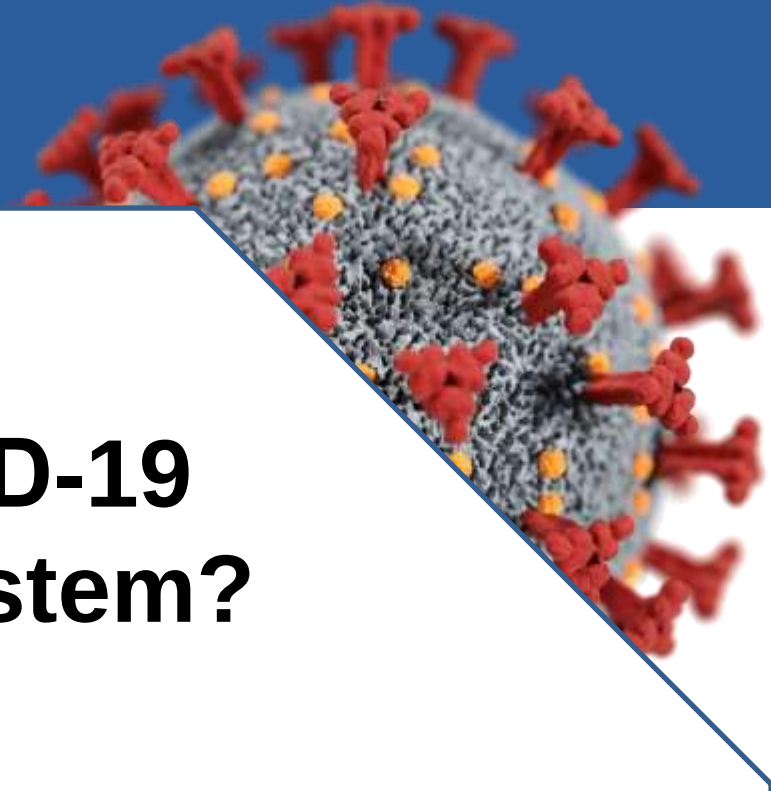

What's New in the Impact of COVID-19 on the Pediatric Cardiovascular System?

Matthew D. Elias, M.D.
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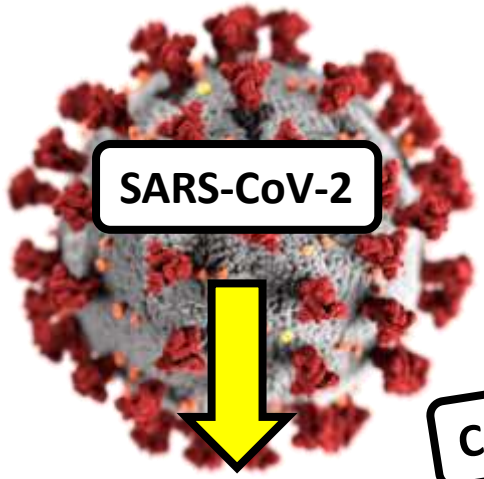
The Children's Hospital of Philadelphia

February 16, 2024

No disclosures

Multisystem Inflammatory Syndrome in Children: The Primary COVID-19 Cardiac Issue in Children



COVID-19 Symptoms

Asymptomatic | Mild | Moderate | Severe

2-6 weeks later in subset of children

Multisystem inflammatory syndrome in children (MIS-C)

- Ventricular dysfunction
- Coronary artery dilation / aneurysms
- Arrhythmias

Initial Reports of Severe Inflammatory Syndrome in Children Temporally Associated with COVID-19

PICS Paediatric Intensive Care Society

NHS England

27 April 2020

PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease

"Over the weekend… small rise in the number of cases of critically ill children … overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID-19 in children."

May 4, 2020

The New York Times

15 Children Are Hospitalized With Mysterious Illness Possibly Tied to Covid-19

May 6, 2020

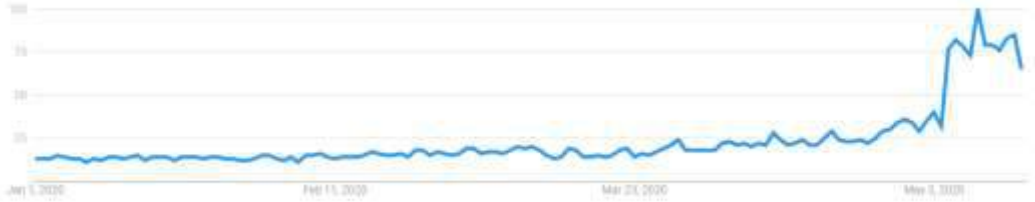
The Washington Post

Officials on alert after children fall ill with mysterious syndrome thought to be tied to covid-19

The number of affected children is relatively very small, and most have responded well to treatment, but the strange nature of the cases, mostly in previously healthy children, has caused concern.

By Ariana Eunjung Cha and Chelsea Janes · 1 hour ago

Google Trends – "Kawasaki Disease"

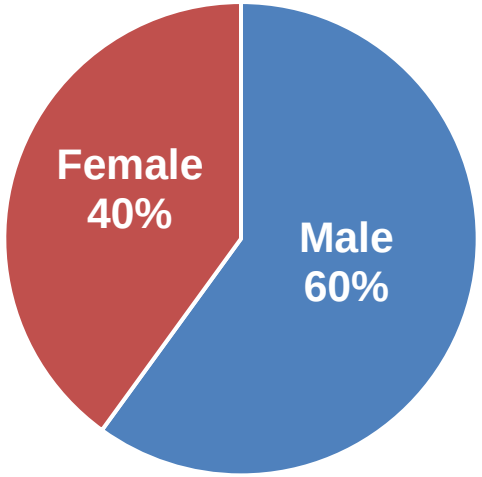


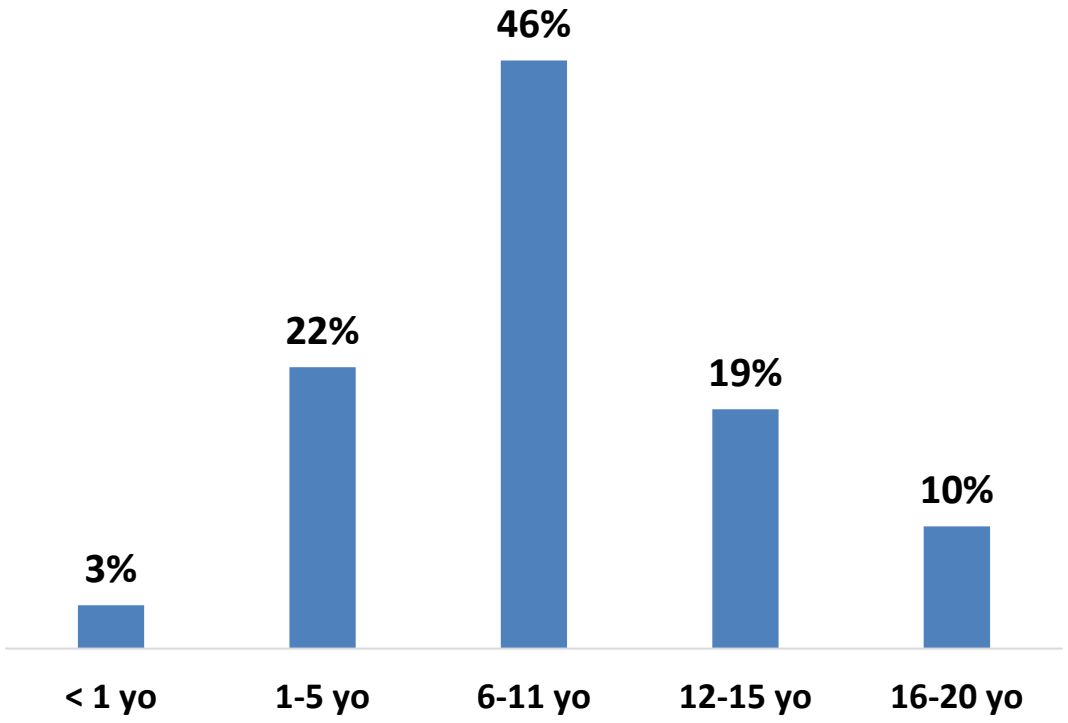
National CDC MIS-C Data

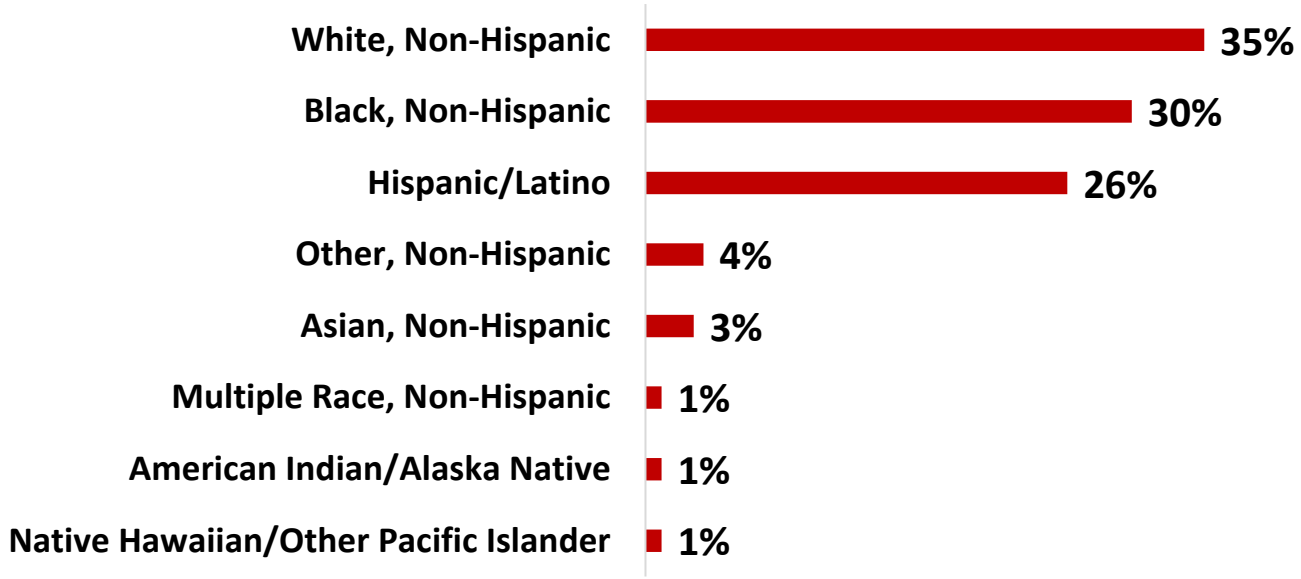
9,645 confirmed cases

79 total deaths

(as of 1/29/24)

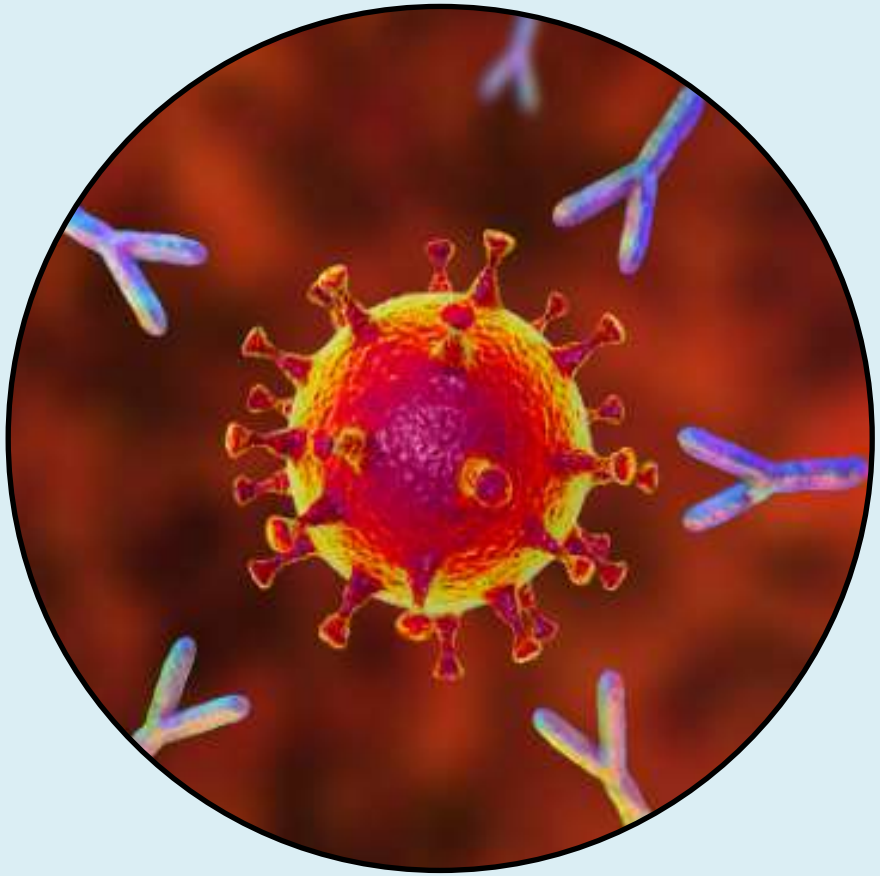




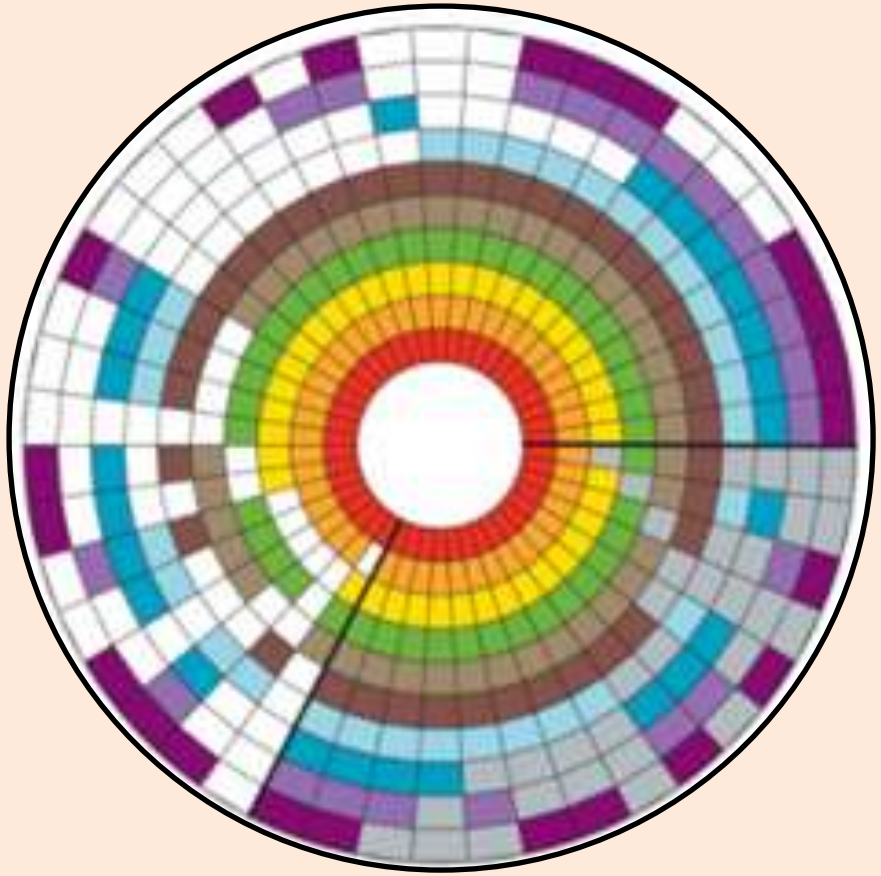


covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

Diagnosis of MIS-C: New Challenges in 2024



Long-Term Outcomes: What Should We Do Now?



MIS-C Case Definition

Clinical Criteria	Laboratory Criteria	Epidemiologic Criteria	Vital Records Criteria
Illness in patient <21 years old with **ALL of the following** (without more likely alternative diagnosis): ❑ **Subjective or documented fever ≥38.0° C** ❑ **Severity requiring hospitalization / death** ❑ **Systemic inflammation, CRP ≥3.0 mg/dL** ❑ New onset manifestations in **at least 2 categories:** 1) **Cardiac involvement** (LVEF <55%, coronary dilation, or elevated troponin) 2) **Mucocutaneous involvement** (rash, inflammation of oral mucosa, conjunctival injection, or extremity findings (erythema/edema hands/feet)) 3) **Shock** 4) **Gastrointestinal involvement** (abdominal pain, diarrhea, or vomiting) 5) **Hematologic involvement** (platelets <150,000 or ALC <1,000)	❑ Positive SARS-CoV-2 test (PCR, antigen) within 60 days prior to/during hospitalization OR ❑ Positive SARS-CoV-2 antibody	❑ Close contact with a confirmed or probable case of COVID-19 in the 60 days prior to hospitalization	❑ Death certificate lists MIS-C as underlying cause of death or a significant condition contributing to death

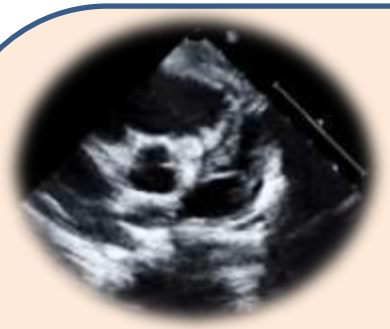
Revised January 2023 Criteria

Confirmed – Clinical AND Laboratory

Probable – Clinical AND Epidemiologic

Suspect – Vital records only

Comparing MIS-C to Kawasaki Disease



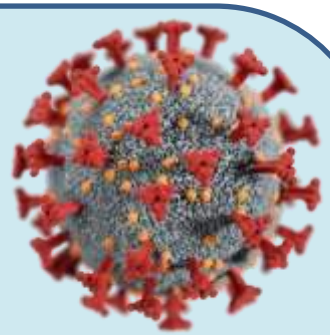
KD

- Younger (median ~3 yo)
- Increased risk among Asian patients
- Less likely to have GI symptoms
- Less significantly abnormal labs
- Decreased risk of LV dysfunction
- Increased risk of CAA, including giant CAA

Similarities

- Similar “classic” symptoms of KD
- Coronary artery involvement
- Viral trigger for KD (hypothesis) and MIS-C
- Responsive to typical KD management

MIS-C



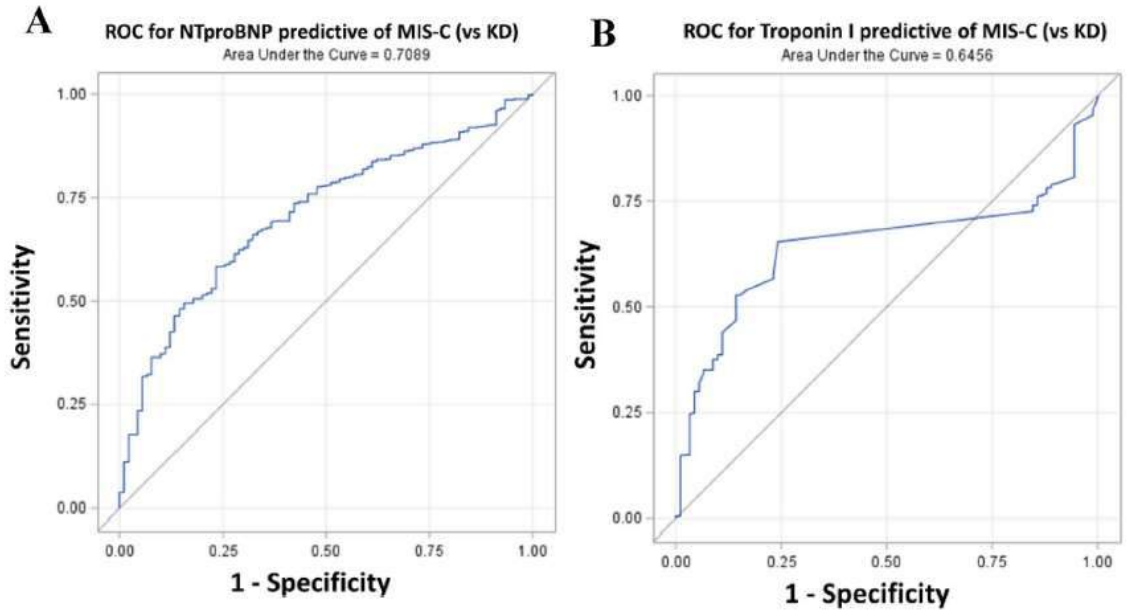
- Older (median ~8 yo)
- Increased risk among Black and Hispanic patients
- More GI symptoms (~90%)
- More profoundly abnormal labs
- Increased risk of LV dysfunction (~50%)
- Decreased risk of CAA, especially persistent CAA

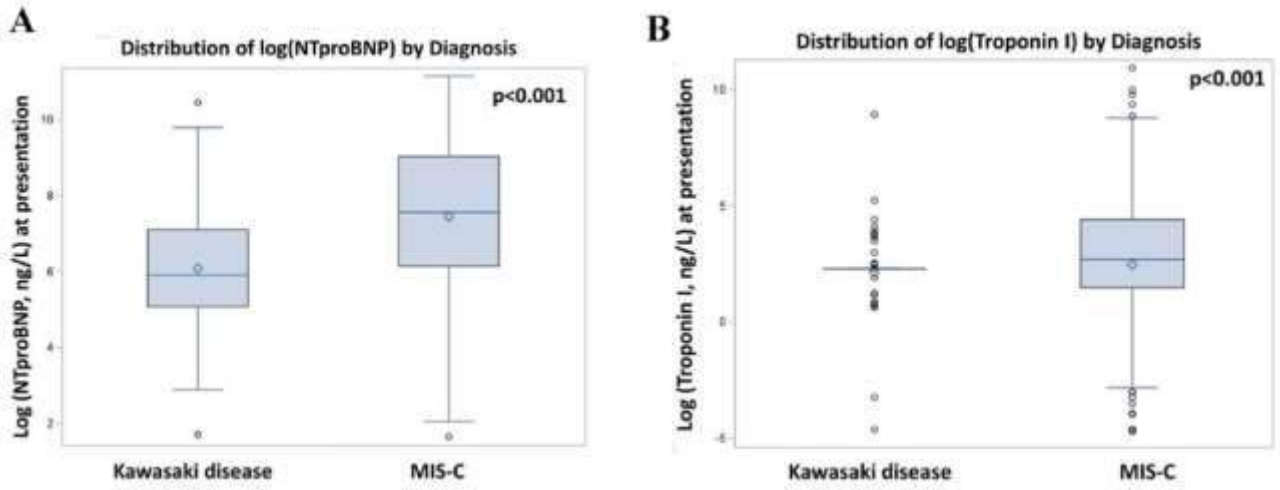
Biomarkers to Distinguish KD and MIS-C

118 KD and 946 MIS-C patients across 42 sites

Higher NTproBNP and troponin-I associated with MIS-C

Specificity:
- NTproBNP ≥ 1500 ng/L – 77%
- TnI ≥ 20 ng/L – 89%





Associated with increased risk of:
- Shock
- ICU admission
- Worse LVEF
- Longer length of stay

IKD Registry

Walton M, et al. *Pediatr Cardiol*. 2023.

Using Machine-Learning Modeling for Diagnosis

KIDMATCH

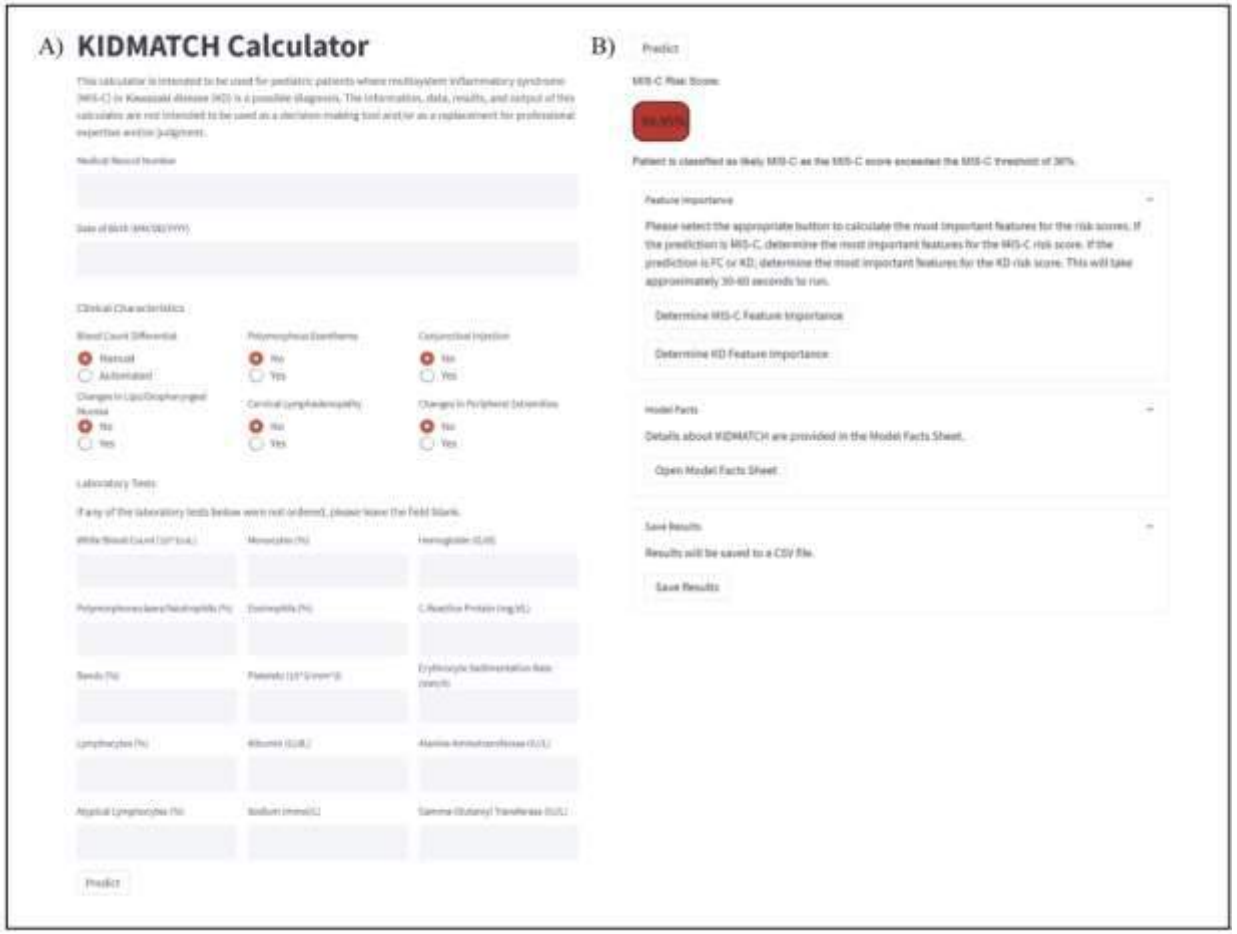
Two-stage algorithm to identify MIS-C or KD developed at Rady Children's Hospital

Input variables:

- Age
- 5 KD clinical signs
- 5 lab tests (CBC, CMP, CRP, ESR, GGT)

Validation and performance

Internal Validation	Description	Sensitivity	Specificity
KIDMATCH-MISC	Risk score for non MIS-C vs MIS-C	93.8% (IQR: 93.8-100%)	97.0% (IQR: 95.8-98.1%)
KIDMATCH-KD	Risk score for other febrile illness vs. KD	94.6% (IQR: 94.6-94.6%)	84.3% (IQR: 82.5-86.1%)
External MIS-C Site	Correctly Classified	Total Patients	Accuracy
14 sites (CHARMS consortium)	76	81	93.8%
Boston Children's Hospital	47	49	95.9%
Children's National Hospital	36	40	90.0%



Lam JY, et al. *Lancet Digit Health.* 2022.

Lam JY, et al. *AMIA Annu Symp Proc*. 2023.

MIS-C Incidence Decreasing with Variants

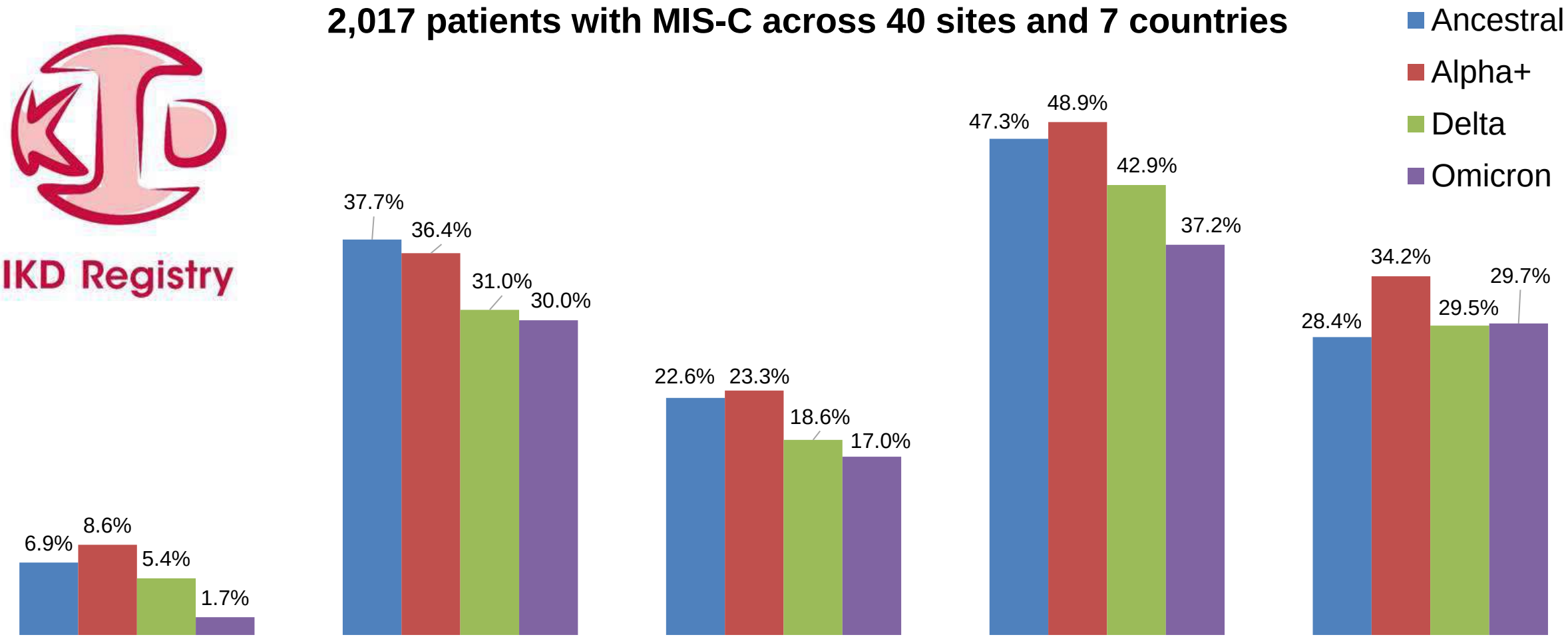
MIS-C Incidence per 100,000 SARS-CoV-2 Infections

	Alpha Strain	Delta Strain	Omicron Strain
US / CDC Payne AB, et al. *JAMA Network Open*. 2021.	31.6 per 100,000		
South Korea Choe YJ, et al. *J Korean Med Sci*. 2023.	38.5 per 100,000	19.8 per 100,000	1.6 per 100,000
Australia Lopez L, et al. *Lancet Reg Health West Pac.* 2022.	100 per 100,000	50 per 100,000	8 per 100,000
Israel Levy N, et al. *JAMA*. 2022.	54.5 per 100,000	49.2 per 100,000	3.8 per 100,000

MIS-C Severity Evolving with Variants - *Maybe*

IKD Registry

2,017 patients with MIS-C across 40 sites and 7 countries



Arrhythmias
p=0.002

Inotropic support
p=0.05

Coronary dilation
p=0.04

ICU admission
p=0.009

LV dysfunction
p=0.17

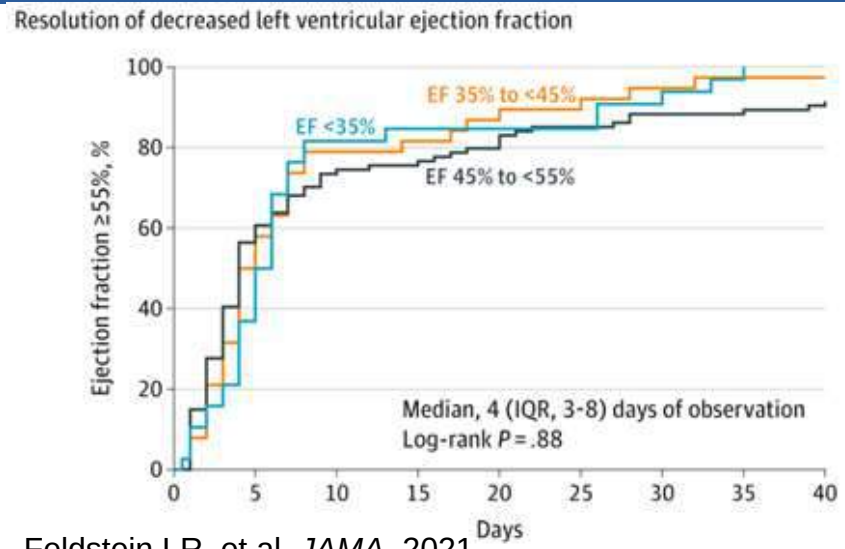
Adapted from McCrindle BW, et al. *NEJM*. 2023 and data presented by Dr. Cedric Manlhiot

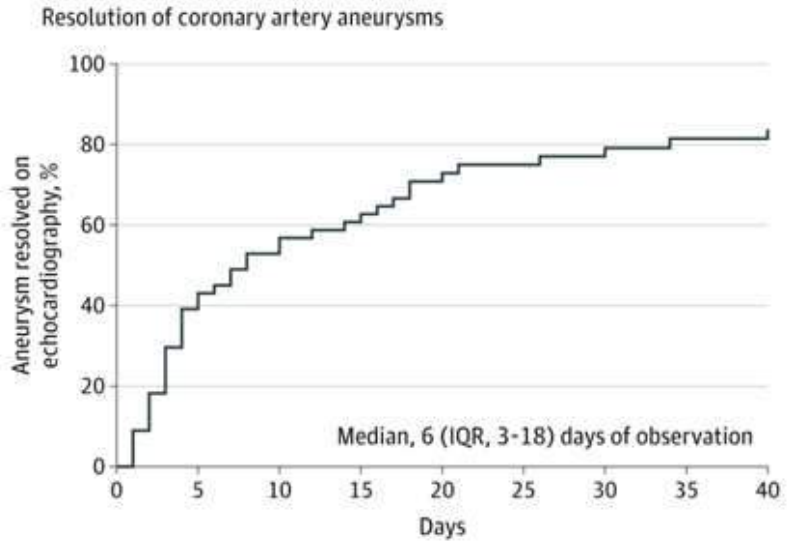
Long-Term Outpatient Management: CHOP *Recommended* Protocol

	2 weeks post-discharge	6 weeks post-discharge	3 months post-discharge	6 months post-discharge	1 year post-discharge
Clinic appointment	X	X		X	X (with further visits at discretion of cardiologist)
ECG	X	X		X	At discretion of cardiologist
Echo	X	X		X	
Cardiac MRI*			X		

* Typically only if patient had at least moderately diminished ventricular function or clinical concern

Evidence of Resolving Ventricular Dysfunction and Coronary Dilation



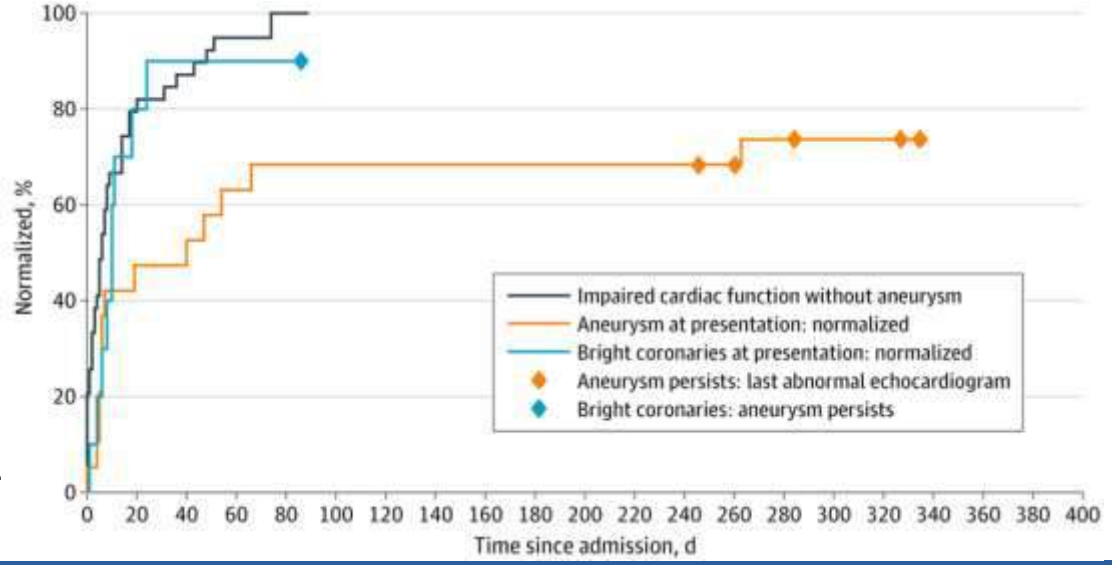


Feldstein LR, et al. *JAMA.* 2021.

Multicenter study of 539 patients with MIS-C in the US

57 (13.4%) with CA z-score ≥2.5
100% resolved by 90 days

172 (34.2%) with decreased LVEF
100% resolved by 142 days



Davies P, et al. *JAMA Pediatr*. 2021.

Multicenter study of
68 patients with MIS-C in the UK

Coronary artery involvement:
14/19 resolved by 1 year

LV systolic dysfunction:
100% resolved by 74 days

MRIs after MIS-C

Early MRI findings after MIS-C

International registry, n = 111

- MRI timing: median 28 days (19-47) after symptom onset
- LGE: 22/110 (20%)
- Myocarditis criteria: 20 (18%)

MRI Study Conclusions:

- Transient myocardial inflammation that often improves quickly
- MRI may help identify long-term follow-up requirements.

Medium-term MRI findings after MIS-C

	Children's Healthcare of Atlanta, n = 51	Children's Hospital Los Angeles, n = 47
Time between MIS-C and MRI, months (IQR)	3.5 (3-5)	7.2 (5.7-9.3)
Elevated T1	11 (22%)	9 (19%)
Elevated T2	0	1 (2%)
Elevated ECV	2 (4%)	18 (38%)
LGE	2 (4%)	6 (13%)
Coronary aneurysms	2 (4%), including one giant aneurysm	2 (4%)

Aeschlimann FA, et al. *J Cardiovasc Magn Reason.* 2021. Dove ML, et al. *J Pediatr.* 2022. Zimmerman D, et al. *Pediatrics*. 2023.

MRIs after MIS-C: Current Recommendations

May be indicated **2-6 months** after diagnosis in patients who presented with significant LV dysfunction or have persistent dysfunction

Henderson LA, et al. *Arthritis Rheumatol*. 2022.

Endorsed by

Consider **1-6 months** after diagnosis in those who had at least moderately diminished LV function

Petersen SE, et al. *JACC Cardiovasc Imaging.* 2022.

CMR during hospitalization or within **1-2 months** of hospitalization, if severe disease with indication of cardiac injury

Ferreira VM, et al. *J Cardiovasc Magn Reson.* 2023.

Consider **~3 months** after diagnosis in those who had at least moderately diminished LV function

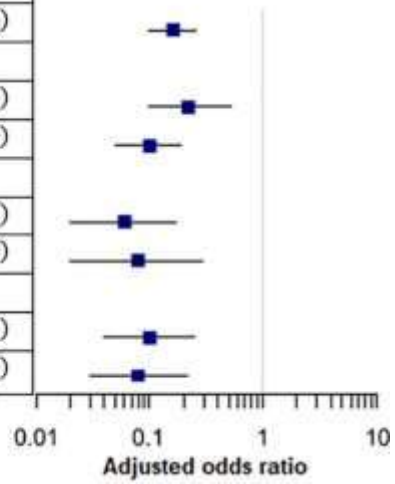
Vaccinations Help Prevent MIS-C

Analysis of 304 MIS-C patients eligible to be vaccinated
(5-18 years old, 7/1/21-4/7/22) across 29 hospitals in 22 states

304 MIS-C patients
- 24 vaccinated (8%)
- **280 unvaccinated (92%)**

502 control patients
- 156 vaccinated (31%)
- 346 unvaccinated (69%)

Subgroup	Vaccinated case-patients / total case-patients (%)	Vaccinated control patients / total control patients (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Overall				
≥28 Days since 2nd dose*	24/304 (7.9)	156/502 (31.1)	0.19 (0.12 - 0.30)	0.16 (0.10 - 0.26)
By age group, y				
5 - 11	10/144 (6.9)	43/230 (18.7)	0.32 (0.16 - 0.67)	0.22 (0.10 - 0.52)
12 - 18	14/160 (8.8)	113/272 (41.5)	0.13 (0.07 - 0.25)	0.10 (0.05 - 0.19)
Ages 12 - 18 y, by period of variant predominance				
Delta	5/122 (4.1)	71/204 (34.8)	0.08 (0.03 - 0.21)	0.06 (0.02 - 0.17)
Omicron	9/38 (23.7)	42/68 (61.8)	0.19 (0.08 - 0.47)	0.08 (0.02 - 0.29)
Ages 12 - 18 y, interval				
28 - 120 Days since 2nd dose	7/153 (4.6)	52/211 (24.6)	0.15 (0.06 - 0.33)	0.10 (0.04 - 0.25)
≥121 Days since 2nd dose	7/131 (5.3)	61/196 (31.1)	0.12 (0.06 - 0.28)	0.08 (0.03 - 0.22)



Conclusions:
- MIS-C associated with decreased likelihood of vaccination
- Estimated overall effectiveness of 84% for vaccination with 2 doses of Pfizer to prevent MIS-C among patients 5-18 years old

* Fully vaccinated was described as ≥28 days after 2nd Pfizer vaccine dose for study, to account for delay between infection and MIS-C and to exclude rare post-vaccination MIS-C.

Zambrano LD, et al. *Clin Infect Dis.* 2023.

Vaccinations are Safe in Patients with History of MIS-C

Multicenter study among 22 North American centers

385 vaccine-eligible patients with history of MIS-C surveyed

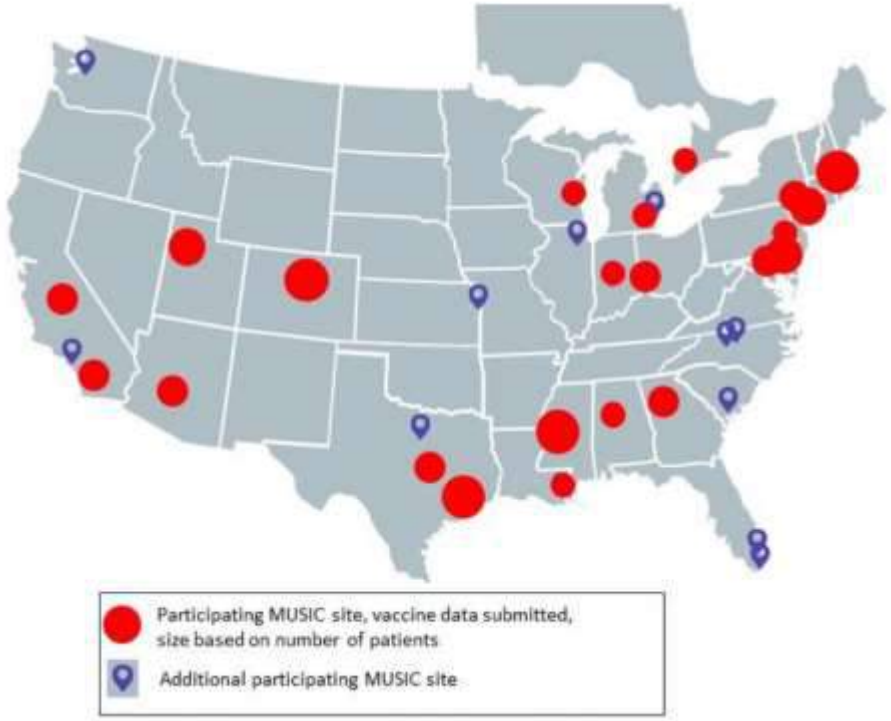
Eligibility: ≥5 years old, ≥90 days after MIS-C diagnosis

- Vaccination status: 185 (48%) with ≥1 dose
- Adverse reactions:
  - Minor reactions: 49%
    - Arm soreness: 34%
    - Fatigue: 17%
  - Medications (acetaminophen, ibuprofen): 17%
  - Sought medical evaluation: 2%
  - Required medical testing or hospitalization: 0%
  - Diagnosed with myocarditis: 0%
  - Diagnosed with recurrent MIS-C: 0%

Conclusion:
Safety profile of COVID-19 vaccination administered ≥90 days after MIS-C similar to general population

COVID MUSIC STUDY
Understanding MIS-C

Pediatric Heart Network



Elias MD, et al. *JAMA Network Open*. 2023.

Conclusions and Future Directions

Incredible Work Thus Far

- Rapid worldwide evaluation of a novel disease during a pandemic
- Collaboration to share evidence for diagnostic evaluation and effective management strategies

Looking Forward

- Improving ability to diagnose MIS-C when the diagnosis has become more challenging
- Broadening understanding of long-term outcomes
- Expanding knowledge generated from MIS-C research to learn more about other cardiac disease

Thank You

Therese Giglia
Cardiology inpatient and outpatient teams
Cardiology Kawasaki Disease Program
Multidisciplinary MIS-C teams: Rheumatology, ICUs, Immunology, ID, Hematology, ED, General Pediatrics

Pediatric Heart Network
Study PIs: Jane Newburger, Dongngan Truong
CHOP team: Kathy Lupton, Tonia Morrison, PHN research leadership

Brian McCrindle, Nagib Dahdah
IKDR Steering Committee
PreVAIL: Cedric Manlhiot
CHOP team: Christina Hayden-Rush, Faith Alunni

And many more! **Thank you!**