Updates on Multisystem Inflammatory Syndrome in Children (MIS-C): Epidemiology, Case Definition, and COVID-19 Vaccination

Clinician Outreach and Communication Activity (COCA) Call

Thursday, December 8, 2022

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- CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

Objectives

At the conclusion of today's session, the participant will be able to accomplish the following:

1. Describe epidemiologic and clinical trends in MIS-C over time.
2. List key features of the CSTE/CDC MIS-C surveillance case definition.
3. Discuss information related to MIS-C and COVID-19 vaccination.

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

Today's Presenters

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Severe Respiratory Illness and Multisystem Inflammatory Syndrome (SIM) Team Lead
Epidemiology Branch
Coronavirus and Other Respiratory Viruses Division (proposed)
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

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Updates on Multisystem Inflammatory Syndrome in Children (MIS-C): Epidemiology, Case Definition, and COVID-19 Vaccination

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Coronavirus and Other Respiratory Viruses Division (proposed)

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MIS-C and Trends Over Time

CDC 2020 MIS-C Case Definition

- Severe hyperinflammatory syndrome occurring 2-6 weeks after acute SARS-CoV-2 infection, resulting in a wide range of manifestations


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

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

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

- CDC 2020 MIS-C Case Definition:
  - An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement; ***AND***
  - No alternative plausible diagnoses; ***AND***
  - Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms

https://emergency.cdc.gov/han/2020/han00432.asp
https://www.cdc.gov/mis/mis-c/hcp/index.html

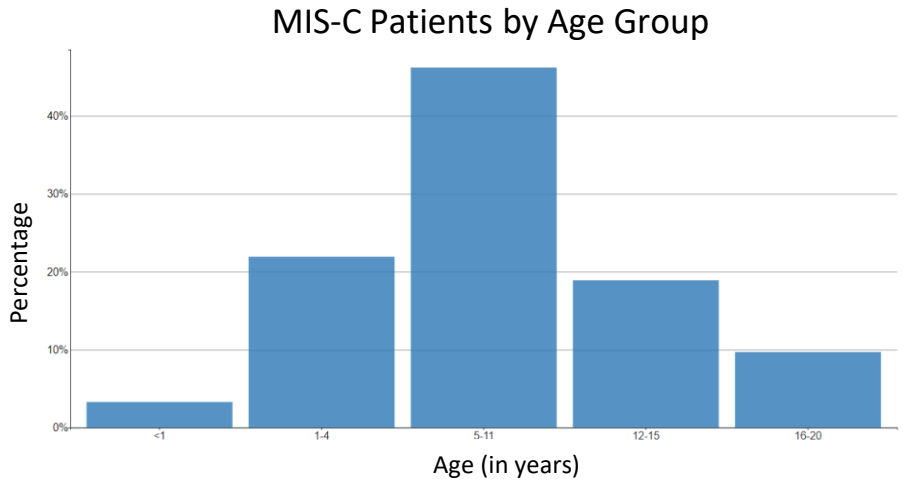
Overview of National Surveillance: Health Department-Reported Cases of MIS-C

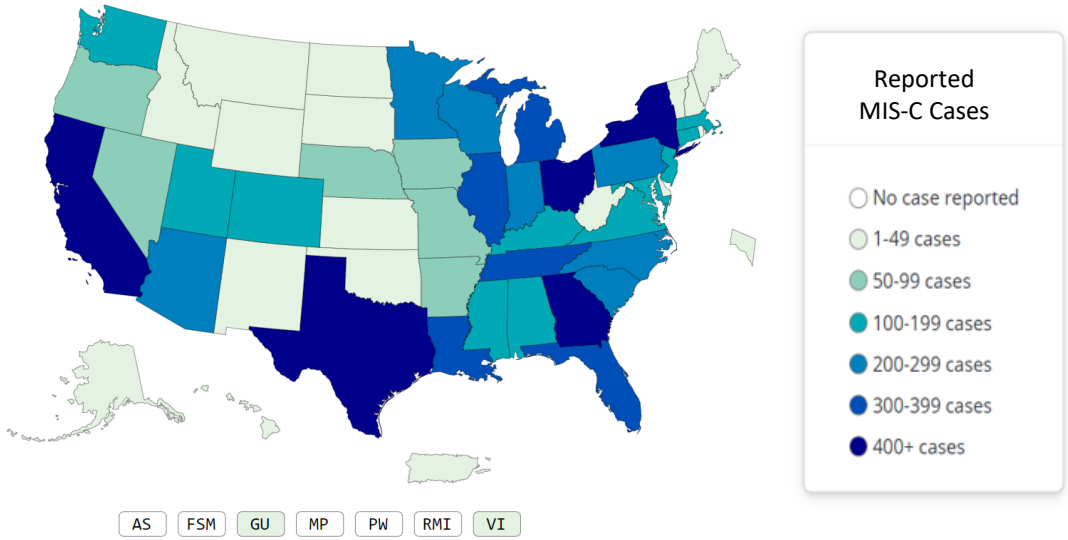
- Passive surveillance
- Healthcare professionals voluntarily report to state, local, and territorial health departments
- Health departments report voluntarily to CDC
- Not nationally notifiable condition, but provides standardized surveillance
- Cases have been reported from 55 U.S. jurisdictions (50 states, New York City, Puerto Rico, Guam, US Virgin Islands, and Washington, DC)
- Reported MIS-C cases are posted each month on the COVID Data Tracker MIS-C page

National Surveillance: Demographic Data from Health Department-reported Cases of MIS-C

Date of reported MIS-C onset
February 19, 2020–October 31, 2022

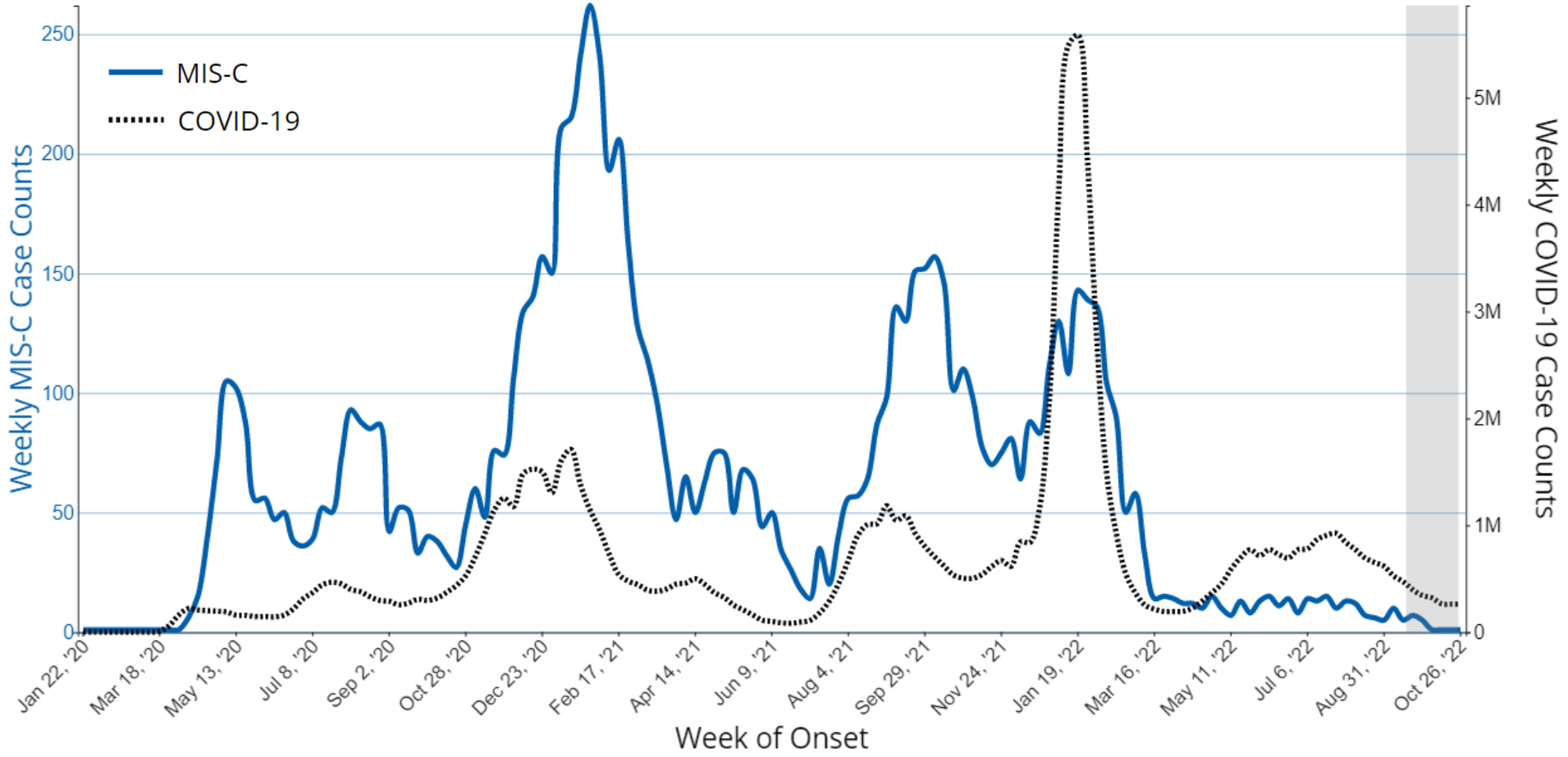
- 9,073 MIS-C cases reported
- 74 deaths
- Median age of 9 years
- 60% male
- 30% occurred in children who are non-Hispanic Black; 26% in children who are Hispanic/Latino





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

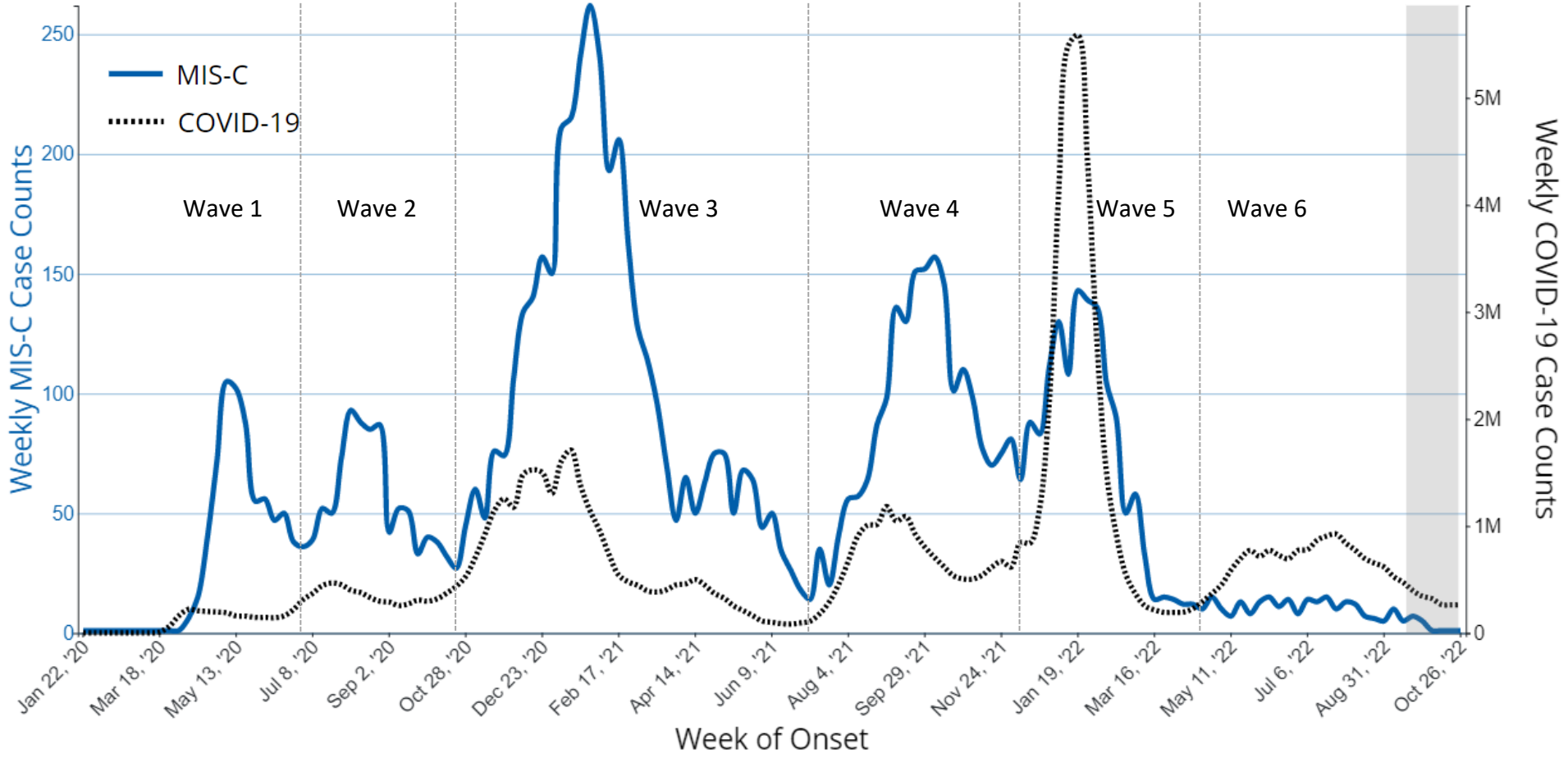
Weekly MIS-C Cases and COVID-19 Cases Reported to CDC, onset Feb 19, 2020 – October 31, 2022 (1 of 4)



The grayed-out area on the right side of the figure represents the most recent 6 weeks of data, for which reporting of MIS-C cases is still incomplete.

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

Weekly MIS-C Cases and COVID-19 Cases Reported to CDC, onset Feb 19, 2020 – October 31, 2022 (2 of 4)



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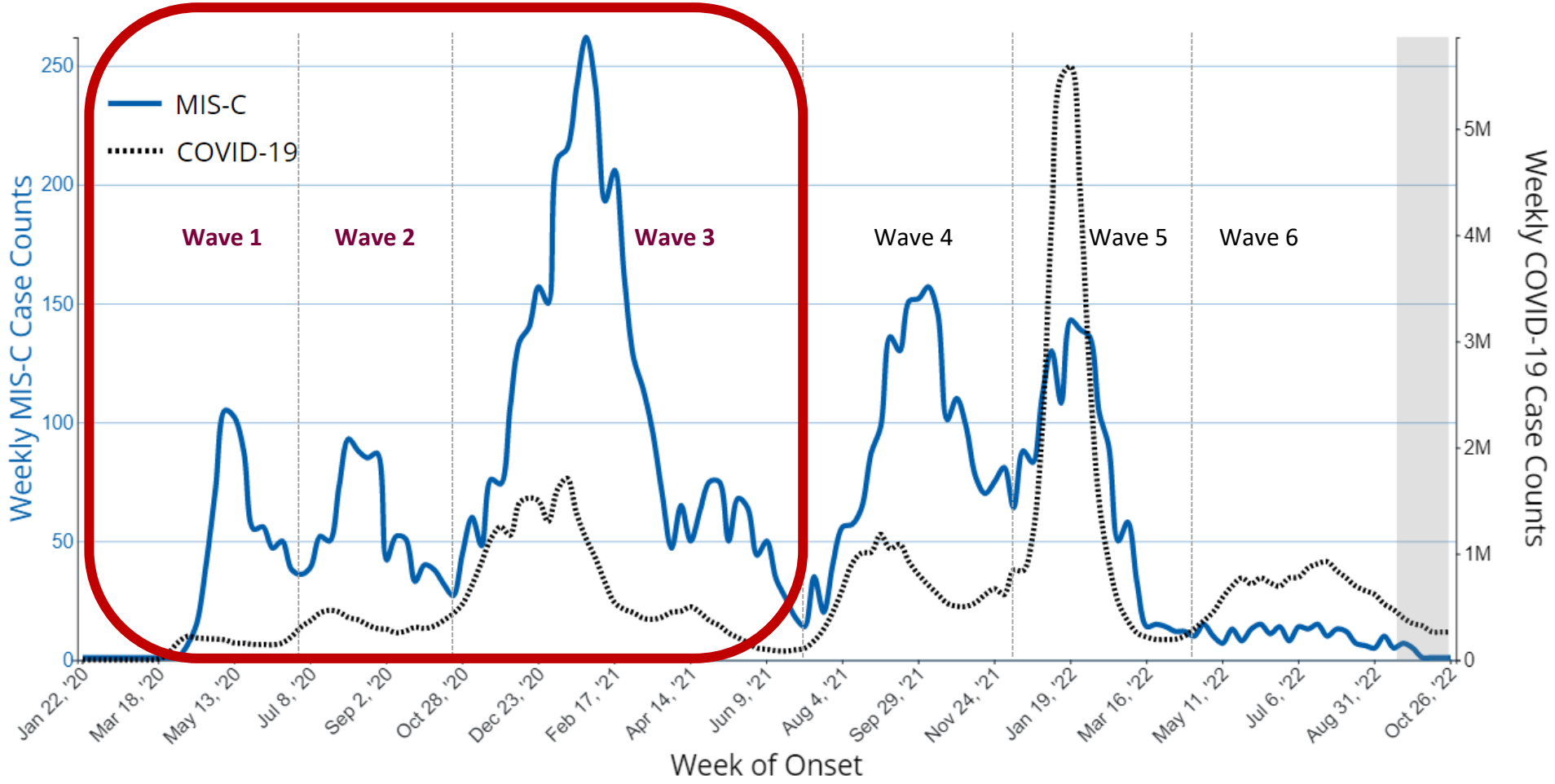
Weekly MIS-C Cases and COVID-19 Cases Reported to CDC, onset Feb 19, 2020 – October 31, 2022 (3 of 4)



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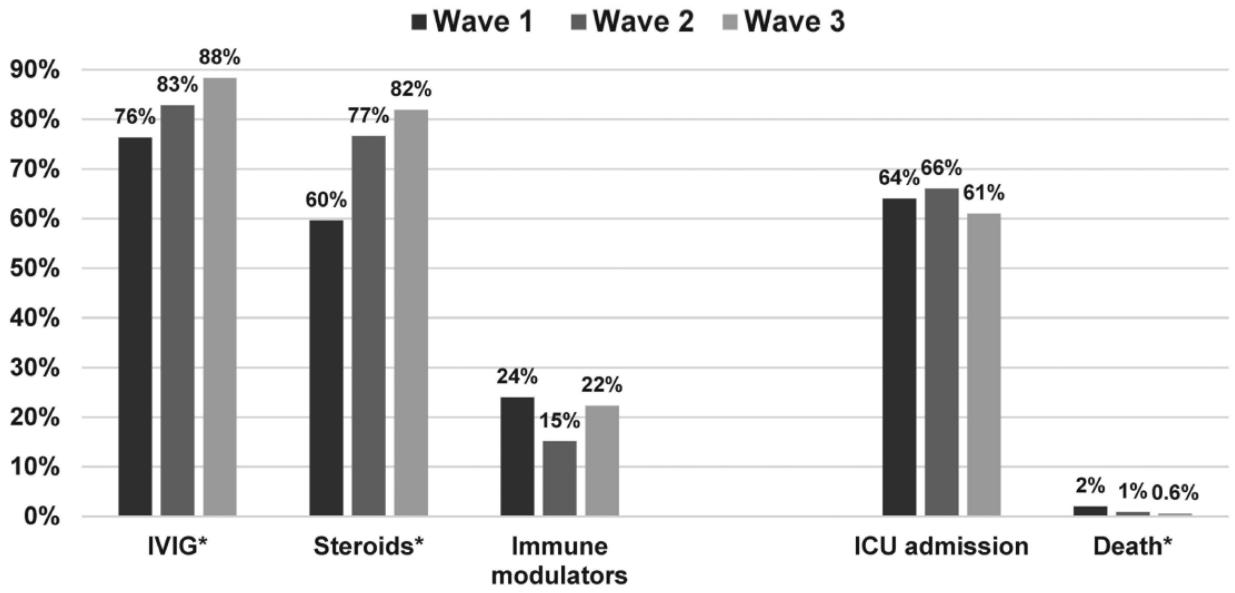
https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

MIS-C and Trends Over Time – United States, February 19, 2020–July 31, 2021

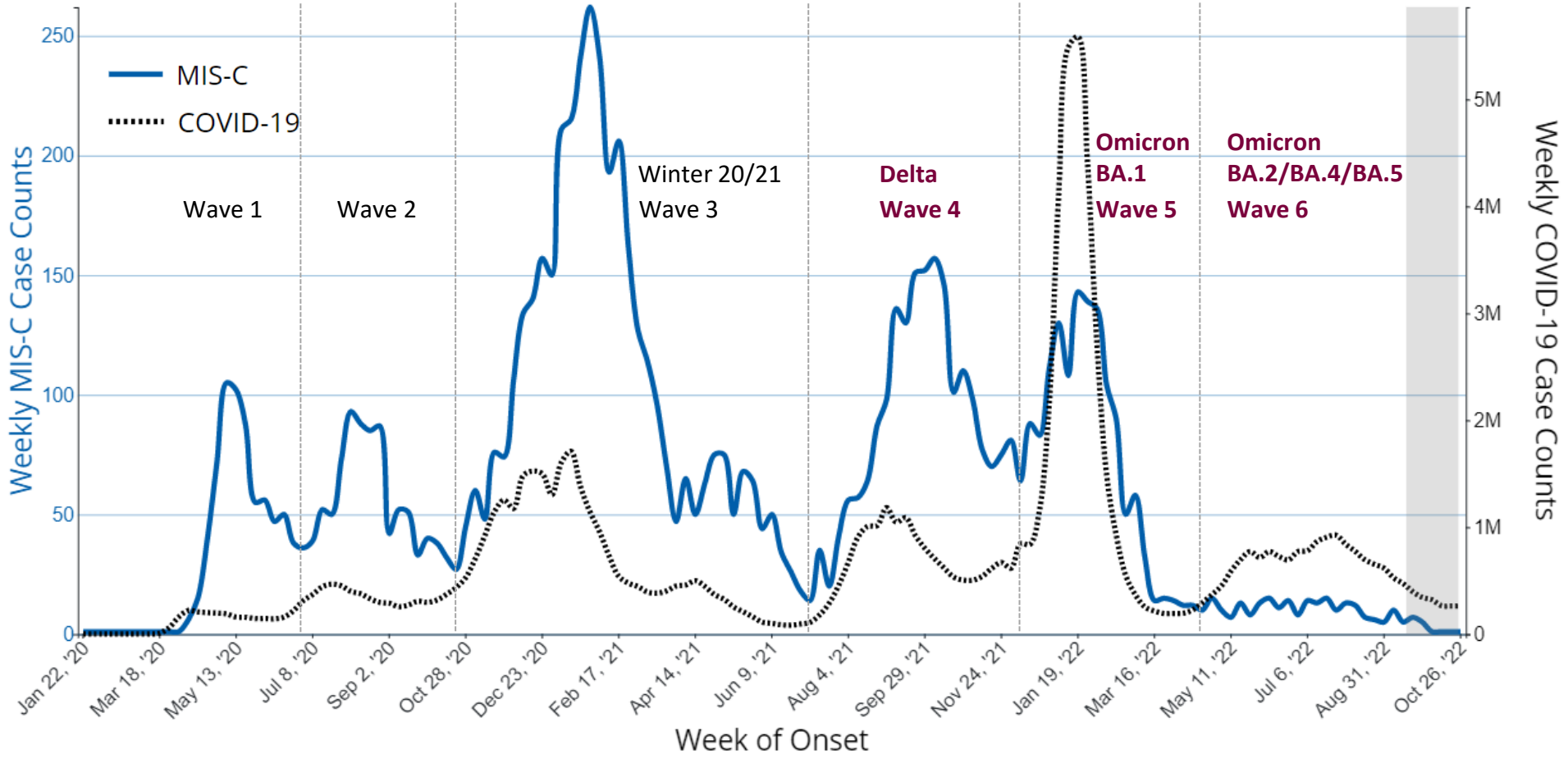
- 4,470 cases of MIS-C reported to CDC's national surveillance system
- Frequency of several cardio-vascular complications including cardiac dysfunction, myocarditis, and shock/vasopressor receipt declined over time



- Clinical outcomes—including length of hospitalization, receipt of mechanical ventilation, ECMO, and death—improved across the first 3 pandemic waves of MIS-C

Miller AD, et al. Clin Infect Dis. Epub 2021 Dec 5; 75(1):e1165-e1175

Weekly MIS-C Cases and COVID-19 Cases Reported to CDC, onset Feb 19, 2020 – October 31, 2022 (4 of 4)



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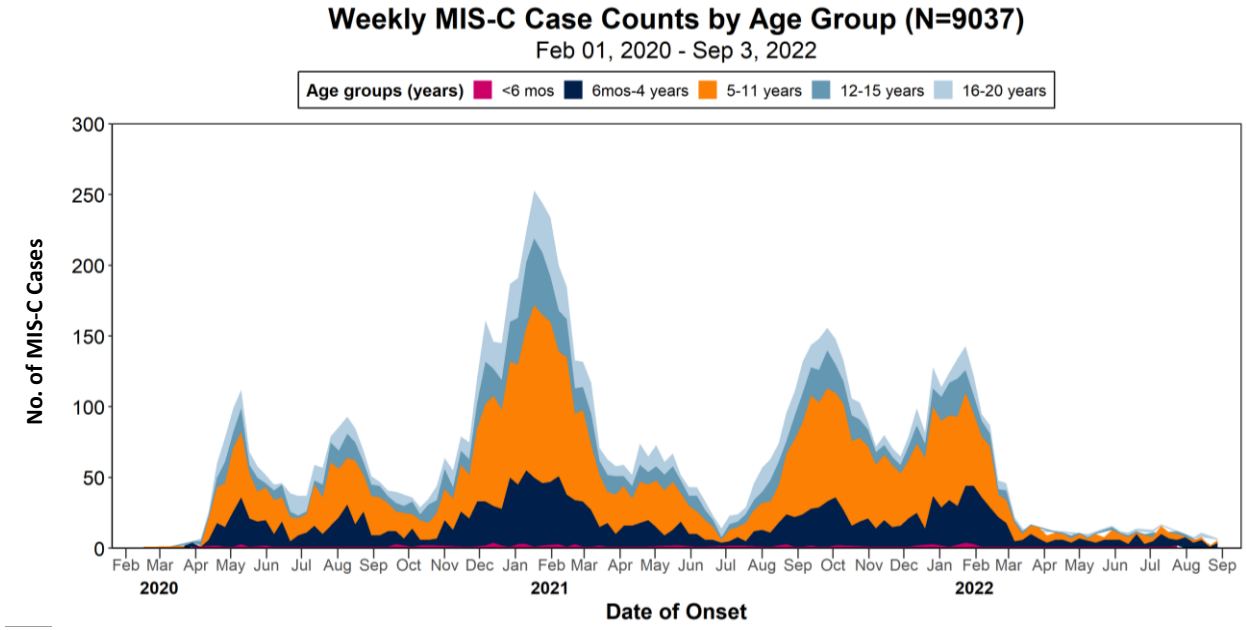
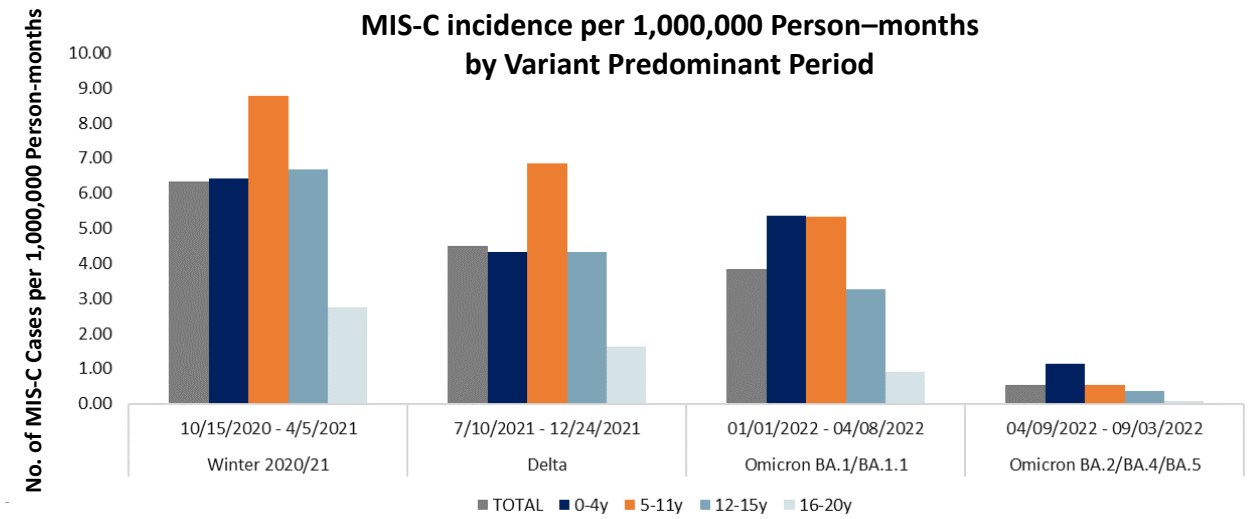
https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

Decline in MIS-C Incidence and Shift in Age Distribution

Variant predominant period	Incidence rate ratio (95% CI)	Age, years, median (IQR)
Winter 2020/21	REF	8 (4 – 12)
Delta	0.68 (0.64 - 0.72)	8 (5 – 11)
Omicron BA.1/BA.1.1	0.59 (0.55 - 0.64)	7 (4 – 11)
Omicron BA.2/BA.4/BA.5	0.08 (0.07 - 0.09)	5 (2 – 10)

While incidence has decreased, the age distribution of reported MIS-C cases has shifted to younger populations.

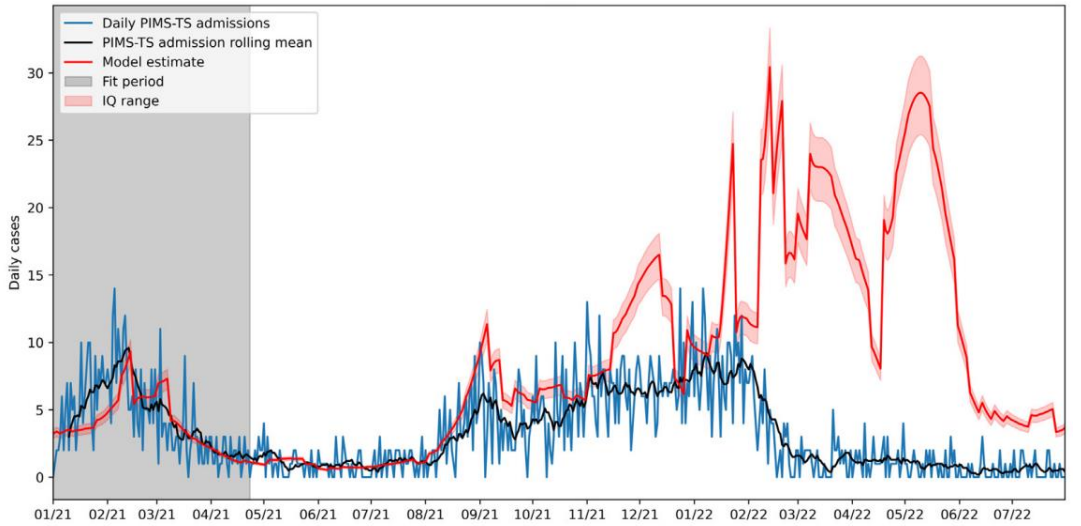


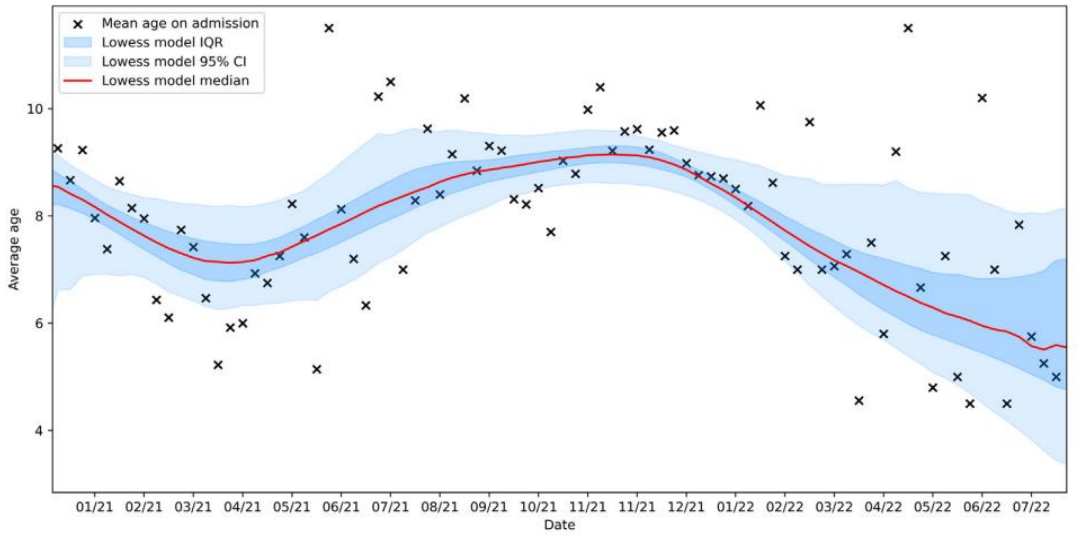


CDC MIS-C national surveillance, unpublished data

Similar changing MIS-C epidemiology observed elsewhere

- Decreased incidence and age distribution shift observed in the UK
  - Top panel: observed cases (blue) 82% lower than predicted cases (red)
  - Bottom: declining trend in age (albeit with large confidence intervals in recent months)
- Potential contributing factors
  - High immunity through SARS-CoV-2 infection and COVID-19 vaccination
  - Viral mutations in key epitopes hypothesized to trigger the hyper-inflammatory response in MIS-C





Shingleton J, et al. J Infect. Epub 2022 Oct 20; S0163-4453(22)00617-X.
Cohen JM, et al. Clin Infect Dis Epub 2022 July 5.
Whittaker R, et al. Pediatrics. Epub 2022 Sep 1;150(3):e2022057564

Self-knowledge Check: The following trends in MIS-C were observed in 2022 (Omicron predominant period) compared to 2020/2021 EXCEPT:

A. The overall incidence of MIS-C decreased, especially with the most recent omicron variants
B. The most commonly affected age group shifted from children 5-11 years to children <5 years
C. The proportion of children with MIS-C who had ICU admission and cardiovascular involvement increased in the United States

Answer: The following trends in MIS-C were observed in 2022 (omicron predominant period) compared to 2020/ 2021 EXCEPT:

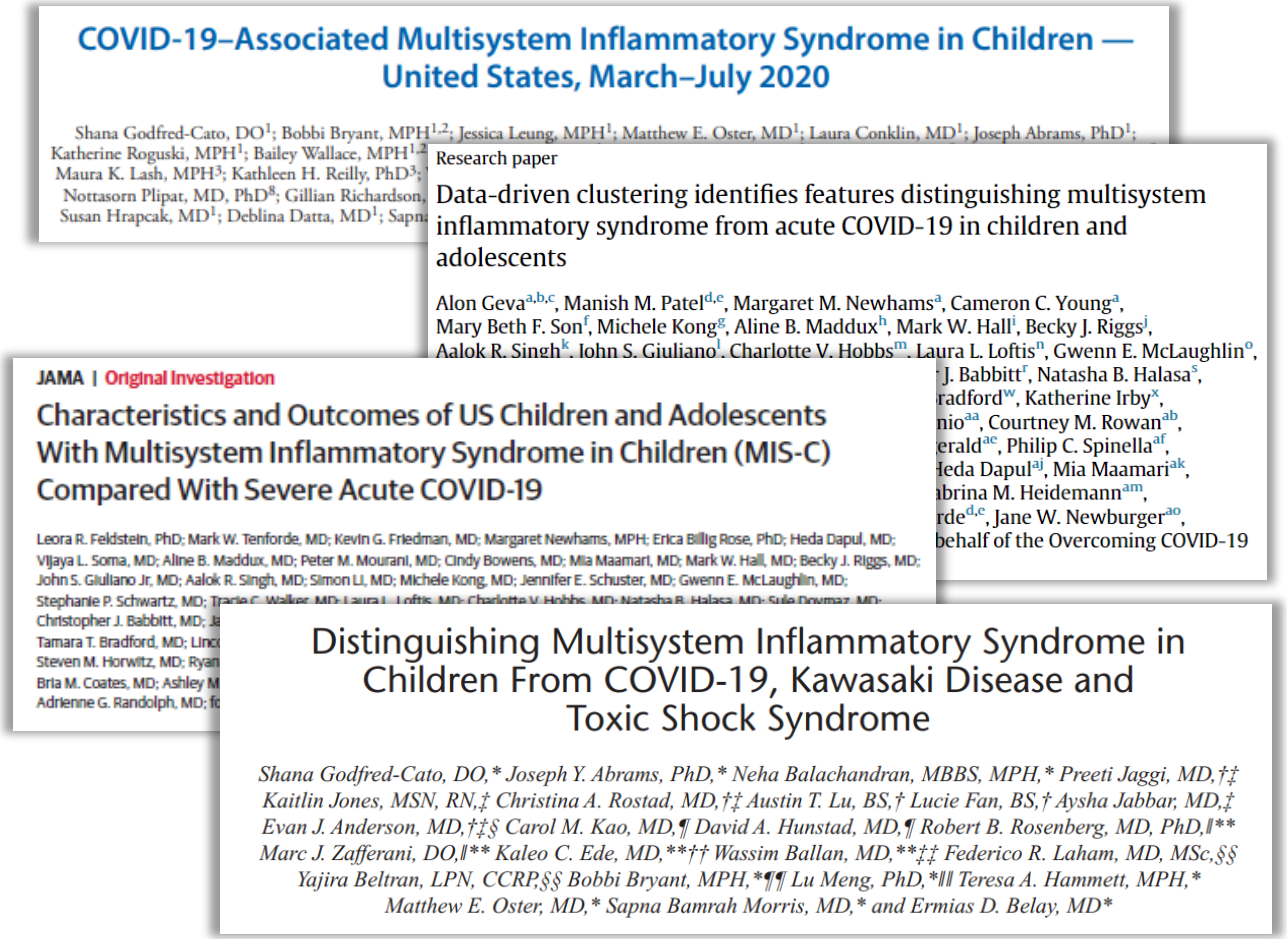
A. The overall incidence of MIS-C decreased, especially with the most recent omicron variants
B. The most commonly affected age group shifted from children 5-11 years to children <5 years
C. **The proportion of children with MIS-C who had ICU admission and cardiovascular involvement increased in the United States**

Rationale: Answer is C – trends in MIS-C phenotype in 2022 are still being investigated but data suggest that ICU admission and severe MIS-C organ involvement decreased in our US MIS-C national surveillance data.

Council of State & Territorial Epidemiologists (CSTE)/CDC surveillance case definition for MIS-C

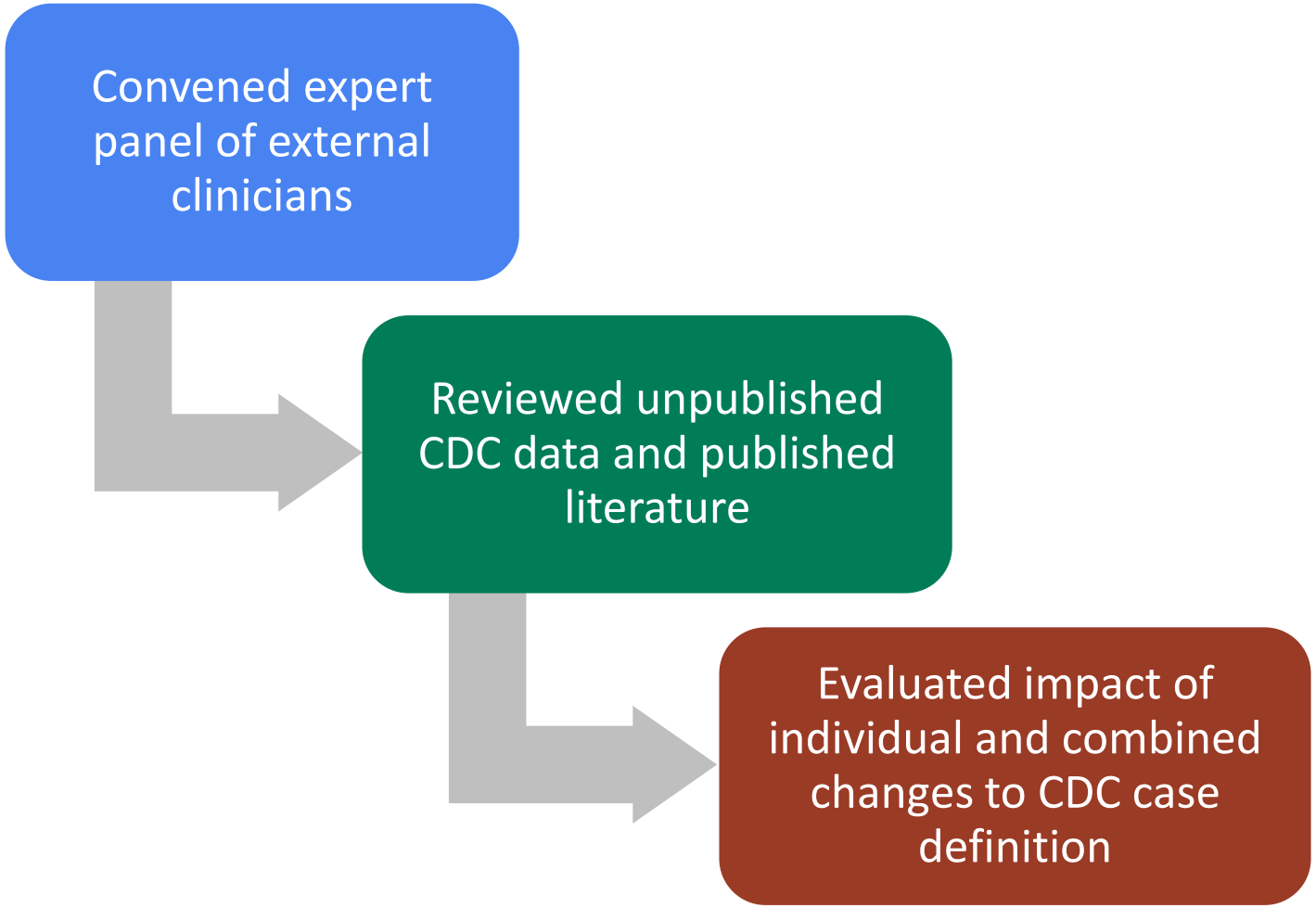
Why create a new MIS-C case definition now?

- CDC 2020 case definition based on public health need and limited number of cases[1,2]
- Recent analyses suggest that CDC case definition may misclassify between MIS-C, COVID-19, and other inflammatory conditions[3,4,5]
- Certain components of the CDC case definition are difficult for surveillance staff to implement
- Need to establish standardized surveillance definition jointly with the Council of State & Territorial Epidemiologists (CSTE)



1. https://emergency.cdc.gov/han/2020/han00432.asp
2. Dufort EM, et al. N Engl J Med. 2020 Jul 23; 383(4):347-358
3. LaRovere KL, et al. JAMA Neurol. 2021 May 1;78(5):536-547
4. Geva A, et al. EClinicalMedicine. 2021 Oct; 40:101112
5. Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Process to create new CSTE/CDC MIS-C surveillance case definition

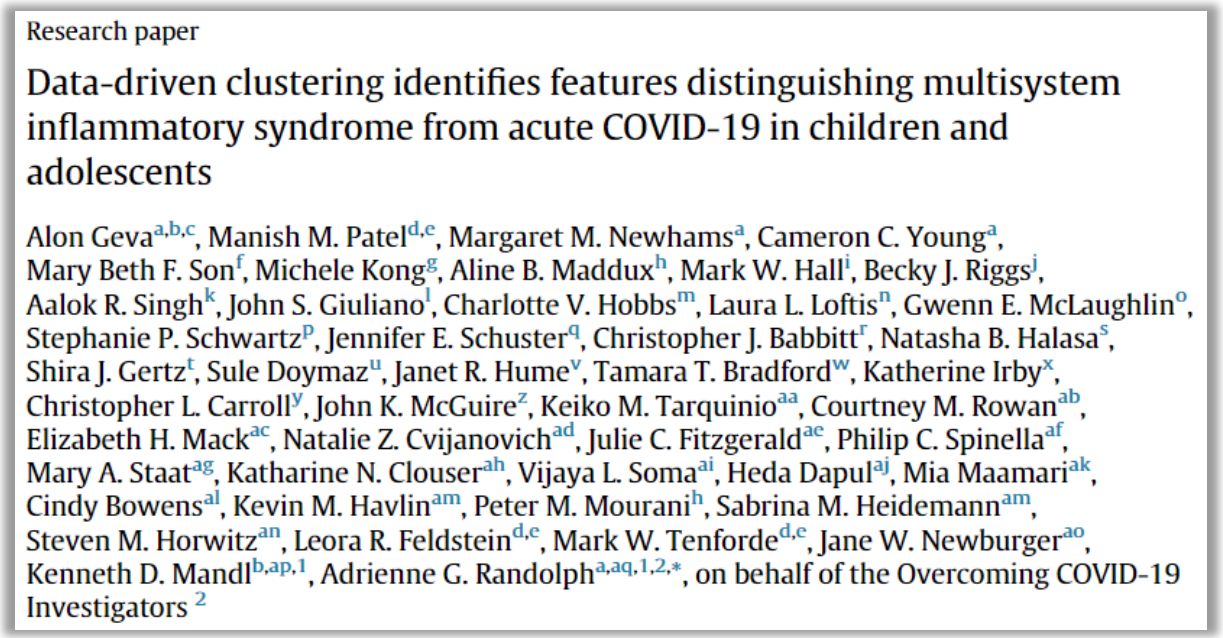


Working group:

- CSTE
  - Ellen Lee (NYC)
  - Sarah Lim (MN)
  - Katie Brown (MA)
- CDC
  - Michael Melgar
  - Allison Miller
  - Anna Yousaf
  - Angie Campbell

Application of the CDC 2020 case definition results in misclassification of some acute COVID-19 as MIS-C

- Overcoming COVID-19 network study identified 3 groups of phenotypically distinct SARS-CoV-2-associated illness
- One group included primarily patients with pulmonary disease and positive nucleic acid testing for SARS-CoV-2
- Most patients in this group were diagnosed with COVID-19
  - —But included nearly 20% of all patients in the study that were diagnosed with MIS-C using the 2020 case definition



Research paper

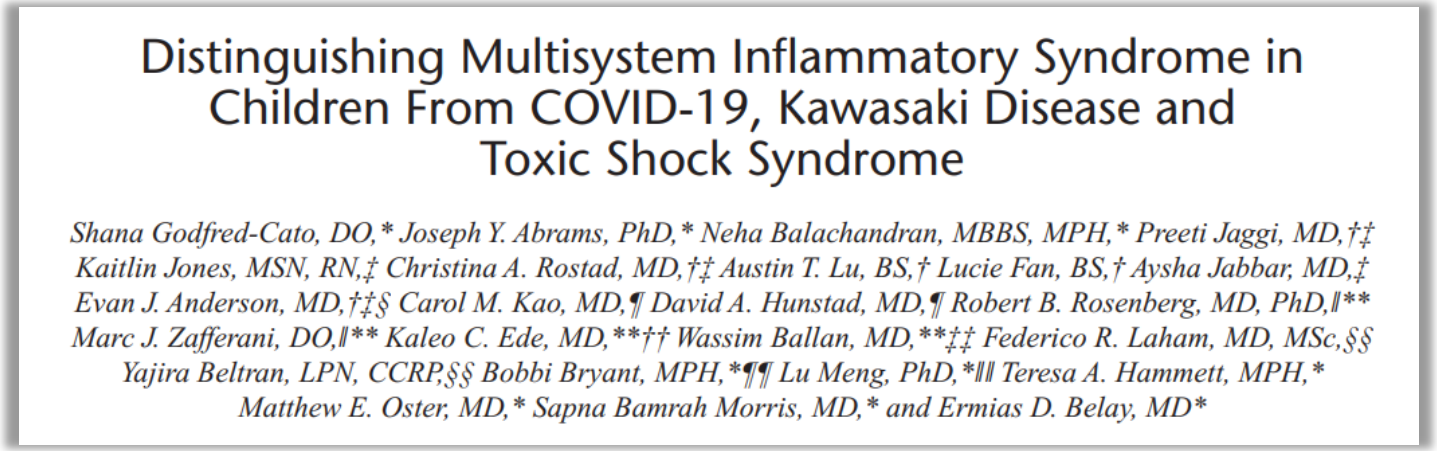
Data-driven clustering identifies features distinguishing multisystem inflammatory syndrome from acute COVID-19 in children and adolescents

Alon Geva[a,b,c], Manish M. Patel[d,e], Margaret M. Newhams[a], Cameron C. Young[a], Mary Beth F. Son[f], Michele Kong[g], Aline B. Maddux[h], Mark W. Hall[i], Becky J. Riggs[j], Aalok R. Singh[k], John S. Giuliano[l], Charlotte V. Hobbs[m], Laura L. Loftis[n], Gwenn E. McLaughlin[o], Stephanie P. Schwartz[p], Jennifer E. Schuster[q], Christopher J. Babbitt[r], Natasha B. Halasa[s], Shira J. Gertz[t], Sule Doymaz[u], Janet R. Hume[v], Tamara T. Bradford[w], Katherine Irby[x], Christopher L. Carroll[y], John K. McGuire[z], Keiko M. Tarquinio[aa], Courtney M. Rowan[ab], Elizabeth H. Mack[ac], Natalie Z. Cvijanovich[ad], Julie C. Fitzgerald[ae], Philip C. Spinella[af], Mary A. Staat[ag], Katharine N. Clouser[ah], Vijaya L. Soma[ai], Heda Dapul[aj], Mia Maamari[ak], Cindy Bowens[al], Kevin M. Havlin[am], Peter M. Mourani[h], Sabrina M. Heidemann[am], Steven M. Horwitz[an], Leora R. Feldstein[d,e], Mark W. Tenforde[d,e], Jane W. Newburger[ao], Kenneth D. Mandl[b,ap,1], Adrienne G. Randolph[a,aq,1,2,*], on behalf of the Overcoming COVID-19 Investigators [2]

Geva A, et al. EClinicalMedicine. 2021 Oct; 40:101112

Certain clinical features distinguish between MIS-C, Kawasaki disease (KD), and toxic shock syndrome (TSS)

- CDC-funded Phenotype Initiative identified clinical characteristics distinguishing MIS-C from pediatric COVID-19 and from pre-pandemic cases of KD and TSS

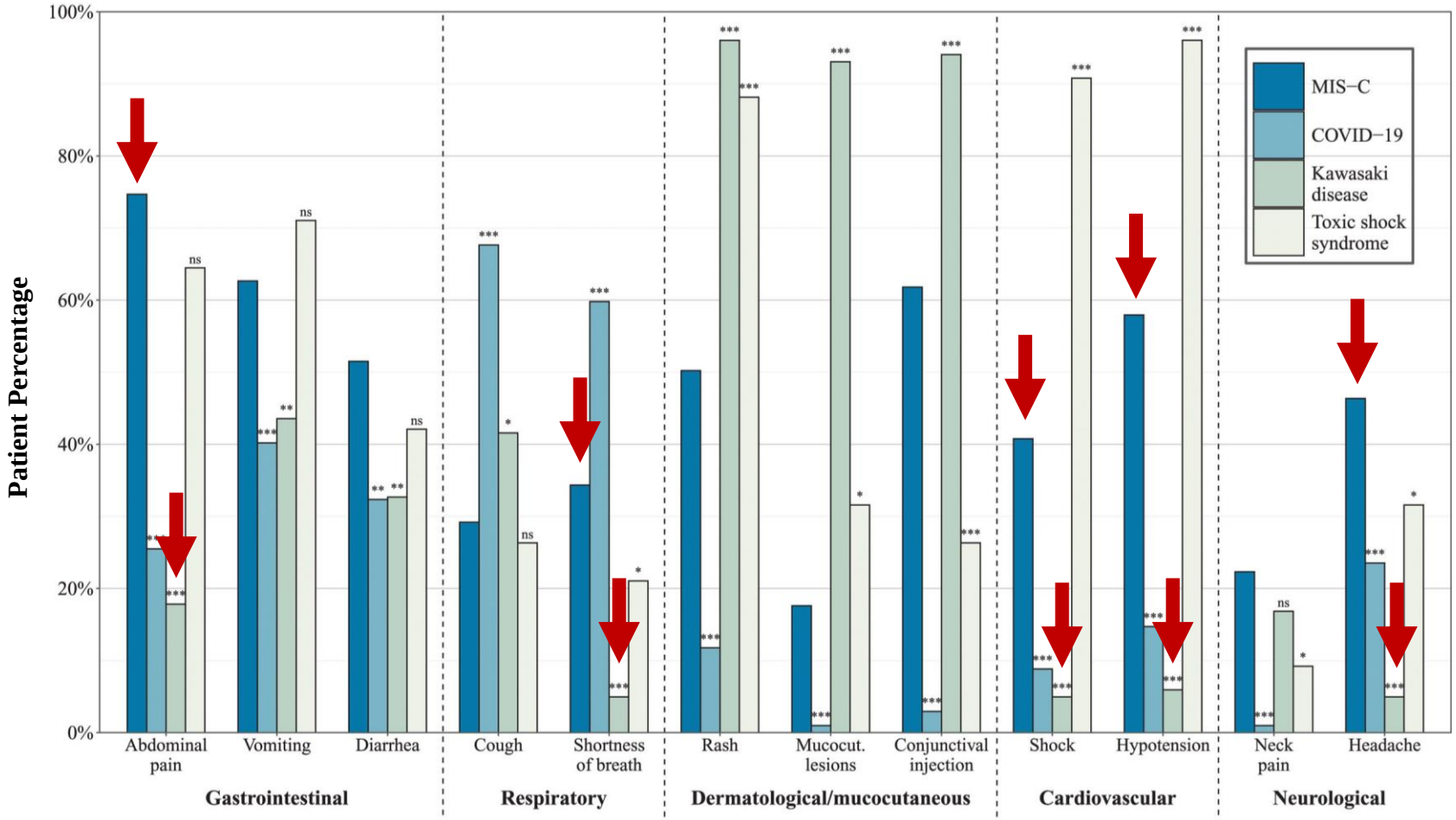


Distinguishing Multisystem Inflammatory Syndrome in Children From COVID-19, Kawasaki Disease and Toxic Shock Syndrome

Shana Godfred-Cato, DO, Joseph Y. Abrams, PhD,* Neha Balachandran, MBBS, MPH,* Preeti Jaggi, MD,†‡ Kaitlin Jones, MSN, RN,‡ Christina A. Rostad, MD,†‡ Austin T. Lu, BS,† Lucie Fan, BS,† Aysha Jabbar, MD,‡ Evan J. Anderson, MD,†‡§ Carol M. Kao, MD,¶ David A. Hunstad, MD,¶ Robert B. Rosenberg, MD, PhD,‖** Marc J. Zafferani, DO,‖** Kaleo C. Ede, MD,**†† Wassim Ballan, MD,**‡‡ Federico R. Laham, MD, MSc,§§ Yajira Beltran, LPN, CCRP,§§ Bobbi Bryant, MPH,*¶¶ Lu Meng, PhD,*‖‖ Teresa A. Hammett, MPH,* Matthew E. Oster, MD,* Sapna Bamrah Morris, MD,* and Ermias D. Belay, MD**

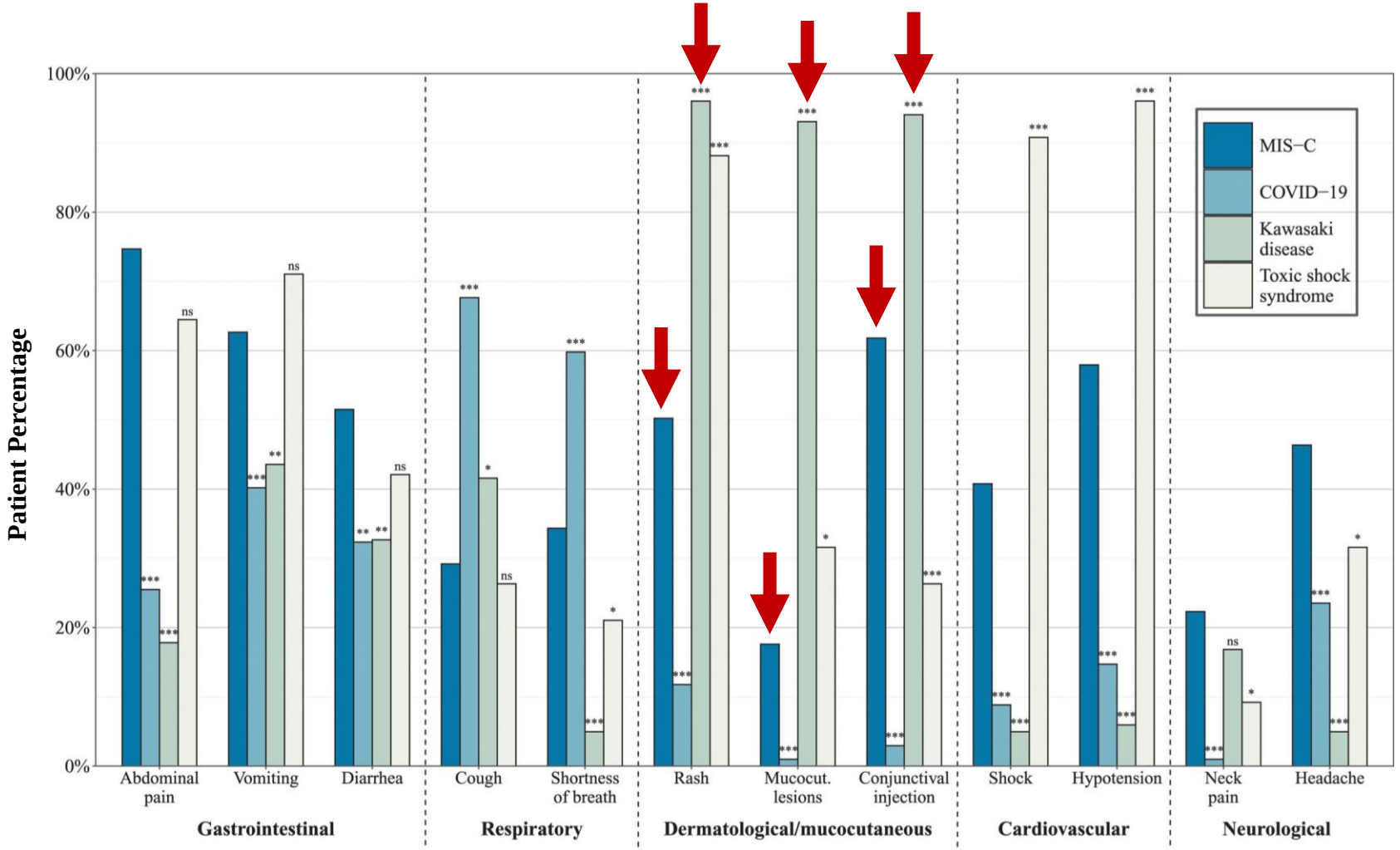
Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Abdominal pain, dyspnea, shock, hypotension, and headache were more common in MIS-C than in KD



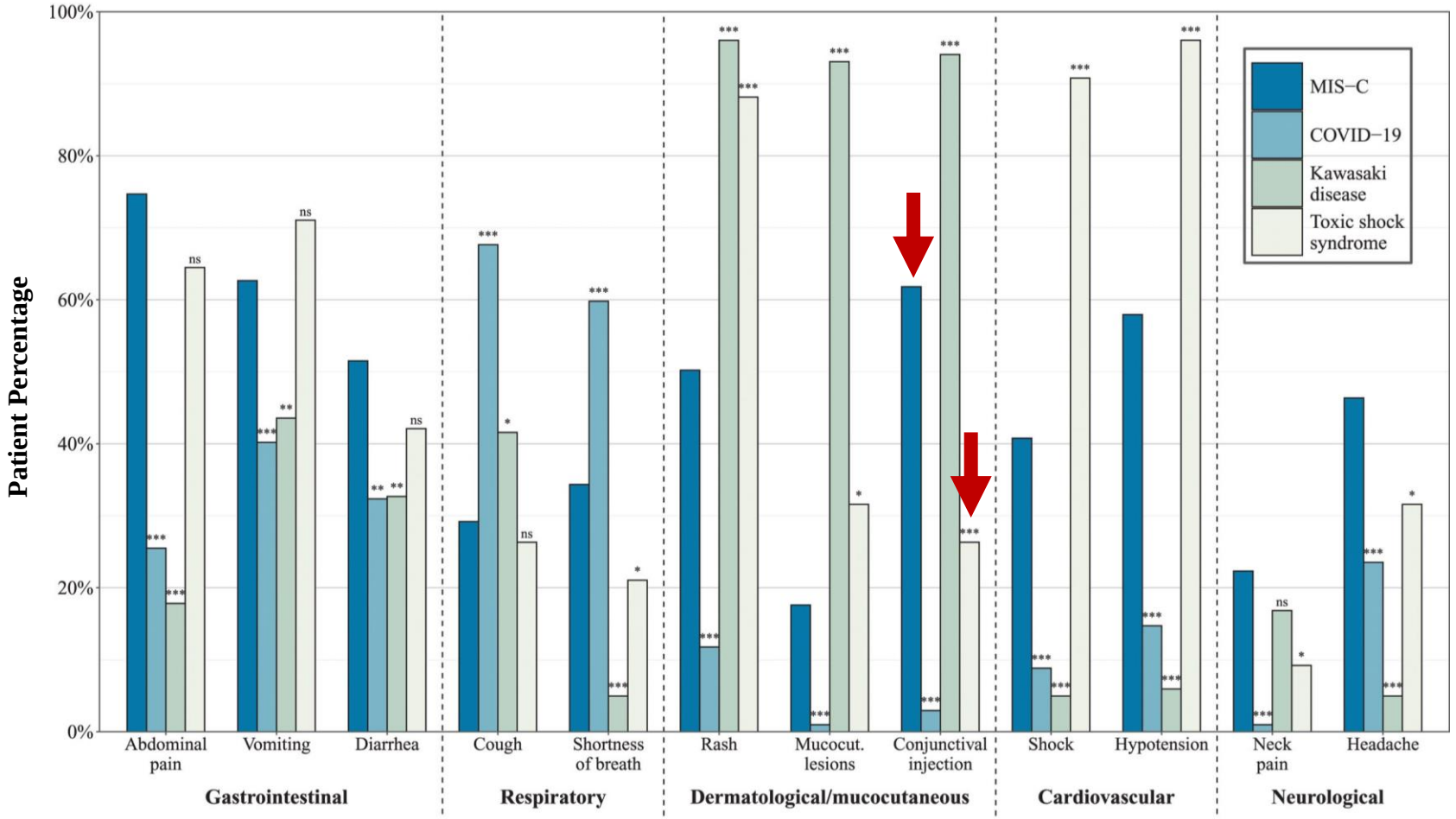
Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Rash, mucocutaneous lesions, and conjunctival injection were more common in KD than in MIS-C



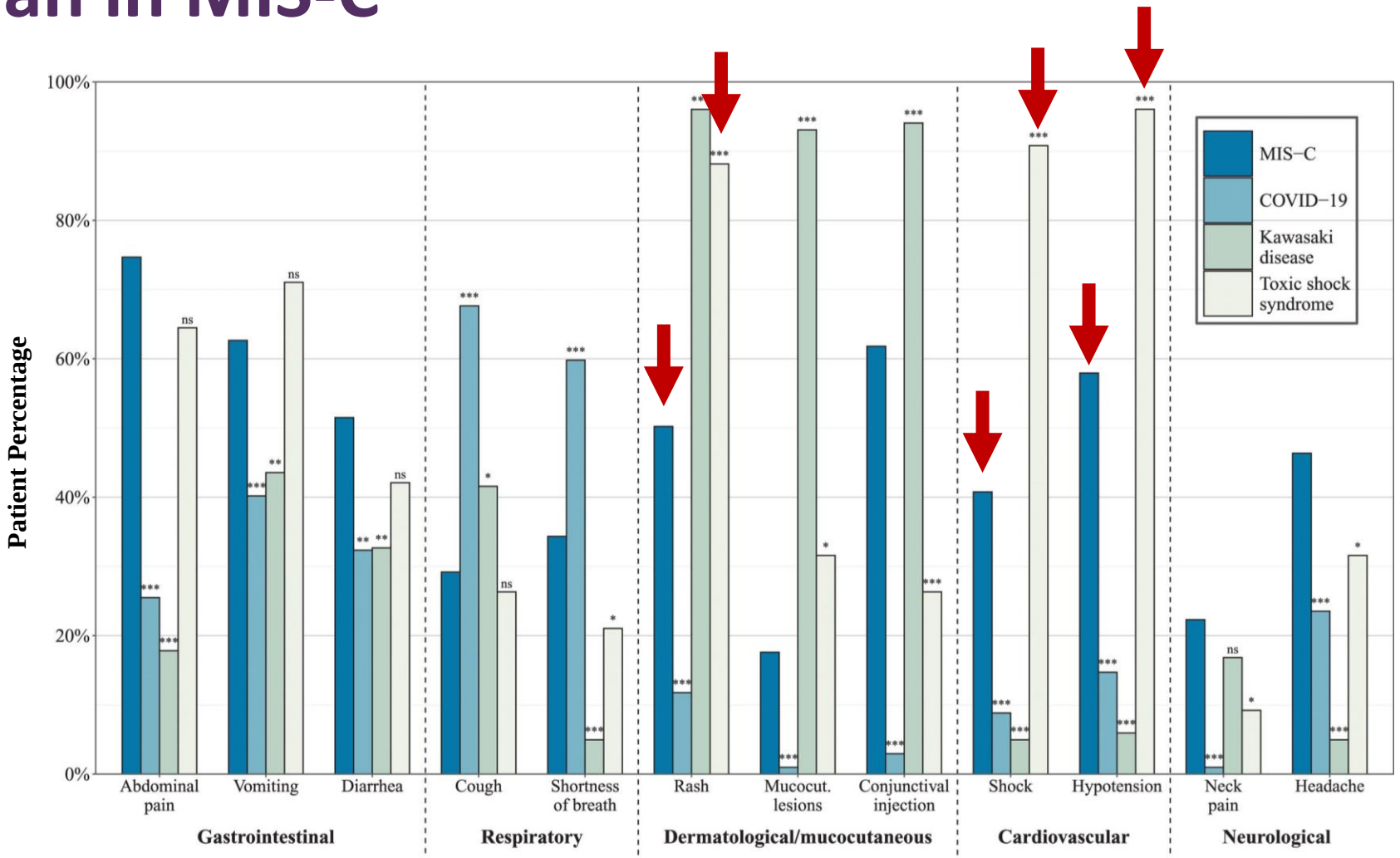
Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Conjunctival injection was more common in MIS-C than in TSS



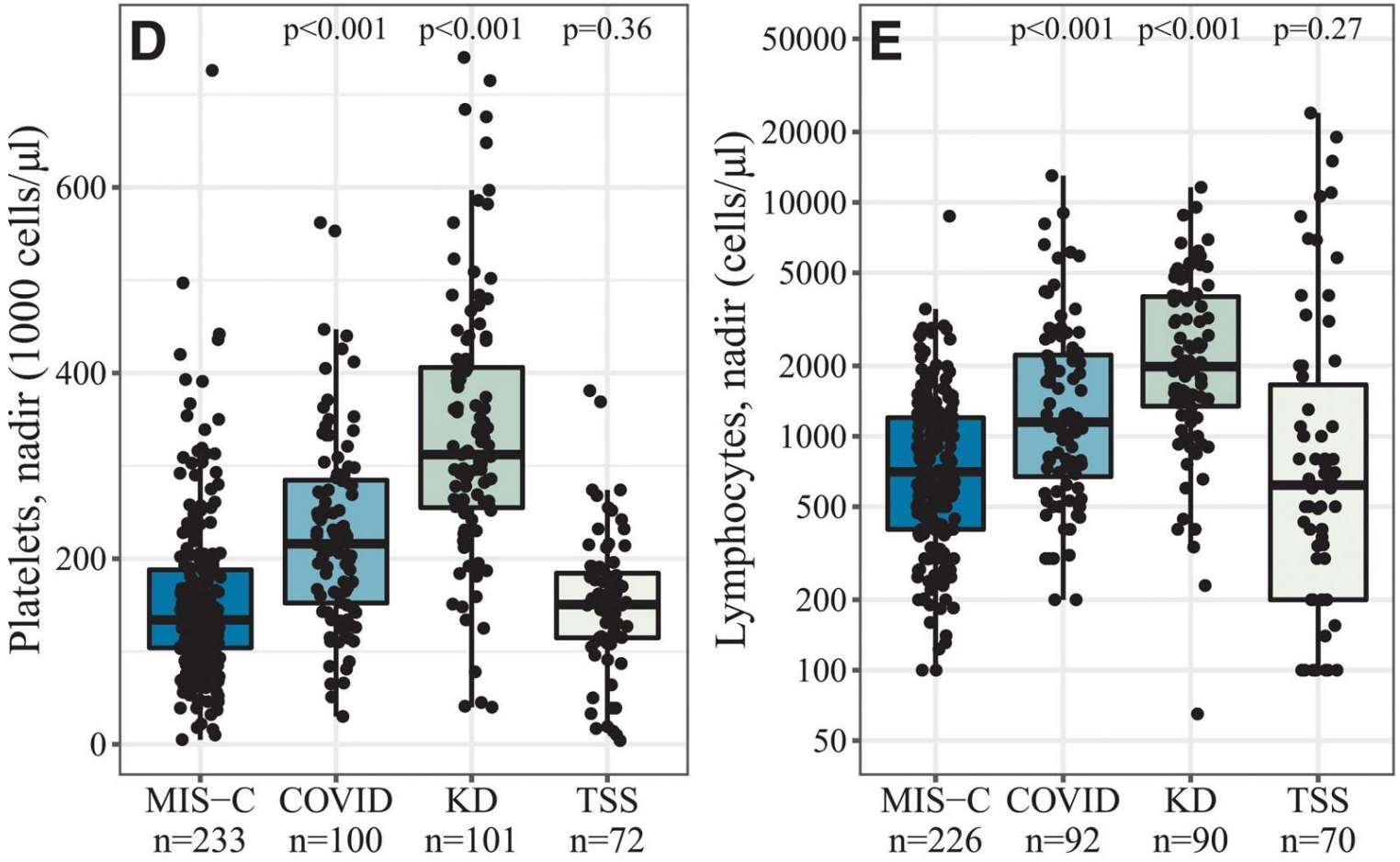
Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Rash, shock, and hypotension were more common in TSS than in MIS-C



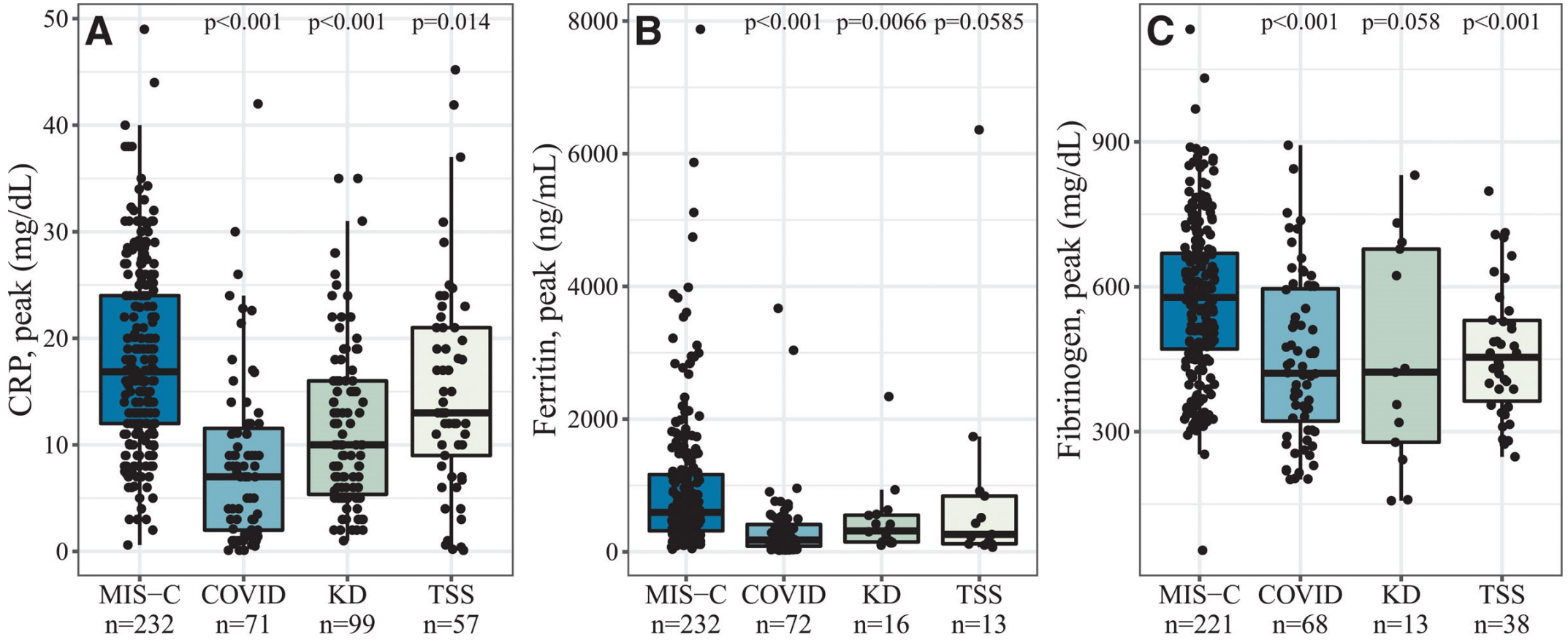
Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Hematologic laboratory values differ significantly between MIS-C and KD



Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

C-reactive protein (CRP) elevation better distinguishes MIS-C from other inflammatory conditions, compared with ferritin and fibrinogen



Godfred-Cato S, et al. Pediatr Infect Dis J. 2022 Apr 1;41(4):315-323

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (1 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	
Illness requiring hospitalization	
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	
• Dermatologic (e.g., rash, mucocutaneous lesions)	
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	
• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (2 of 10)

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Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	
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Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (3 of 10)

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Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	
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Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (4 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	
• Dermatologic (e.g., rash, mucocutaneous lesions)	
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• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (5 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
	• Shock
• Dermatologic (e.g., rash, mucocutaneous lesions)	
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	
• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (6 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
	• Shock
• Dermatologic (e.g., rash, mucocutaneous lesions)	• Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	
• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (7 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
	• Shock
• Dermatologic (e.g., rash, mucocutaneous lesions)	• Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	• GI: abdominal pain, vomiting, or diarrhea
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	
• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (8 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
	• Shock
• Dermatologic (e.g., rash, mucocutaneous lesions)	• Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	• GI: abdominal pain, vomiting, or diarrhea
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	• Hematologic: platelet count <150k / µL, ALC <1,000 / µL
• Neurologic, Renal, Respiratory	
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (9 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
	• Shock
• Dermatologic (e.g., rash, mucocutaneous lesions)	• Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	• GI: abdominal pain, vomiting, or diarrhea
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	• Hematologic: platelet count <150k / µL, ALC <1,000 / µL
• Neurologic, Renal, Respiratory	• ~~Neurologic, Renal, Respiratory~~
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	

Comparison – CDC 2020 & CSTE/CDC Surveillance Case Definitions for MIS-C (10 of 10)

In a person aged <21 years, and in the absence of a more likely alternative diagnosis:

CDC 2020 MIS-C Surveillance Case Definition	CSTE/CDC MIS-C Surveillance Case Definition (Effective 1/1/2023) Highlighted text indicates substantive change from 2020 CDC definition
Fever ≥38.0 C or subjective fever lasting ≥24 hours	Subjective or documented fever (T ≥38.0 C) ~~lasting ≥24 hours~~
Illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
Laboratory evidence of inflammation (e.g., ↑CRP, ↑ESR, …)	CRP ≥3.0 mg/dL
Multisystem organ involvement, ≥2 of the following:	New onset manifestations in ≥2 of the following categories:
• Cardiac (e.g., shock, ↑troponin, ↑BNP, abnormal echo, arrhythmia)	• Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
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• Dermatologic (e.g., rash, mucocutaneous lesions)	• Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
• GI (e.g., ↑bilirubin, ↑liver enzymes, diarrhea)	• GI: abdominal pain, vomiting, or diarrhea
• Hematologic (e.g., ↑D-dimer, thrombophilia, ↓platelets)	• Hematologic: platelet count <150k / µL, ALC <1,000 / µL
• Neurologic, Renal, Respiratory	• ~~Neurologic, Renal, Respiratory~~
Positive SARS-CoV-2 RT-PCR/serology/antigen, OR exposure within the 4 weeks prior to symptom onset	Detection of SARS-CoV-2 nucleic acid/antigen up to 60 days prior to or during hospitalization, or in a post-mortem specimen*, OR Detection of antibody associated with current illness*, OR Close contact with a confirmed/probable COVID-19 case in the 60 days prior to hospitalization

*confirmatory lab evidence

CSTE/CDC MIS-C Surveillance Case Classification

- Confirmed:

Meets the clinical criteria AND the confirmatory laboratory evidence

- Probable:

Meets the clinical criteria AND the epidemiologic linkage criteria

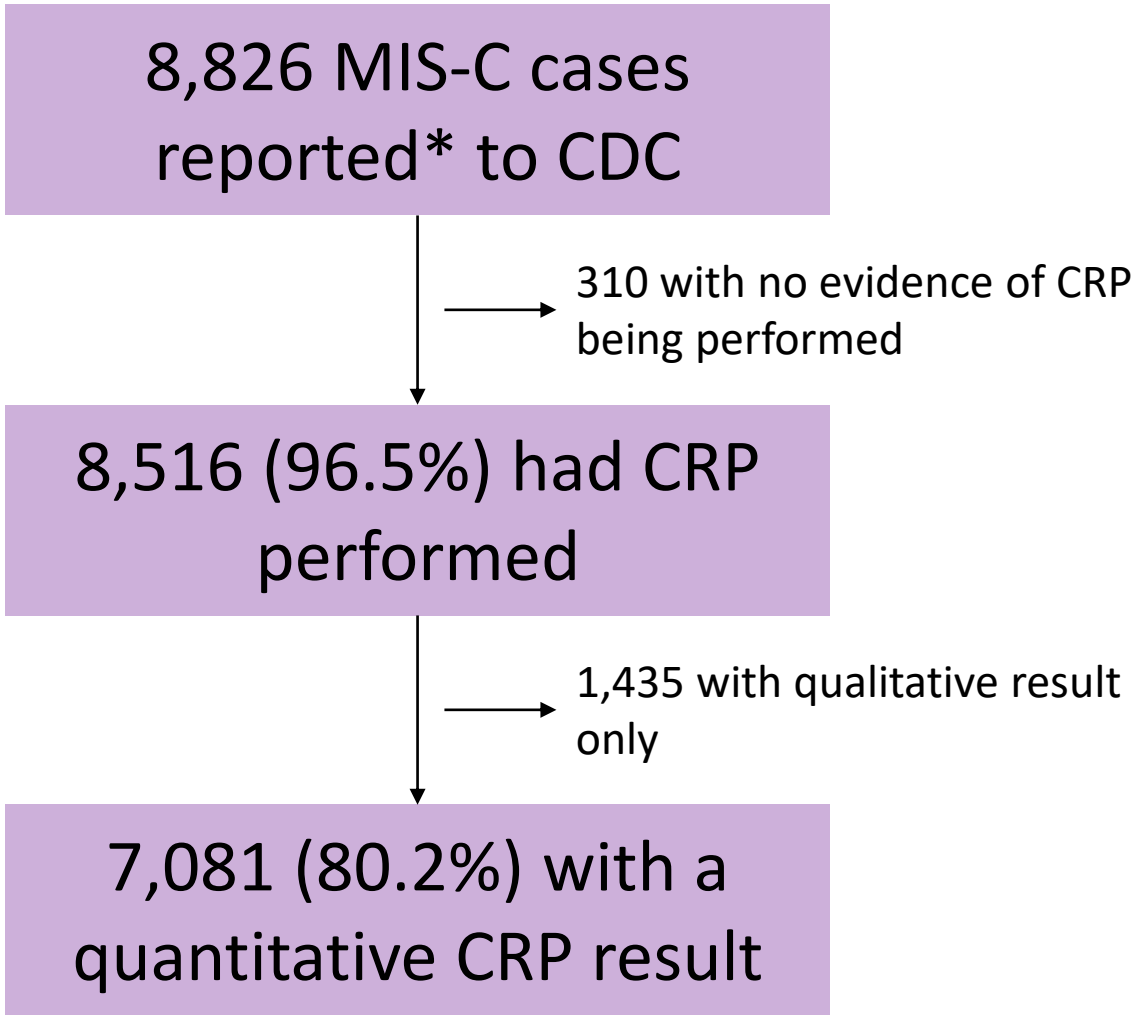
- Suspect:

Meets vital records criteria*

*Death occurring in a person aged <21 years whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death

Of previously reported cases of MIS-C, how many would meet the new CSTE/CDC surveillance case definition?

Evaluating the CSTE/CDC MIS-C surveillance case definition requires a quantitative C-reactive protein (CRP) result



* Reported to CDC national surveillance as of August 31, 2022, with illness onset on or before June 17, 2022, and meeting the CDC 2020 case definition for MIS-C

Of previously reported cases of MIS-C, how many would meet the new CSTE/CDC MIS-C surveillance case definition? (cont.)

Criterion from CSTE/CDC surveillance case definition for MIS-C	MIS-C cases meeting criterion (n=7,081)
Full CSTE/CDC case definition*	**6,158 (87.0%)**
Age <21 years	100%
Subjective or documented fever (T ≥38.0 C)	100%
Clinical severity requiring hospitalization or resulting in death	100%
CRP ≥3.0 mg/dL	**6,635 (93.7%)**
New onset manifestations in at least 2 organ systems	**6,492 (91.7%)**
SARS-CoV-2 testing** or exposure criteria	100%
No more likely alternative diagnosis	100%

* Confirmed OR probable criteria

** Due to missing dates, positive SARS-CoV-2 test results were accepted regardless of timing relative to hospitalization

Guidance documents on MIS-C adjudication during the case definition transition period provided to state, local, and territorial health departments by email and web posting.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES CENTERS FOR DISEASE CONTROL AND PREVENTION ATLANTA, GA 30329

Multisystem Inflammatory Syndrome Associated with SARS-CoV-2 Infection Interim Case Reporting Guide

Purpose

The purpose of this document is to assist local, state, and territorial health departments with reporting cases of MIS-C to CDC after the 2023 CDC MIS-C case definition has gone into effect. This guide is to be used for cases that are **reported to CDC after January 1, 2023** but have an **MIS-C illness onset before January 1, 2023.** These potential MIS-C illnesses should be adjudicated as MIS-C cases using the 2020 CDC MIS-C case definition, but submitted to CDC using the 2023 MIS-C case report form. The following table provides detailed guidance on how to adjudicate using the 2020 case definition while reporting with the 2023 case report form.

	CDC MIS-C 2020 Case Definition Inclusion Criteria	CDC MIS-C 2023 Case Definition Inclusion Criteria	Instructions for completing 2023 MIS-C Case Report Form*
Age	Age <21 years	Age <21 years	Select 1.1 if age <21 years
Fever	Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours	Subjective or documented fever (≥38.0°C)	Select 1.2 only if fever ≥24 hours (per 2020 case definition)
Illness Severity	Clinically severe illness requiring hospitalization	Illness with clinical severity requiring hospitalization or resulting in death	Select 1.3 only if patient hospitalized for their potential MIS-C illness
Alternative Diagnosis	No alternative plausible diagnosis	A more likely alternative diagnosis is not present	Select 1.4 if an alternative plausible diagnosis is not present
Laboratory markers of inflammation	Including, but not limited to one or more: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6)	C-reactive protein ≥3.0 mg/dL (30 mg/L)	• If CRP ≥3.0 mg/dL (30 mg/L), select 1.5 • If CRP is elevated but <3.0 mg/dL (30 mg/L, do not select 1.5 (i.e. leave blank) • If CRP result is not available but the patient has another elevated lab marker of inflammation that was previously included in the 2020 case definition do not select 1.5 (i.e. leave blank)
Organ System Involvement			
	Multisystem (≥2) organ involvement	New onset manifestations in ≥2 of the following categories:	
Cardiac	Cardiac involvement includes: • Shock/receipt of vasopressors • Elevated troponin • Elevated BNP/NT-proBNP • Abnormal echocardiogram • Arrhythmia • Congestive heart failure	Includes only: • I-Left ventricular ejection fraction <55% • Coronary artery dilatation, aneurysm, or ectasia	Select 1.6.1 if any 2020 markers of cardiac involvement are present **except shock**. If shock plus other 2020 markers of cardiac involvement are present, select 1.6.1 and 1.6.3 and report shock in 5.6. If shock is the only 2020 marker of cardiac involvement, select 1.6.3 only (do not select 1.6.1) and report shock in 5.6. Report elevated troponin in 4.1.1. Report congestive heart failure, myocarditis, pericarditis, pericardial

Self-knowledge Check: The new CSTE/CDC MIS-C surveillance case definition includes the following changes:

A. Laboratory markers of inflammation are limited to just C-reactive protein (CRP) ≥ 3 mg/dL
B. Renal, respiratory, and neurologic organ system involvement have been removed
C. Kawasaki Disease is now an acceptable alternative diagnosis to MIS-C
D. A and B
E. All of the above

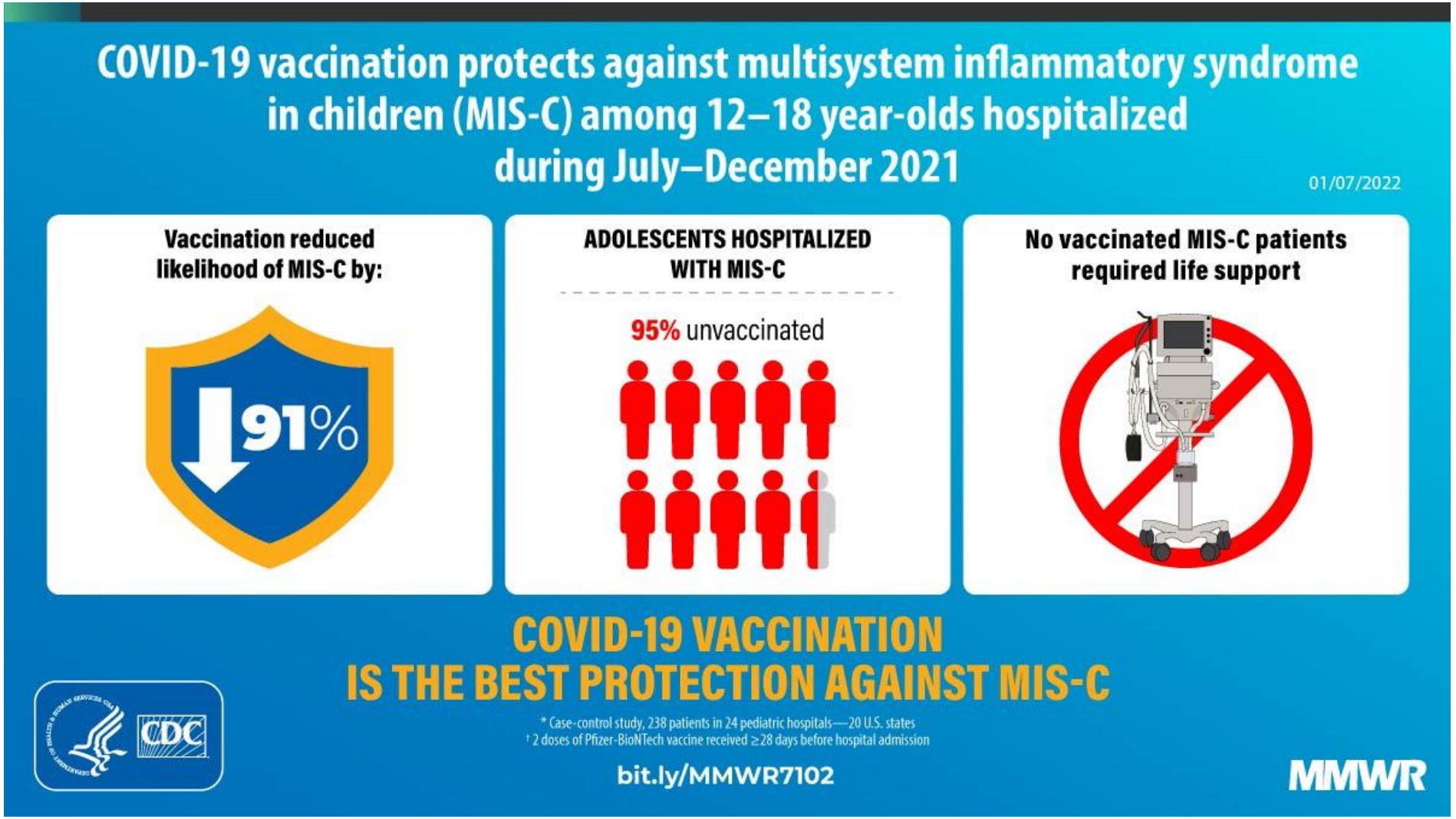
Answer: The new CSTE/CDC MIS-C surveillance case definition includes the following changes:

A. Laboratory markers of inflammation are limited to just C-reactive protein (CRP) ≥ 3 mg/dL
B. Renal, respiratory, and neurologic organ system involvement have been removed
C. Kawasaki Disease is now an acceptable alternative diagnosis to MIS-C
D. A and B
E. **All of the above**

Rationale: The correct answer is E – the CSTE/CDC MIS-C case definition includes all of the above changes compared with the 2020 CDC MIS-C case definition.

MIS-C and COVID-19 Vaccination

COVID-19 Vaccine Effectiveness against MIS-C



Vaccine effectiveness of two doses of the Pfizer-BioNTech vaccine against MIS-C was **91% (95% CI = 78-97%)**

Zambrano LD, et al. MMWR. 2022;71(2):52-58

COVID-19 Vaccine Effectiveness against MIS-C in Children Ages 5-18 Years

- Multicenter case-control public health investigation from July 1, 2021 to April 7, 2022
- Compared odds of being fully vaccinated (2 doses of BNT162b2 vaccine ≥28 days before admission) between MIS-C case-patients and hospital-based controls who tested negative for SARS-CoV-2

304 MIS-C case patients (92% unvaccinated)	**502** controls (69% unvaccinated)

- **MIS-C was associated with decreased likelihood of vaccination:** **aOR, 0.16** 95% CI, 0.10-0.26 → this corresponds to an estimated overall vaccine effectiveness of 84%
  - For 12–18-year-olds who had a longer period of vaccine eligibility, the protective association persisted 4 to 7 months after vaccination
- **Among children ages 5–11 years, MIS-C also associated with decreased likelihood of vaccination:** **aOR, 0.22** 95% CI, 0.10-0.52

Zambrano LD, et al. MMWR. 2022;71(2):52-58 Zambrano LD, et al. Clin Infect Dis. 2022 Aug 4:ciac637

Other Evidence of Decreasing MIS-C Incidence Associated with COVID-19 Vaccination Prior to Omicron Emergence

- Levy M, et al; France
  - N = 33 adolescents 12 – 18 years, 7 (21%) vaccinated
  - MIS-C incidence from September 1 to October 31, 2021, decreased by **91%** after the first dose of BNT162b2 vaccine compared with unvaccinated adolescents (hazard ratio for MIS-C was 0.09; 95% CI, 0.04-0.21; P < .001)

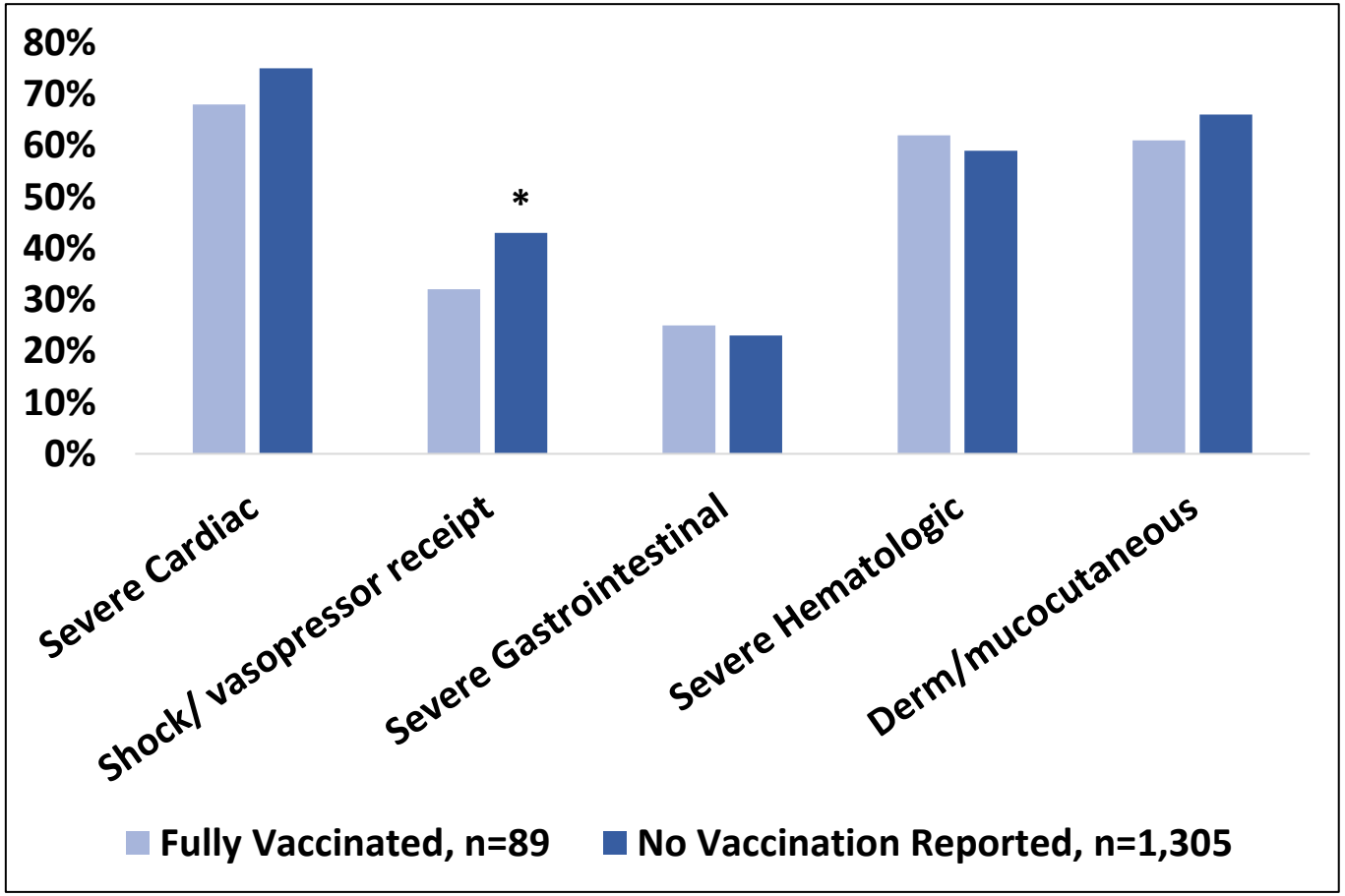
- Nygaard U, et al; Denmark
  - MIS-C incidence among children ages 0-17 years declined among vaccinated children between August 1, 2021, and February 1, 2022, with estimated vaccine effectiveness of **94%** (95% CI 55–99; p=.006)
  - Clinical phenotype during Delta wave was comparable to pre-delta era

Levy M, et al. JAMA. 2022. doi:10.1001/jama.2021.23262 Nygaard U, et al. Lancet Child Adolesc Health 2022; 6:459-65

MIS-C in Vaccinated vs Unvaccinated Children (1 of 2)

- National surveillance data as of Sept 6, 2022, comparing MIS-C in fully, partially, and unvaccinated children (vaccination status self-reported)
- Compared three groups:
  1. Full vaccination = receipt of a 2-dose mRNA primary vaccine series with MIS-C onset ≥28 days after vaccine dose 2
  2. Partial vaccination = MIS-C onset after dose 1 or <28 days from dose 2 or receipt of Janssen [Johnson & Johnson]
  3. No vaccination reported

Comparing MIS-C organ involvement between those with full vaccination reported to those with no vaccination reported



* P value <.05

Yousaf AR, et al. Poster presentation IDWeek 2022; October 19-23, 2022; Washington, DC

MIS-C in Vaccinated vs Unvaccinated Children (2 of 2)

- National surveillance data as of September 6, 2022, comparing MIS-C in fully, partially, and unvaccinated children (vaccination status self-reported)

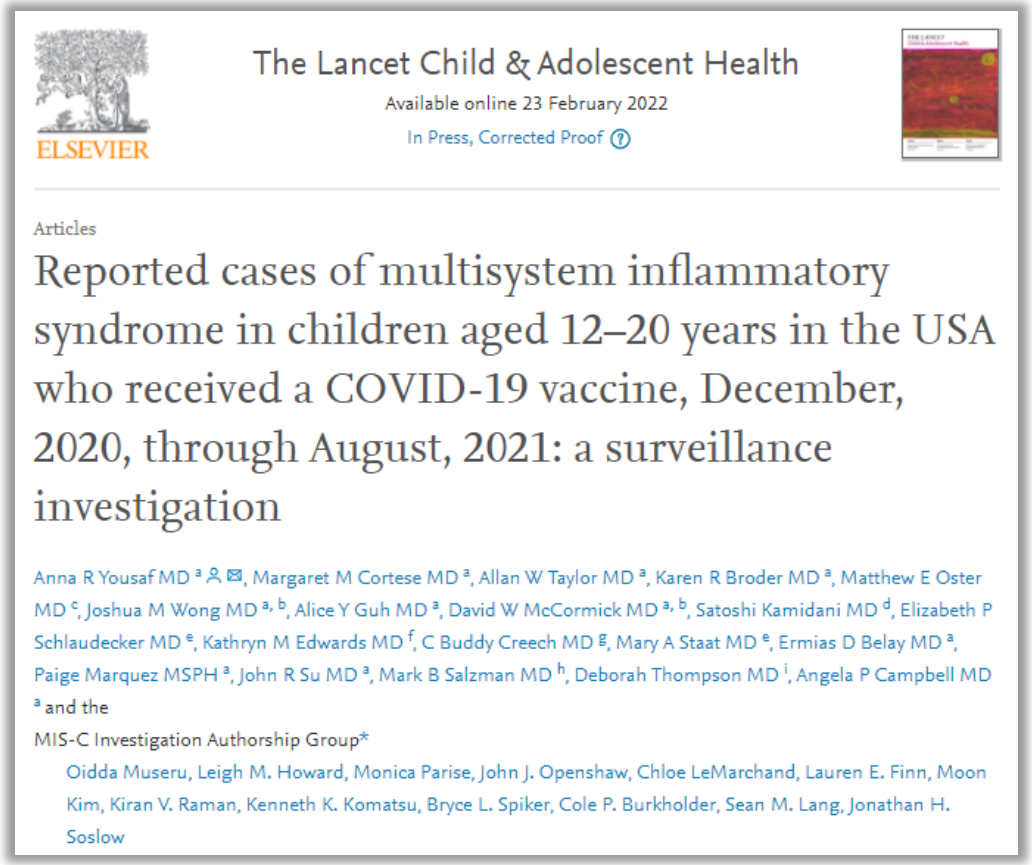
	No Vaccination Reported (n=1,305)	Partially Vaccinated (n=91)		Fully Vaccinated (n=89)	
	n (%)	n (%)	p value	n (%)	p value
ICU-level care	768 (59)	45 (50)	0.08	40 (45)	0.01
Death	21 (2)	0 (0)	0.22	0 (0)	0.23
Hospital length of stay, median, IQR (days)	5 (4-7)	5 (3-7)	0.51	5 (3-7)	0.13
ICU length of stay, median, IQR (days)	3 (2-5)	3 (2-5)	0.94	3 (1-4)	0.20

Yousaf AR, et al. Poster presentation IDWeek 2022; October 19-23, 2022; Washington, DC

COVID-19 Vaccine Safety and MIS-C

Has surveillance observed an association between receipt of COVID-19 mRNA vaccination and subsequent MIS-C illness?

- CDC surveillance for MIS-C after COVID-19 vaccination from December 14, 2020, to August 31, 2021, using national surveillance, Vaccine Adverse Event Reporting System (VAERS), and clinical consultations



ELSEVIER

The Lancet Child & Adolescent Health

Available online 23 February 2022

In Press, Corrected Proof

Articles

Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation

Anna R Yousaf MD [a], Margaret M Cortese MD [a], Allan W Taylor MD [a], Karen R Broder MD [a], Matthew E Oster MD [c], Joshua M Wong MD [a, b], Alice Y Guh MD [a], David W McCormick MD [a, b], Satoshi Kamidani MD [d], Elizabeth P Schlaudecker MD [e], Kathryn M Edwards MD [f], C Buddy Creech MD [g], Mary A Staat MD [e], Ermias D Belay MD [a], Paige Marquez MSPH [a], John R Su MD [a], Mark B Salzman MD [h], Deborah Thompson MD [i], Angela P Campbell MD [a] and the

MIS-C Investigation Authorship Group*

Oidda Museru, Leigh M. Howard, Monica Parise, John J. Openshaw, Chloe LeMarchand, Lauren E. Finn, Moon Kim, Kiran V. Raman, Kenneth K. Komatsu, Bryce L. Spiker, Cole P. Burkholder, Sean M. Lang, Jonathan H. Soslow

1 case of MIS-C after vaccination per million vaccinated persons

ELSEVIER

The Lancet Child & Adolescent Health

Available online 23 February 2022

In Press, Corrected Proof

Comment

When vaccine adverse event reporting generates hope, not fear

Joyce C Chang [a, b], Mary Beth F Son [a, b]

[a] Division of Immunology, Boston Children's Hospital, Boston, MA, USA

[b] Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA

Yousaf et al. Lancet Child Adolesc Health. 2022 May. doi: 10.1016/S2352-4642(22)00028-1

COVID-19 Vaccine Safety after MIS-C

How is COVID-19 vaccine tolerated when initiated after a patient has had MIS-C?

- We enrolled children previously hospitalized for MIS-C from 3 academic institutions
- Abstracted charts and interviewed children and parents/guardians regarding vaccine adverse events and acceptability
- COVID-19 vaccination was well tolerated in children with prior MIS-C
- Another study followed 15 children hospitalized for MIS-C who subsequently initiated COVID-19 vaccination
  - Well tolerated without developing hyperinflammation, myocarditis, or MIS-C reoccurrence up to 9.5 months after vaccination

	Dose 1, n, (%) (n=20)	Dose 2, n, (%) (n=19)
Pain at injection site	10 (50)	4 (21)
Redness at injection site	1 (5)	2 (11)
Swelling at injection site	1 (5)	1 (5)
Subjective or objective (≥38°C) fever	0 (0)	1 (5)
Chills	2 (10)	1 (5)
Fatigue	2 (10)	2 (11)
Headache	3 (15)	2 (11)
Vomiting	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)
New or worsened muscle pain	4 (20)	2 (11)
New or worsened joint pain	2 10)	2 (11)
Rash	2 (10)	1 (5)
Other symptom	0 (0)	1 (5)
Used fever-reducing or pain medicine for symptoms/side effects	5 (25)	3 (16)
Symptoms/side effects interfered with normal daily activities	2 (10)	0 (0)

The Phenotype Initiative Project, unpublished data
Wisniewski M, et al. JAMA Netw Open. 2022;5(3):e224750

Acceptability of COVID-19 Vaccination after MIS-C

What are parent/caregiver attitudes toward COVID-19 vaccination after a patient has had MIS-C?

- 63% of unvaccinated respondents had not discussed COVID-19 vaccine with the doctors
- 63% of unvaccinated respondents were unsure of COVID-19 vaccine safety
- 75% of unvaccinated respondents listed doctors in their top 3 most trusted sources of COVID-19 vaccine information

	Vaccine-eligible at Time of Interview		
	Vaccinated, n (%) (n=20)	Unvaccinated, n (%) (n=16)	P-value
Have you discussed with a doctor if they would recommend a COVID-19 vaccine for [you/your child]?			
Yes	13 (65)	6 (38)	0.095
No	6 (30)	10 (63)	
Has [your/your child's] doctor(s) recommended that [you/your child] get a COVID-19 vaccine, if or when available for [your/their] age group?			
Yes, recommended to get it as soon as possible	10 (50)	4 (25)	0.176
Yes, but recommended to wait to get it	3 (15)	2 (13)	1.000
No	5 (25)	10 (63)	0.041
Not sure	2 (10)	0 (0)	0.492
How safe do you think a COVID-19 vaccine will be for [you/your child]?			
Not at all	0 (0)	2 (13)	<.001
A little	0 (0)	3 (19)	
Moderately	3 (15)	0 (0)	
Very	15 (75)	1 (6)	
Not sure	2 (10)	10 (63)	0.002
Top *3 most trusted* sources of information about COVID-19 vaccines			
Doctors	17 (85)	12 (75)	0.678
Family and friends	9 (45)	4 (25)	0.301
Social Media	1 (5)	0 (0)	1.000

CDC MIS-C national surveillance, unpublished data

CDC Recommendations on COVID-19 Vaccination and MIS-C

Initiation of COVID-19 vaccination in persons with a history of MIS-C

Experts consider the benefits of COVID-19 vaccination for people with a history of MIS-C/A (i.e., a reduced risk of severe disease including potential recurrence of MIS-C after reinfection) to outweigh a theoretical risk of an MIS-like illness or the risk of myocarditis following COVID-19 vaccination for those who meet the following:

- **Clinical recovery has been achieved, including return to baseline cardiac function; and**
- **It has been at least 90 days after the diagnosis of MIS-C/A**

These recommendations are the same for administration of subsequent COVID-19 vaccine doses in persons who had onset of MIS 90 days or more after their most recent COVID-19 vaccine dose

Administration of subsequent COVID-19 vaccine doses in persons with onset of MIS-C fewer than 90 days after their most recent COVID-19 vaccine dose

Subsequent COVID-19 vaccine dose(s) should be deferred at this time until additional data are available. However, on a case-by-case basis, a provider may offer subsequent dose(s) if the two criteria above are met and there is strong evidence that the MIS-C/A was a complication of a recent SARS-CoV-2 infection.

Clinical Guidance for COVID-19 Vaccination | CDC

Self-knowledge Check: The following are all true regarding MIS-C and COVID-19 vaccination EXCEPT:

A. COVID-19 vaccination is protective against MIS-C, with reported vaccine effectiveness of 80-90%.

B. CDC recommends that children who have had MIS-C should not receive COVID-19 vaccination

C. Several studies have found that COVID-19 mRNA vaccines are well tolerated in children who initiate vaccine after MIS-C illness

D. The FDA requires that MIS-C occurring after COVID-19 vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS)

Answer: The following are all true regarding MIS-C and COVID-19 vaccination EXCEPT:

A. COVID-19 vaccination is protective against MIS-C, with reported vaccine effectiveness of 80-90%.

B. **CDC recommends that children who have had MIS-C should not receive COVID-19 vaccination**

C. Several studies have found that COVID-19 mRNA vaccines are well tolerated in children who initiate vaccine after MIS-C illness

D. The FDA requires that MIS-C occurring after COVID-19 vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS)

Rationale: The correct answer is B – The CDC recommends COVID-19 vaccination for children with a history of MIS-C as long as they are clinically recovered, and it has been 90 days since their MIS-C diagnosis.

Summary

- MIS-C incidence has decreased, and age distribution has shifted to younger children
- On-going surveillance is critical, particularly should newly emerging variants arise
- A new CSTE/CDC MIS-C surveillance case definition will be effective January 1, 2023
  - Continues to require illness in a person aged <21 years requiring hospitalization or resulting in death that is characterized by evidence of systemic inflammation
  - Narrows what types of signs and symptoms count toward clinical criteria
  - Changes some of the laboratory criteria, as well as the timeframes during which laboratory and epidemiologic linkage criteria must be met
  - Prioritizes features of MIS-C that distinguish it from similar pediatric inflammatory conditions
  - May not capture all cases and is not intended to replace clinical judgment
- COVID-19 vaccination is the best protection against MIS-C
- COVID-19 vaccination is recommended for children with a history of MIS-C as long as they are clinically recovered and it has been 90 days since their MIS-C diagnosis

MIS-C Resources

- COVID Data Tracker – MIS-C | CDC
- Multisystem Inflammatory Syndrome (MIS) (cdc.gov)
- CSTE/CDC MIS-C surveillance case definition position statement
- Reporting MIS-C after vaccination to VAERS
- Clinical Guidance for COVID-19 Vaccination | CDC

Closing

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

Continuing Education

- All continuing education for COCA Calls is issued online through the CDC Training & Continuing Education Online system at https://tceols.cdc.gov/.

- Those who participate in today's COCA Call and wish to receive continuing education please complete the online evaluation by **January 9, 2023,** with the course code **WC4520-120822**. The access code is **COCA120822.**

- Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between **January 10, 2023,** and **January 10, 2025,** and use course code **WD4520-120822.** The access code is **COCA120822.**

- Continuing education certificates can be printed immediately upon completion of your online evaluation. A cumulative transcript of all CDC/ATSDR CEs obtained through the CDC Training & Continuing Education Online System will be maintained for each user.

Today's COCA Call Will Be Available to View On-Demand

- **When:** A few hours after the live call ends*
- **What:** Video recording
- **Where:** On the COCA Call webpage https://emergency.cdc.gov/coca/calls/2022/callinfo_120822.asp
- **Sign up to receive future COCA Call Announcements and other timely information:** https://emergency.cdc.gov/coca/subscribe.asp

**A transcript and closed-captioned video will be available shortly after the original video recording posts at the above link.*

Additional Resources

- Join us for our next COCA Call on Tuesday, December 13, 2022, at 2 PM ET.
  - ✓ **Topic:** *COVID-19 Update: Clinical Guidance and Patient Education for Bivalent COVID-19 Vaccines*
  - ✓ Further information is available at https://emergency.cdc.gov/coca/calls/2022/callinfo_121322.asp
- Continue to visit emergency.cdc.gov/coca for more details about upcoming COCA Calls.
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