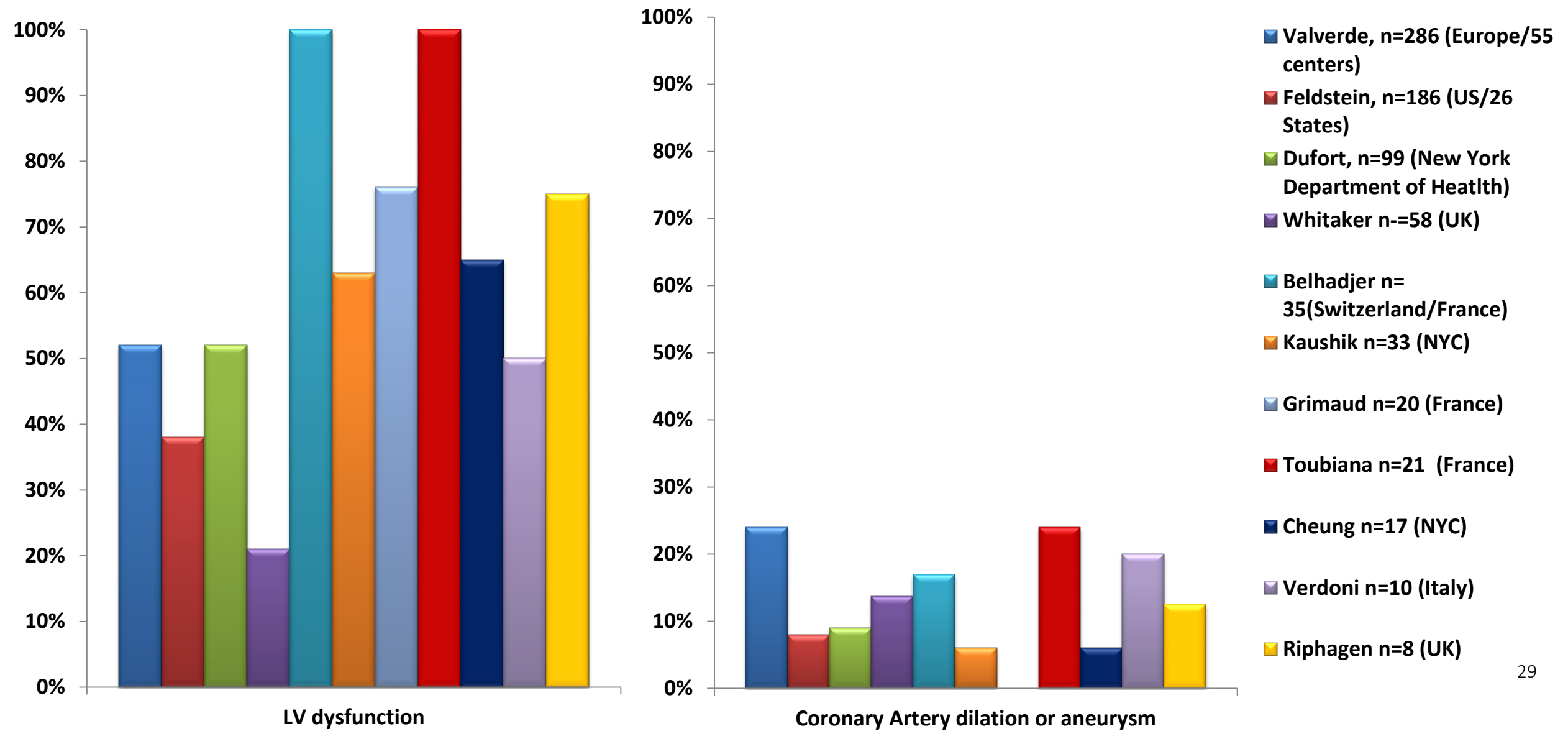
Ventricular Dysfunction



Coronary Dilation and Aneurysms

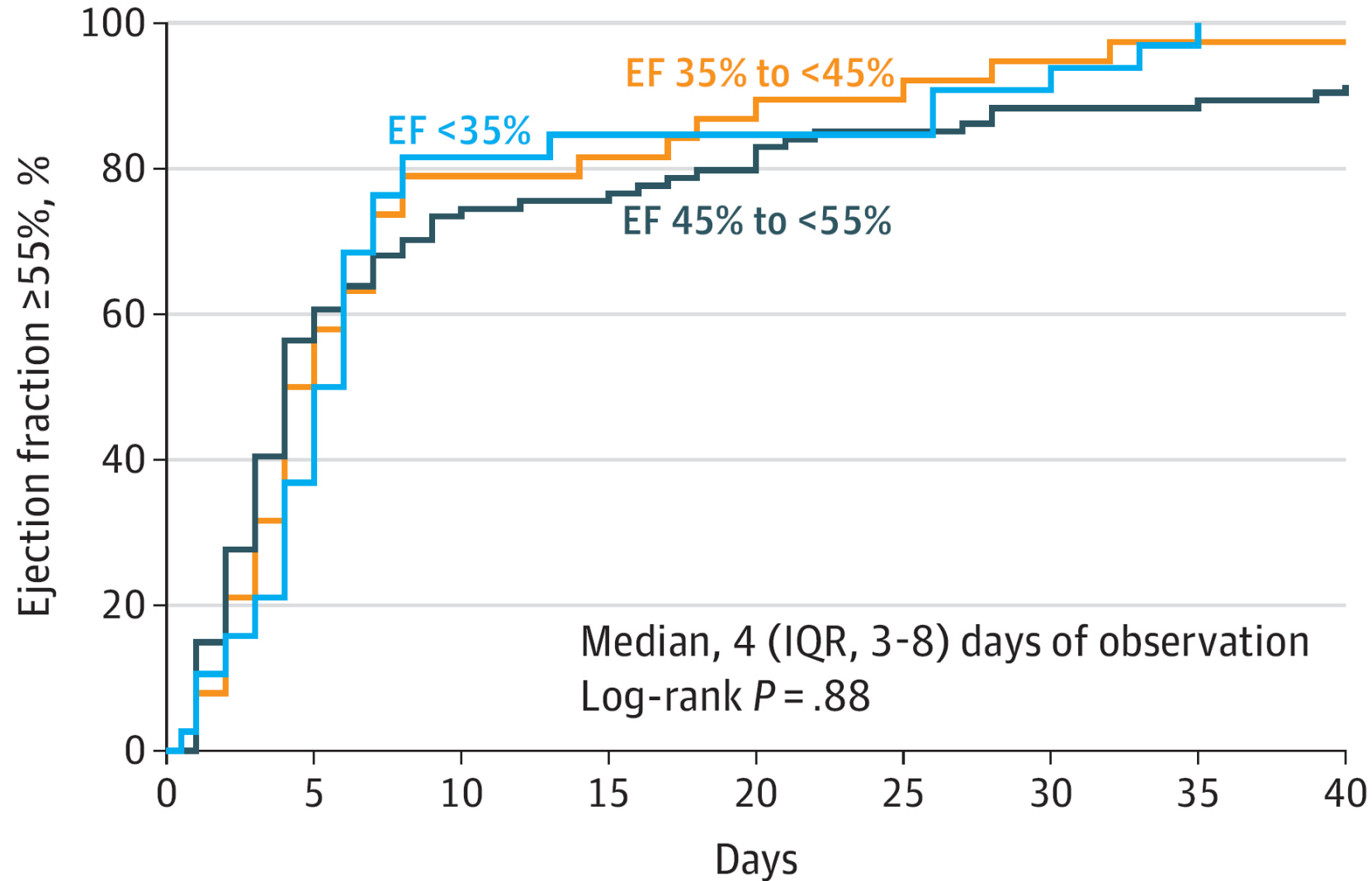


EKG and Conduction Abnormalities



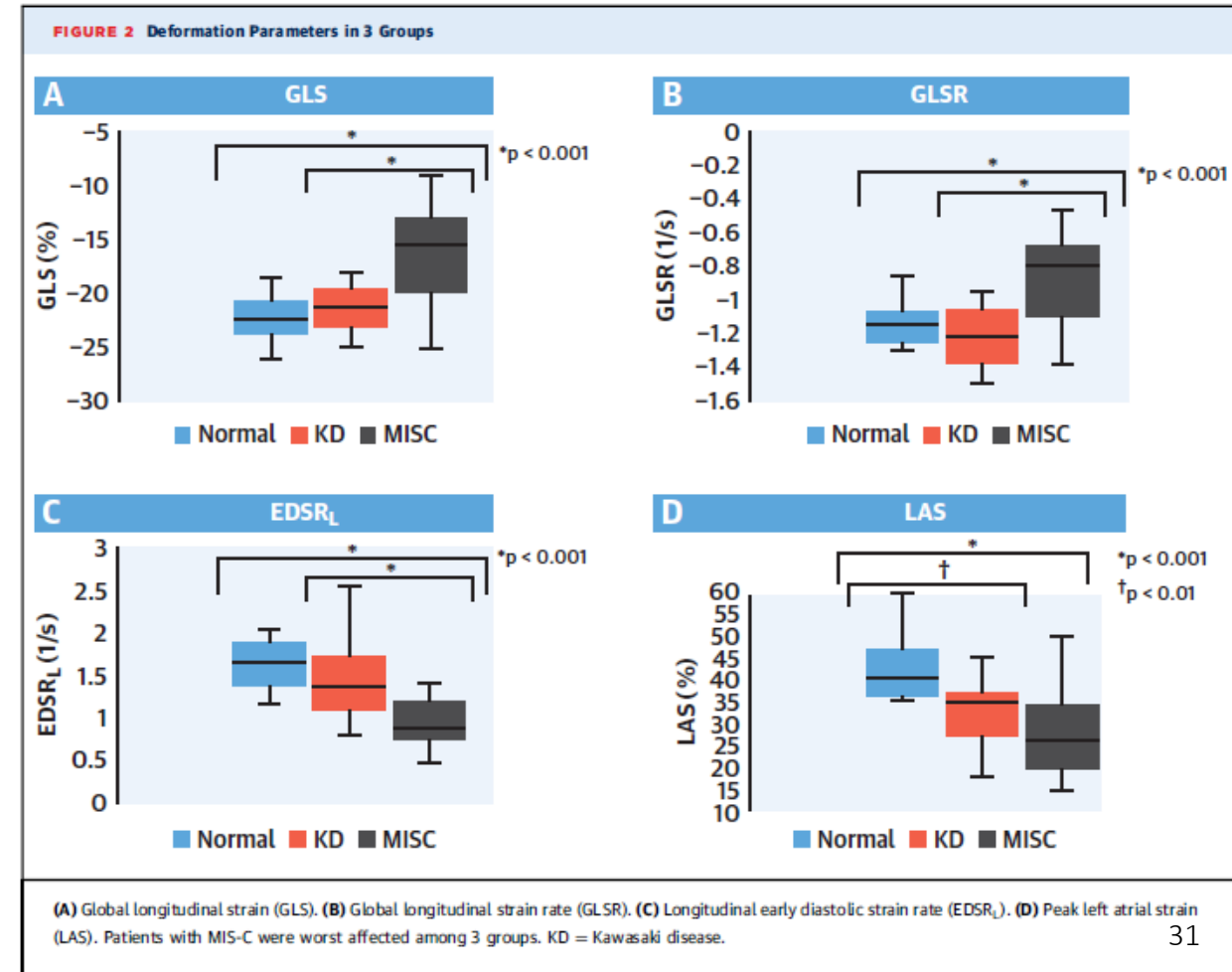
Resolution of decreased left ventricular ejection fraction

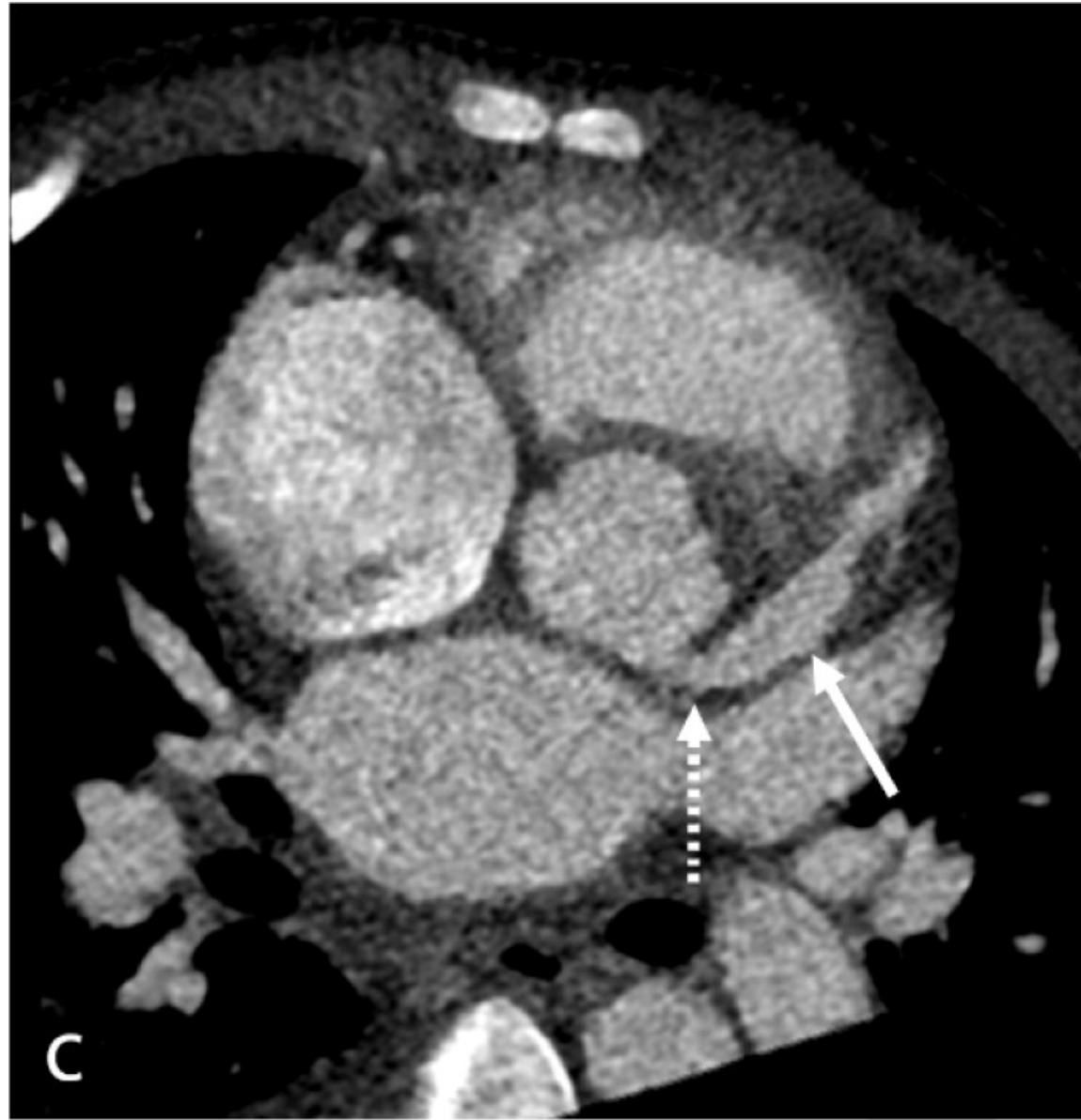
172/503 pts, 34.2%



Diastolic Dysfunction

- 28 patients with MIS-C, 20 healthy control, 20 Kawasaki disease patients
- Diastolic dysfunction was found in all MIS-C patients, even those with normal systolic function
- Patients with myocardial injury (elevated troponin) were more affected
- Diastolic dysfunction persisted after normalization systolic function

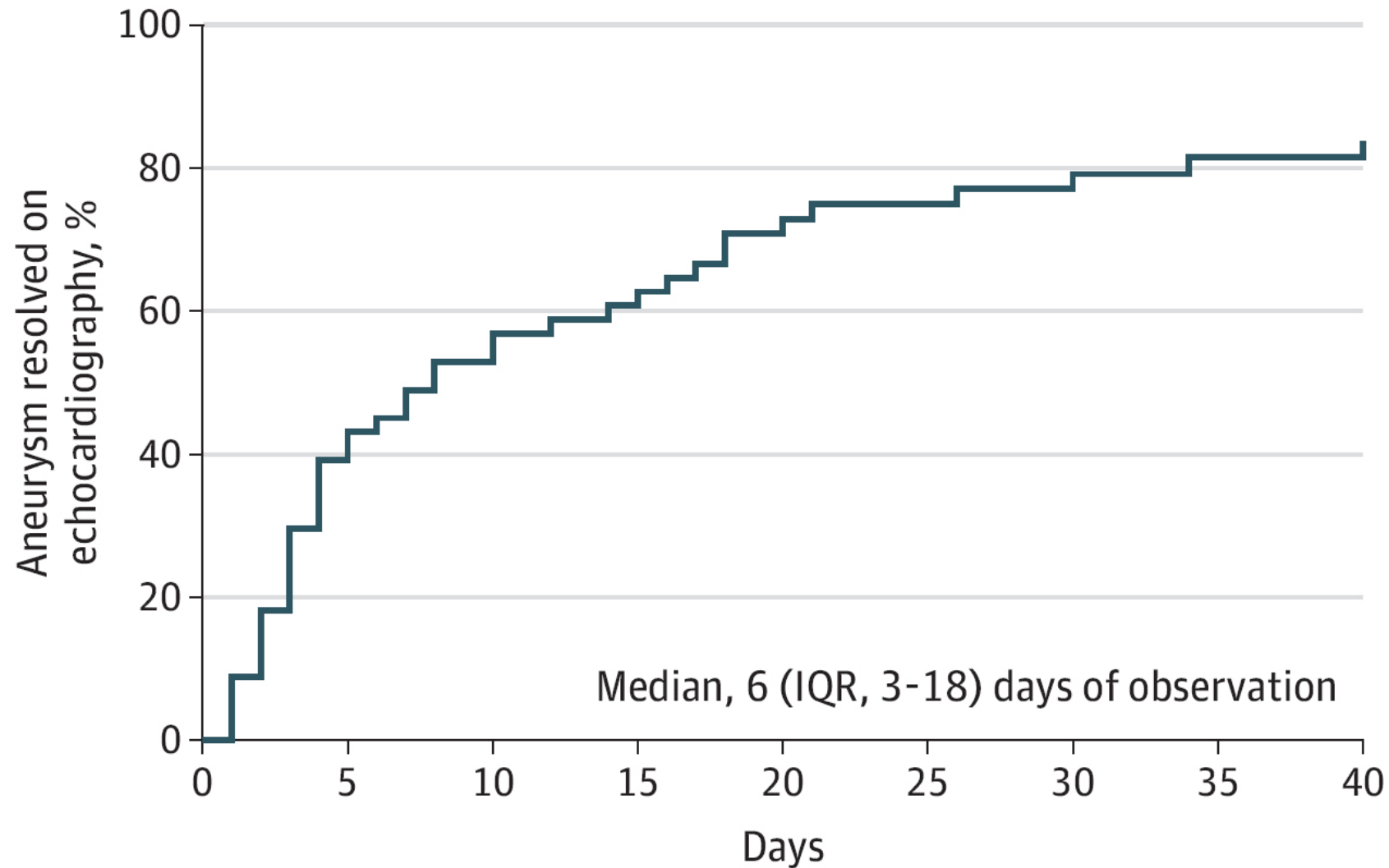




Hameed et al, Radiology, 2020

Resolution of coronary artery aneurysms

57/424 pts, 13.4%



Cardiac MRI after MIS-C (20 patients)

- Mean time to CMR 20 days (range 11-29 days)
- Myocardial edema in 10 patients (50%)
 - Global increase T2 weighted imaging most common (n=6), followed basal septal segments (n=3)
 - Global MR strain analysis demonstrated impaired systolic strain indices in all pts
- Myocardial scar with late gadolinium enhancement in 1 patient (5%)
- EF and strain did not correlate with persistent myocardial edema, scarring, age or timing presentation

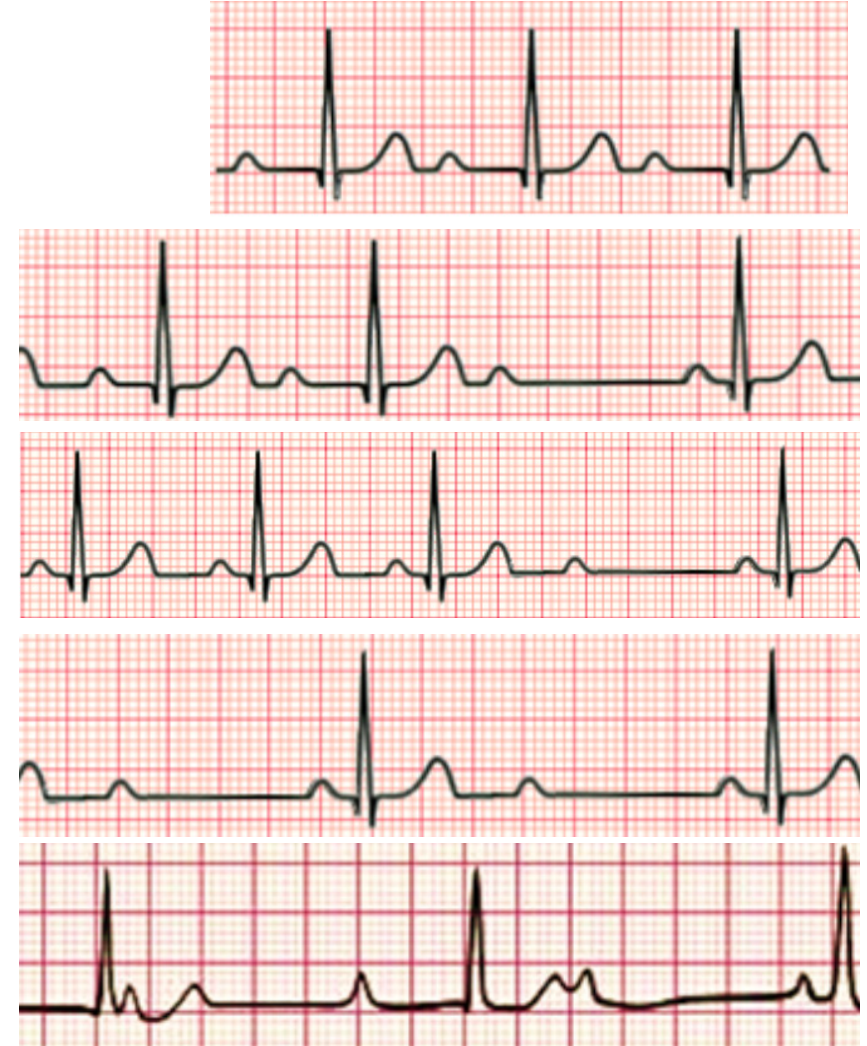


Figure 3 MRI: short axis view of the left ventricle showing late gadolinium enhancement imaging (indicated by arrow) of a transmural myocardial infarction.

Theocharis et al, Eur Heart J Cardiovasc Imaging, 2020

Arrhythmias and ECG changes

- 7-60% patients with MIS-C
- ECG changes
 - Non-specific ST segment changes
 - Prolonged QTc interval
- Atrial arrhythmias
 - Atrial ectopy
 - Atrial fibrillation
- Ventricular arrhythmias
 - Ventricular ectopy
 - NSVT/VT, some requiring resuscitation and ECMO
- AV block
 - 1st, 2nd, 3rd degree AV block
 - Often preceded by PR prolongation



How do we manage MIS-C?

Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children

- French consortium studied 111 children with MIS-C
- Propensity score analysis for children treated with IVIG versus IVIG + Steroids
- Primary outcome was fever at 48 hours
- Secondary outcomes: second line treatments, hemodynamic support, LVEF and PICU stay
- **IVIG + Steroids led to improved outcomes**

Table 2. Primary and Secondary Analyses in the Propensity Score-Matched Cohorts

Outcomes	After propensity score matching		Absolute risk difference between groups (95% CI) [reference: IVIG alone]	Odds ratio (95% CI) [reference: IVIG alone]	P value
	No. (%)				
	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)			
Primary outcome					
Treatment failure ^a	3 (9)	24 (38)	−0.28 (−0.48 to −0.08)	0.25 (0.09 to 0.70)	.008
Secondary outcomes					
Second-line treatment ^b	3 (9)	20 (31)	−0.22 (−0.40 to −0.04)	0.19 (0.06 to 0.61)	.004
Hemodynamic support ^{c,d}	2 (6)	15 (23)	−0.17 (−0.34 to −0.004)	0.21 (0.06 to 0.76)	.01
LVEF <55% ^c	2/12 (17)	14/40 (35)	−0.18 (−0.35 to −0.01)	0.20 (0.06 to 0.66)	.007
Duration of PICU stay, median (IQR), d	4 (2 to 5)	6 (4 to 8.5)	Reduction of days: −2.4 (−4.0 to −0.7)		.005

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Published online June 16th, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes

M.B.F. Son, N. Murray, K. Friedman, C.C. Young, M.M. Newhams, L.R. Feldstein, L.L. Loftis, K.M. Tarquinio, A.R. Singh, S.M. Heidemann, V.L. Soma, B.J. Riggs, J.C. Fitzgerald, M. Kong, S. Doymaz, J.S. Giuliano, Jr., M.A. Keenaghan, J.R. Hume, C.V. Hobbs, J.E. Schuster, K.N. Clouser, M.W. Hall, L.S. Smith, S.M. Horwitz, S.P. Schwartz, K. Irby, T.T. Bradford, A.B. Maddux, C.J. Babbitt, C.M. Rowan, G.E. McLaughlin, P.H. Yager, M. Maamari, E.H. Mack, C.L. Carroll, V.L. Montgomery, N.B. Halasa, N.Z. Cvijanovich, B.M. Coates, C.E. Rose, J.W. Newburger, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators*

IVIG + glucocorticoids as initial treatment on Day 0 was associated with
less cardiovascular dysfunction 2 or more days later; and
less adjunctive therapies 1 or more days later

N Engl J Med 2021; 385:23-34

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ESTABLISHED IN 1812

JULY 1, 2021

VOL. 385 NO. 1

Treatment of Multisystem Inflammatory Syndrome in Children

A.J. McArdle, O. Vito, H. Patel, E.G. Seaby, P. Shah, C. Wilson, C. Broderick, R. Nijman, A.H. Tremoulet, D. Munblit, R. Ulloa-Gutierrez, M.J. Carter, T. De, C. Hoggart, E. Whittaker, J.A. Herberg, M. Kaforou, A.J. Cunningham, and M. Levin, for the BATS Consortium*

“We found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone.”

Cohort Differences

- Inclusion criteria: OC-19 participants were adjudicated and met CDC definition. BATS included suspected cases.
- OC-19 patients were much sicker (47% on vasopressors, 41% with LV dysfunction, 18% on mechanical ventilation) than BATS patients (12% on vasopressors, 12% with LV dysfunction, 1.5% on mechanical ventilation).
- Different study endpoints
 - CO-19 – LV dysfunction or shock
 - BATS – composite of inotropic support or mechanical ventilation or death OR reduction in disease severity score

Guidelines



Immunomodulatory treatment

Version 3

- First tier treatments in hospitalized patients:
 - High-dose IVIG (2 gm/kg based upon ideal body weight to max 100 gm) and IV methylprednisolone 1-2mg/kg/day.
 - If LV dysfunction, IVIG may be given as 1 gm/kg daily over 2 days.
- Refractory MIS-C despite IVIG and low-moderate dose glucocorticoids:
 - IV pulse dose steroids (10-30 mg/kg/day) for non-responders, especially if they require high-dose or multiple inotropes and/or vasopressors.
 - Anakinra (4 mg/kg/day IV or SC) for treatment of MIS-C refractory to IVIG and steroids, with features of MAS, or with contraindications to long-term steroids.
 - Infliximab (5-10 mg/kg/day IV X 1 dose) may be considered an alternative biologic agent to anakinra or in patients with contraindications to long-term use of steroids.
- Serial laboratory testing and cardiac assessment guide immunomodulatory treatment and tapering
- Patients often require a 2-3-week taper of immunomodulatory medications



WHO issues guidelines on the treatment of children with multisystem inflammatory syndrome associated with COVID-19



Conditional recommendation for steroids.
Level of evidence – very low

23 November 2021 | News release | Geneva, Switzerland | Reading time: Less than a minute (171 words)

WHO today issued updated [guidelines](#) on the management of multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C).

MIS-C is a rare but serious condition where children with COVID-19 develop inflammation affecting different organs of the body. Children with this condition need specialized care, and may need to be admitted to intensive care.

Media Contacts



WHO Media inquiries

Telephone: +41 22 791 2222

Email: mediainquiries@who.int

Cardiac Management of MIS-C

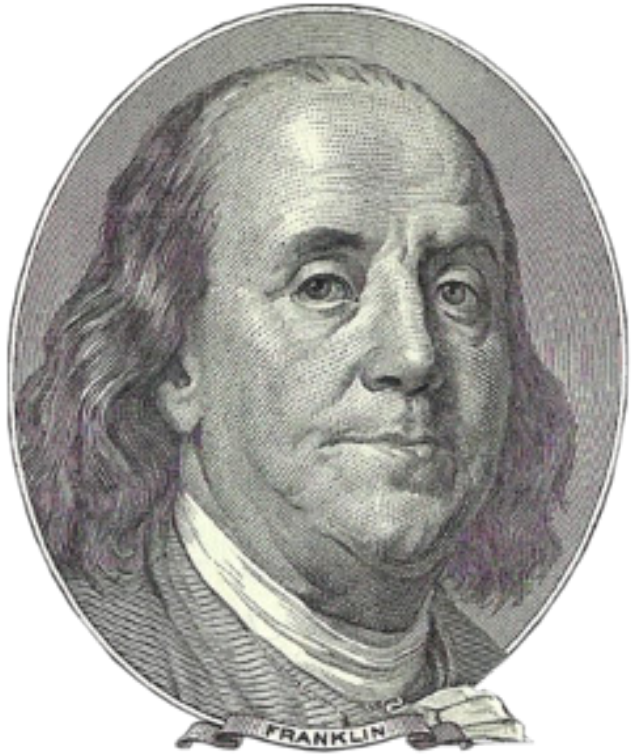
Alsaied et al. Circulation, 2021

- Baseline Cardiac Testing: ECG, BNP, troponin, echo
- During Active Disease Course:
 - EKG q 1-2 days
 - Trend BNP and troponin daily if abnormal
 - Repeat echo as clinically indicated
- Outpatient F/U
 - Echo and ECG at 1-2 weeks, 4-6 weeks
 - Continue to follow BNP and troponin if not normalized
 - Holter monitors for patients with EKG/conduction abnormalities

Cardiac Management of MIS-C

Alsaied et al. Circulation, 2021

- For patients with history of LV dysfunction
 - Echo/EKG at one year or sooner
 - Exercise restrictions considered for 3-6 months
 - MRI can be considered in acute phase or at 3-4 mo
- For patients with coronary artery aneurysms
 - Follow in accordance with KD guidelines
 - CT may be indicated if coronaries can not be well imaged in larger patients in whom aneurysms are suspected.



"An ounce of prevention
is worth a pound of cure."
Benjamin Franklin

Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France

Table. Multisystem Inflammatory Syndrome in Children (MIS-C) Risk by COVID-19 Vaccination Status of Adolescents

COVID-19 vaccination status ^a	No. of patients with MIS-C (N = 33)	Hazard ratio (95% CI) ^b	P value
Unvaccinated	26	1 [Reference]	<.001
One dose	7	0.09 (0.04-0.21)	
Sensitivity analysis: fully vaccinated ≥14 d after first dose ^c			
Unvaccinated	28	1 [Reference]	<.001
One dose	5	0.07 (0.03-0.18)	
Sensitivity analysis: fully vaccinated ≥28 d after first dose ^c			
Unvaccinated	31	1 [Reference]	<.001
One dose	2	0.03 (0.01-0.12)	
Sensitivity analysis: fully vaccinated ≥42 d after first dose ^c			
Unvaccinated	31	1 [Reference]	<.001
One dose	2	0.04 (0.01-0.16)	

Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021

Laura D. Zambrano, PhD^{1,*}; Margaret M. Newhams, MPH^{2,*}; Samantha M. Olson, MPH¹; Natasha B. Halasa, MD³; Ashley M. Price, MPH¹; Julie A. Boom, MD⁴; Leila C. Sahni, PhD⁴; Satoshi Kamidani, MD⁵; Keiko M. Tarquinio, MD⁶; Aline B. Maddux, MD⁷; Sabrina M. Heidemann, MD⁸; Samina S. Bhumbra, MD⁹; Katherine E. Blin, MD¹⁰; Ryan A. Nofziger, MD¹¹; Charlotte V. Hobbs, MD¹²; Tamara T. Bradford, MD¹³; Natalie Z. Cvijanovich, MD¹⁴; Katherine Irby, MD¹⁵; Elizabeth H. Mack, MD¹⁶; Melissa L. Cullimore, MD¹⁷; Pia S. Pannaraj, MD¹⁸; Michele Kong, MD¹⁹; Tracie C. Walker, MD²⁰; Shira J. Gertz, MD²¹; Kelly N. Michelson, MD²²; Melissa A. Cameron, MD²³; Kathleen Chiotos, MD²⁴; Mia Maamari, MD²⁵; Jennifer E. Schuster, MD²⁶; Amber O. Orzel, MPH²; Manish M. Patel, MD¹; Angela P. Campbell, MD^{1,†}; Adrienne G. Randolph, MD^{2,27,†}; Overcoming COVID-19 Investigators

TABLE 1. (Continued) Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,* July 1–December 9, 2021

Characteristic	No. (%)			p-value [†]
	Total (N = 283)	MIS-C case-patients (n = 102)	Controls (n = 181)	
Laboratory test results^{††}				
RT-PCR or antigen-positive, antibody not performed	11 (3.9)	11 (10.8)	0 (—)	<0.01
RT-PCR or antigen-positive, antibody-positive	12 (4.2)	12 (11.8)	0 (—)	
Antibody positive only	76 (26.9)	76 (74.5)	0 (—)	
Pre-admission results available only	3 (1.1)	3 (2.9)	0 (—)	
Fully vaccinated^{§§}	70 (24.7)	5 (4.9)	65 (35.9)	<0.01
Median interval from receipt of second vaccine dose to reference hospitalization date, days (IQR) ^{¶¶}	84 (51–122)	63 (48–89)	88 (52–122)	0.37

TABLE 1. (Continued) Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,* July 1–December 9, 2021

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TABLE 3. Effectiveness* of 2 doses of Pfizer-BioNTech vaccine against multisystem inflammatory syndrome in children among hospitalized patients aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,[†] July–December 2021

	No. vaccinated [§] /Total (%)		Adjusted VE, % (95% CI)
	MIS-C case patients	Control patients	
Control groups			
All controls	5/102 (4.9)	65/181 (35.9)	91 (78–97)
Test-negative	5/102 (4.9)	34/90 (37.8)	92 (77–97)
Syndrome-negative	5/102 (4.9)	31/91 (34.1)	89 (70–96)
Sensitivity analysis			
MIS-C case patients with serologic evidence present [¶]	5/88 (5.7)	61/161 (37.9)	90 (75–96)

Return to Play after Coronavirus Infection

- Return to play guidelines have been released by the AAP, ACC, and other organizations
 - Graduated return to play protocols
- Reasonable to treat pediatric patients who have had MIS-C as if they had myocarditis.
- If cardiac abnormalities acutely, patient should be restricted for 3-6 months
- Only resume activities when/if ECG, echo, Holter, CPET, CMR have normalized.



MIS-C

What We Don't Know About the Heart

- To date, there are limited data on:
 - MIS-C-associated coronary aneurysms or heart function using standardized assessments in Core Labs (echo, MRI)
 - Long-term cardiac outcomes
 - Association of heart complications with clinical and laboratory risk factors or treatments

NHLBI's MUSIC Study

Long-TerM OUtcomes after the Multisystem
Inflammatory Sndrome In Children

Overarching Goals

- To characterize the occurrence and time course of
 - Cardiac outcomes: coronary abnormalities, ventricular dysfunction, and arrhythmias/conduction disturbances
 - Systemic organ dysfunction
 - Inflammatory response
 - Major medical events
- To develop clinical risk stratification models
- To provide phenotyping for correlation with basic/translational mechanistic studies

Study Design

- Observational cohort study
- Research funding available for echoes and CMRs not ordered by primary provider.
- Annual medical history forms for up to 5 years.
- Adjudication Committee to review MIS-C diagnoses (specialists in Rheumatology, ID, and Cardiology).

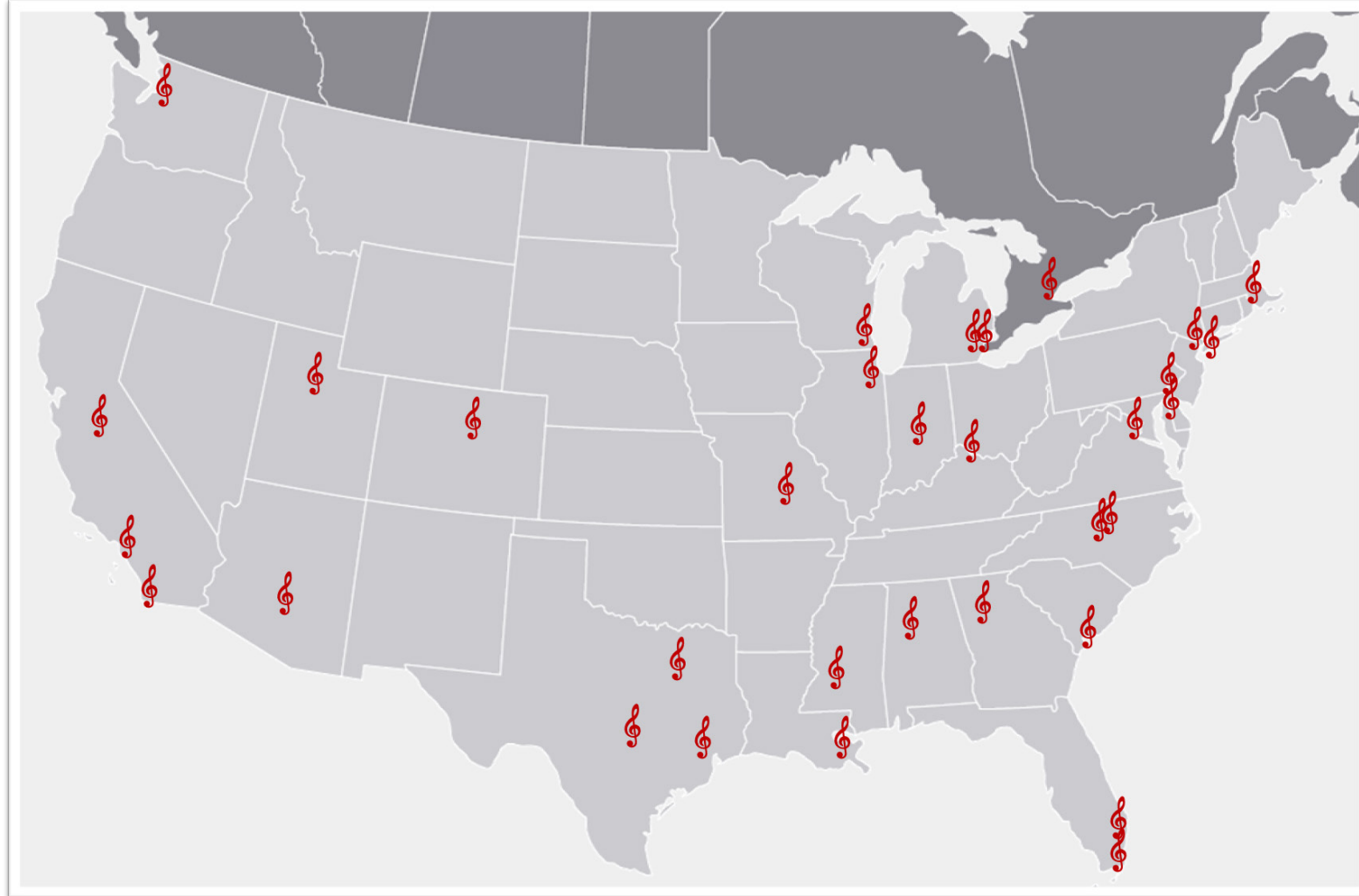
Recruitment

- Enrollment of at least 600 subjects
- Participants can be enrolled any time in the first year after MIS-C onset
- Prospective cases can be enrolled as early as during hospitalization
- For retrospective cases or those in whom consent could not be obtained during hospitalization, we will send a letter and opt out card (English or Spanish), then after 2 weeks, phone, text, or email to discuss study
- Written consent and assent in-person OR virtual
- Waiver of consent for inclusion of routine clinical data if:
 - 3 unsuccessful attempts to reach patient/family
 - Death before consent can be obtained

NHLBI's MUSIC Study

COVID  MUSIC STUDY
Understanding MIS-C

Long-TerM Outcomes after the Multisystem Inflammatory Syndrome In Children



Primary Outcomes

- Worst-ever LVEF by 6-month visit
- Maximum z score of the proximal LAD or RCA (zMax) by 6-month visit

Secondary Cardiac Outcomes

1. Coronary Outcomes
 - a. Proximal LAD or RCA z score of ≥ 2.5 on any echocardiogram
 - b. Occurrence of aneurysms by Japanese Ministry of Health criteria
 - c. Individual z scores for LMCA, RCA and LAD
2. Ventricular Function Outcomes
 - a. LV size and function (LVEDV z score, LVEF, LVSF)
 - b. % with LVEF < 55%, and with LVEF 45-54%, 35-44%, and < 35% on any echo.
 - c. LV strain (global circumferential and longitudinal)
 - d. Qualitative assessment of RV systolic function and RV strain (global longitudinal)
 - e. LV diastolic function, i.e., tissue Doppler imaging and mitral valve (MV) inflow
3. Valve regurgitation: presence and degree of mitral and aortic regurgitation
4. Presence and size of pericardial effusion
5. Arrhythmias and conduction system disturbances
6. MRI outcomes of LVEF, RVEF, valvar regurgitation, % and distribution of LGE, abnormal T2-weighted imaging (%), elevated T2 (%), elevated native T1 (%), elevated ECV (%), coronary artery dilation/aneurysm (%), and overall interpretation of CMR as abnormal, equivocal, or normal

Secondary Non-Cardiac Outcomes

1. Other organ abnormalities by medical history: Immunologic, rheumatologic, renal, pulmonary, hematologic, gastrointestinal, dermatologic or neurologic
2. Laboratory markers of inflammation
3. Admission to ICU
4. Hospital length of stay
5. Symptom duration
6. Major medical events (e.g., stroke, renal replacement therapy, plasma exchange, ECMO, VAD)
7. Mortality

Rheumatologic

Has the participant experienced any symptoms, clinical findings, or diagnoses related to this organ system since the last visit?

☐ Yes ☐ No

If yes, has the participant been evaluated by a rheumatologist since the last visit?

☐ Yes ☐ No

Has the participant experienced any of the following symptoms, clinical findings, or diagnoses since the last visit? (choose all that apply)

- ☐ Joint pain and/or swelling
- ☐ Muscle weakness or muscle pain
- ☐ Post-exertional fatigue
- ☐ Systemic lupus /mixed connective tissue disease
- ☐ Juvenile idiopathic arthritis/psoriatic arthritis
- ☐ Vasculitis (such as Henoch-Schonlein Purpura)
- ☐ Other, specify

If joint pain or swelling, how many joints were involved (choose best answer; please note that each joint is counted separately. For example, if both the right and left shoulder joints are involved, that would count as 2 joints)?

☐ < 5 joints ☐ 5 or more joints

If joint pain or swelling, was there medical treatment?

☐ Yes ☐ No

What medications were used for joint pain or swelling
(choose all that apply)

- ☐ NSAIDS
- ☐ Oral steroids
- ☐ Steroid injection
- ☐ Methotrexate
- ☐ Infliximab (Remicade), Etanercept (Enbrel),
Adalimumab (Humira)
- ☐ Tocilizumab (Actemra)
- ☐ Other

Other medication used for joint pain or swelling:

Other rheumatologic condition, specify

Neurologic

Has the participant experienced any symptoms, clinical findings, or diagnoses related to this organ system since the last visit?

☐ Yes ☐ No

Has the participant been evaluated by a neurologist since the last visit?

☐ Yes ☐ No

Has the participant experienced any of the following symptoms, clinical findings, or diagnoses since the last visit (choose all that apply)?

- ☐ Headaches frequent or severe enough to impact school attendance or activities
- ☐ Seizures
- ☐ Cerebrovascular accident (TIA or stroke)
- ☐ Choreoathetoid movements
- ☐ Coma
- ☐ Decreased vision
- ☐ Decreased hearing
- ☐ Decreased sense of taste
- ☐ Decreased sense of smell
- ☐ Difficulty concentrating
- ☐ "Mental slowness" or "COVID fog"
- ☐ Limb numbness
- ☐ Limb paresthesia/tingling
- ☐ Iritis
- ☐ Uveitis
- ☐ Ataxia (or loss of balance or accuracy of reach)
- ☐ Change in mood
- ☐ Guillain-Barre
- ☐ Limb weakness
- ☐ Other

If cerebrovascular accident (TIA or stroke), what type (choose all that apply)?

- ☐ Transient ischemic attack (TIA)
- ☐ Ischemic stroke
- ☐ Hemorrhagic stroke
- ☐ Mixed ischemic and hemorrhagic
- ☐ Unknown type

If limb weakness, please specify if

- ☐ Unilateral
- ☐ Bilateral

Other neurologic condition, please specify

Core Laboratories

- Echo Core Lab
- MRI Core Lab
- Biorepository
- Kevin Friedman, MD, PI
- Michael Taylor, MD, PI
- Andrew Powell, MD, Co-PI
- Mark Russell, MD

Schedule of Measurements

Variable	Day 1	Discharge	2 wks	6 wks	3 mo	6 mo	Years 1-5
Demographics	X						
Medical History	X	X	X	X		X	X
PROMIS Global Health			X	X		X	X
Echo	X	X	X	X		X*	X**
EKG	X	X	X	X		X	
Cardiac MRI and ETT					X***		
Clinical Labs	X	X	X	X		X*	
WGS, other research Labs	X	X	X	X		X	

* ≥6-mo echo and labs optional if all earlier echoes normal; ** if abnormal echo at 6 months, repeat ≥ annually until 2 consecutive normal echoes; *** All with history mod-severe LV dysfunction by protocol; CMR Core Lab will read any CMR for any indication.

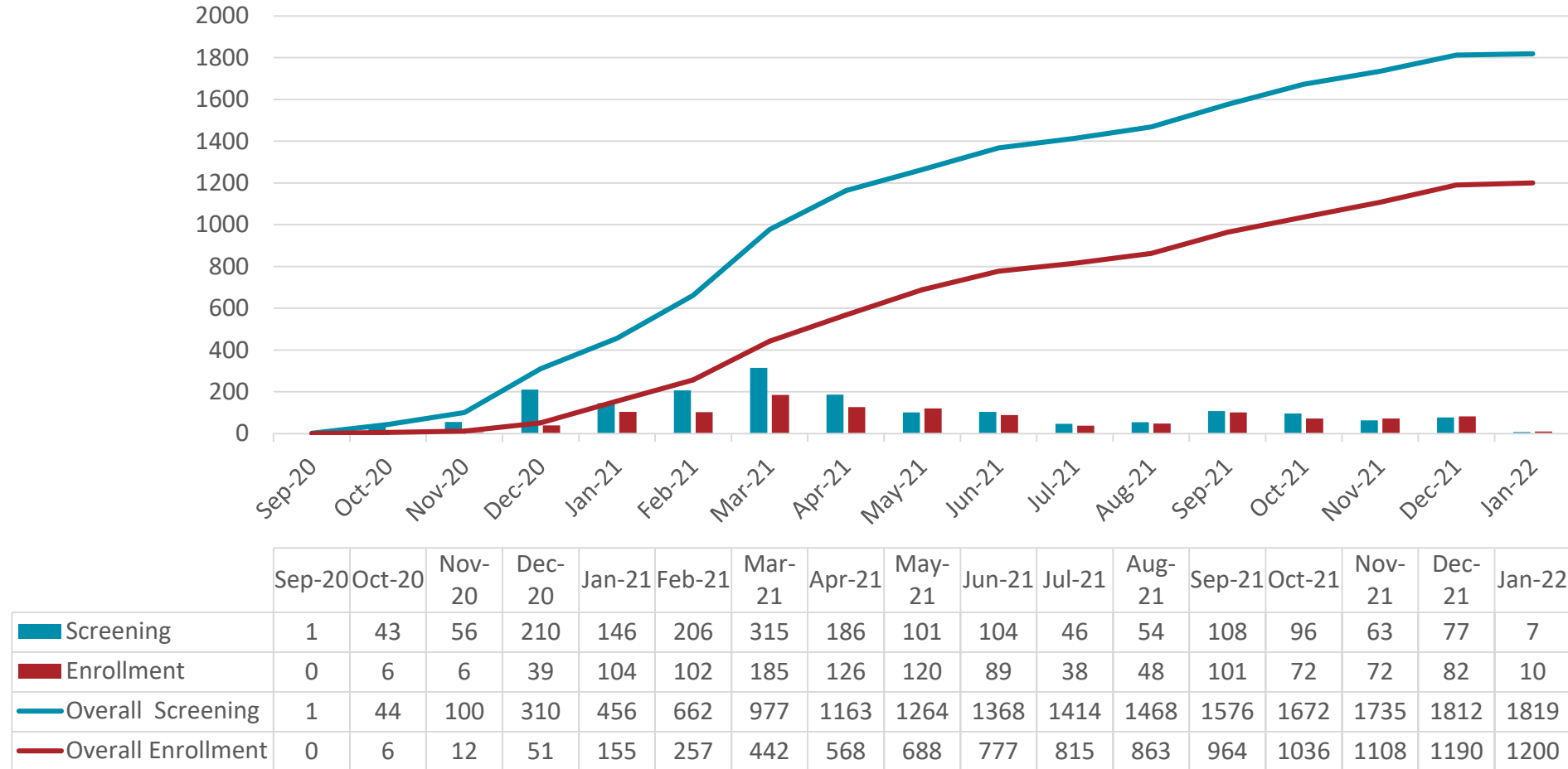
Informed Consent and Data Sharing

- Allows us to share clinical and genetic data broadly
- Allows Electronic Health Record review

Center Data Warehouses

- Benefits of using center data warehouses: decreased coordinator burden, increased accuracy, and analytics
- Paul Avillach (BCH) is conducting a pilot study of BCH and Utah data warehouses to analyze completeness of collection of data elements
- If successful, CDW extraction will extend to other MUSIC centers with data warehouses

STUDY UPDATE: Screening/Enrollment



MUSIC Demographics (1/14/2022)

% Children According to Race and Ethnicity

HISPANIC
OR LATINO

26%

BLACK,
NON-HISPANIC

26%

WHITE,
NON-HISPANIC

30%

OTHER,
NON-HISPANIC

9%

UNKNOWN

10%

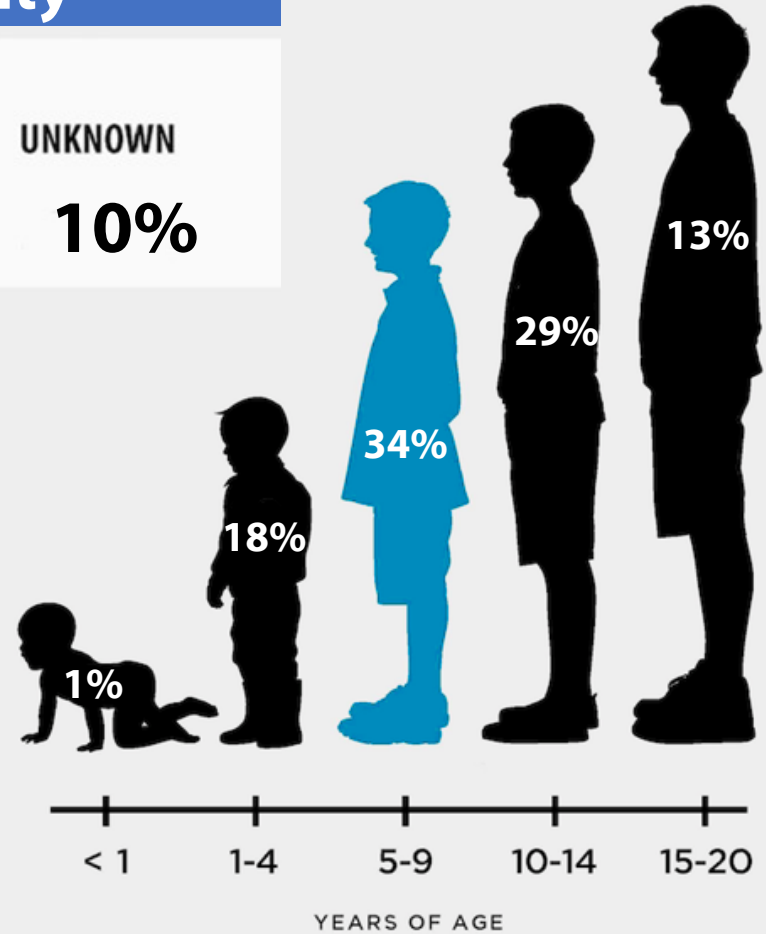
*Race categories were non-exclusive



MALE



FEMALE



CORE LAB UPDATES

BIOREPOSITORY SAMPLES RECEIVED

- 280 Child
(192 blood, 88 saliva)
- 207 Mother
(73 blood, 134 saliva)
- 84 Father
(26 blood, 58 saliva)
- *50 complete trios*

ECHO LAB

- 867 echos received
(592 reviewed and finalized)
- Reminder to update echo form in REDCap when sent.

CMR LAB

- 85 CMRs received;
73 reviewed
- Please use MUSIC ID number with visit identifier during anonymization.

Summary

The MUSIC longitudinal cohort study will:

1. Contribute important new information on acute cardiac findings and long-term cardiac health status following MIS-C
2. Facilitate surveillance for abnormalities in other systemic organs and overall well-being
3. Provide a unique framework including phenotype for basic and translational research studies
4. Facilitate creation of a clinical care pathway for children with suspected or confirmed MIS-C

RECOVER Components: A Comprehensive and Complementary Approach

RECOVER Core Elements

Clinical Science Core

Data Resource Core

Biorepository Core

Meta-Cohort Elements

RECOVER
ENROLLING
COHORTS



EHR/
HEALTH
SYSTEMS
STUDIES



AUTOPSY-
BASED
STUDIES



Data Resource Elements

Clinical

Imaging

Mobile and Digital
Health

EHR / Other Real-
World Data

Pathology

RECOVER Components: A Comprehensive and Complementary Approach

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Data Resource Elements

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EHR / Other Real-
World Data

Pathology

Myocarditis Temporally Related to COVID-19 Vaccination



COVID-19 Vaccine

- May 2020: Plans for Operation Warp Speed
- December 11, 2020: Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 mRNA vaccine for ≥ 16 years old
 - May 10, 2021: EUA for 12-15 year-olds
- April 2021: Cases of myocarditis in men < 30 years old following Pfizer-BioNTech's COVID-19 mRNA vaccine

COVID-19

Apr 27, 2021, 06:08pm EDT | 66,640 views

Are Rare Cases Of Myocarditis Linked To Pfizer, Moderna Covid-19 Vaccines?



Bruce Y. Lee Senior Contributor

Health

I am a writer, journalist, professor, systems modeler, computational and digital health expert, avocado-eater, and entrepreneur, not always in that order.



The U.S. Department of Defense (DoD) is looking further into 14 cases of myocarditis after ...

[+] UNITED STATES FORCES KOREA VIA GETTY IMAGES

There are now reports of 62 people in Israel and 14 people in the U.S. military being diagnosed with myocarditis after receiving Covid-19 mRNA vaccines. Does this necessarily mean that the Pfizer/BioNTech and Moderna vaccines were the cause? Well, let's

- May 2020: Plan
- December 11, 2020: BioNTech COVID-19 vaccine
• May 10, 2021: Pfizer COVID-19 vaccine
- April 2021: Case of myocarditis in a 16-year-old male following BioNTech's COVID-19 vaccine

ation (EUA) for Pfizer-
16 years old

16 years old following Pfizer-

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination

Mayme Marshall, MD, Ian D. Ferguson, MD, Paul Lewis, MD, MPH, Preeti Jaggi, MD,
Christina Gagliardo, MD, James Steward Collins, MD, Robin Shaughnessy, MD,
Rachel Caron, BA, Cristina Fuss, MD, Kathleen Jo E. Corbin, MD, MHS,
Leonard Emuren, MBBS, PhD, Erin Faherty, MD, E. Kevin Hall, MD, Cecilia Di Pentima, MD,
MPH, Matthew E. Oste, MD, MPH, Elijah Paintsil, MD, Saira Siddiqui, MD,
Donna M. Timchak, MD, Judith A. Guzman-Cottrill, DO

E-published June 4, 2021

What We Know

- Typically post mRNA vaccination
- Predominantly male
- Typically after 2nd dose, within 7 days of vaccination
- Symptoms
 - Chest pain
 - SOB
 - Palpitations
 - Fatigue
- 18.7% ICU
- 1.4% Vasoactive support
- No ECMO or death
- 70% with ECG changes
- 19% LVEF <55%
- 77% had abnormal CMR
 - 99% Late gadolinium enhancement
 - 72% myocardial edema
- Hospital LOS: 2 days (1-10 days)₈₀

Rare Event: VAERS Data

Reporting Rates of Myocarditis (per 1 million doses administered) after Pfizer-BioNTech COVID-19 vaccination, 7-day risk interval

	Males		Females	
Age group	Dose 1	Dose 2	Dose 1	Dose 2
5–11 years	0.0	4.3	Not calculated [†]	2.0
12–15 years	4.8	45.7	1.0	3.8
16–17 years (included for reference)	6.1	70.2	0.0	7.6

37,810,998 total 1st and 2nd vaccine doses administered

81

In Conclusion

- Nearly 2 years after the start of the pandemic, we know a bit more about COVID-19 and MIS-C
 - Incidence
 - Some data on therapies
 - Short-term effects on the heart
- There are still many things we do not know
 - Risk factors
 - Best therapies
 - Long-term outcomes
- Vaccination appears to prevent MIS-C
- Myocarditis following COVID-19 vaccination is a rare event
 - Highest reporting risk in teen-age males
 - Mild clinical course; long-term outcomes needed

MUSIC Study Leadership Team

MUSIC Study Leaders

- Jane Newburger (BCH)
- Dongngan Truong (Primary Children's)

MUSIC Small Working Group

- Audrey Dionne (BCH)
- Matthew Elias (CHOP)
- Brian McCrindle (Sick Kids)
- Matthew Oster (Emory)
- Lara Shekerdemian (TCH)

Echo Core Lab: Kevin Friedman

MRI Core Lab: Michael Taylor,
Andrew Powell

Biorepository: Mark Russell

Lead Coordinators: David Garuba
Tonia Morrison

NHLBI: Gail D. Pearson, Vicki Pemberton

PHN Chair: Lynn Mahony

HealthCore

- Felicia Trachtenberg
- Julie Miller
- Kerri Hayes
- Amanda Marshall



**OVERCOMING
COVID-19**

- Adrienne Randolph
- Manish Patel
- Mary Beth Son (CARRA)

MUSIC Participating Centers (n = 33)

Boston Children's	Atlanta	Lurie Children's	Nemours/duPont
CHOP	Texas Children's	Seattle Children's	Cohen Children's
MUSC	Sick Kids	Rady Children's	U. of Alabama
Primary Children's	Columbia	Children's National	CHLA
U. Michigan (CS Mott)	U. of Mississippi	UT Southwestern	Children's Hospital of Michigan (Detroit)
Cincinnati Children's	Valley Children's	Children's Hospital of Colorado	Children's Hospital New Orleans
Riley Children's	Mercy (Kansas City)	Dell Medical Center	Nicklaus Children's Hospital (Miami)
Children's Hospital of Wisconsin	U. of North Carolina	DiMaggio Children's	Duke
Phoenix Children's			

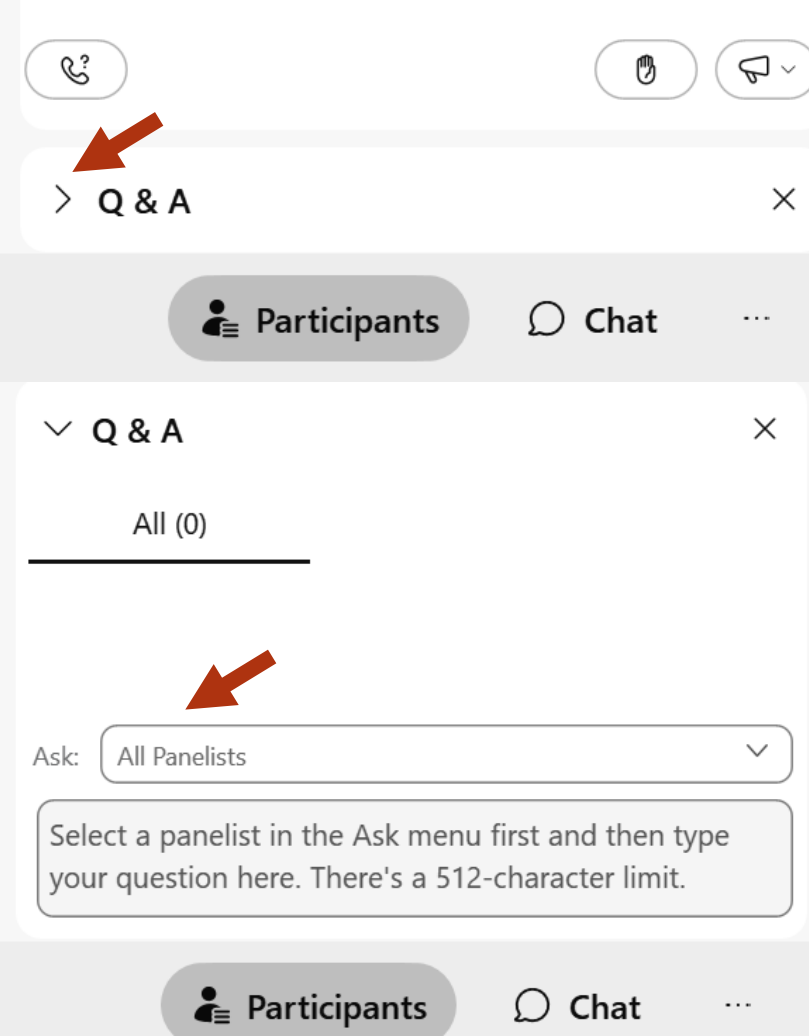
Questions?



Prevention SIG Webinar Series

Q & A Session

Please send us your questions via the
Q & A pod directed to All Panelists





Thank You!



prevention.nih.gov



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