

# Analysis of National Surveillance Data to Support Case Definition Revisions for Multisystem Inflammatory Syndrome in Children (MIS-C), United States, February 2020–June 2022

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## BACKGROUND

- Classification of MIS-C, other pediatric inflammatory conditions, and COVID-19 is challenged by phenotypic overlap and absence of diagnostic laboratory evidence.
- Due to public health need and limited data, CDC developed a necessarily broad MIS-C surveillance case definition in May 2020.
- Some case definition criteria do not distinguish between MIS-C and other conditions and may contribute to misclassification.
- We evaluated the impact of narrowing these criteria on case inclusion in national MIS-C surveillance.

## METHODS

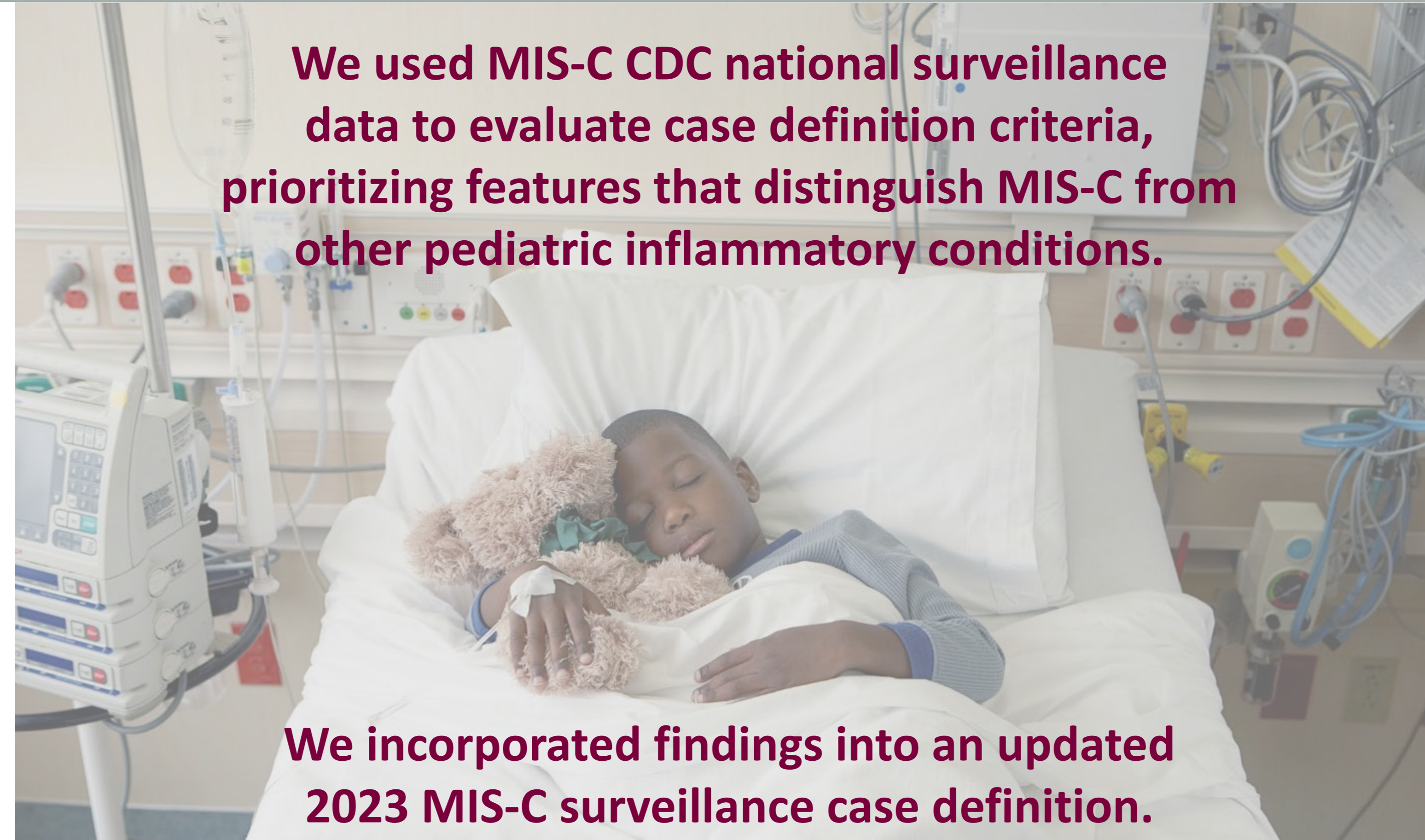
- Using a national surveillance MIS-C dataset of health department-reported cases meeting the 2020 MIS-C case definition reported as of 08/31/2022:
  - We describe the proportion that met revised criteria under consideration including fever duration, C-reactive protein (CRP) elevation using a defined cutoff, and organ involvement represented by specific criteria.
  - We also evaluated cases identified using potential combinations of revised criteria.

## RESULTS

- Of 8,826 MIS-C cases fulfilling the original case definition, 7,081 (80%) had a quantitative CRP, allowing evaluation of full criteria.
- Of 6,937 with documented fever duration, 6,672 (96%) had fever for ≥2 days; 94% had a CRP ≥ 3.0 mg/dL.
- Cardiac involvement defined by key features of MIS-C was present in 84% of cases (62% if BNP/proBNP elevation was excluded); 42% had shock. Dermatologic, gastrointestinal (GI) and hematologic involvement were present in 74%, 89% and 56% of cases, respectively. Neurologic (excluding headache), renal, and respiratory involvement were present in 16%, 20%, and 63% of cases, respectively.
- The number of cases with ≥2 of cardiac (without BNP/proBNP elevation), shock, dermatologic, GI, or hematologic involvement was 6,492 (92%).

## CONCLUSIONS

- The CDC 2020 MIS-C case definition is intentionally broad.
- Using national surveillance data, we evaluated case inclusion under narrower criteria, prioritizing features of MIS-C that distinguish it from similar pediatric inflammatory conditions.
- We incorporated findings into an updated 2023 MIS-C surveillance case definition.
- A surveillance case definition may not capture all cases and is not intended to replace clinical judgment.



We used MIS-C CDC national surveillance data to evaluate case definition criteria, prioritizing features that distinguish MIS-C from other pediatric inflammatory conditions.

We incorporated findings into an updated 2023 MIS-C surveillance case definition.

Table 1. CDC 2020 MIS-C surveillance case definition components and evaluation of potential revised criteria (N=7,081 cases)

Original 2020 MIS-C Surveillance Case Definition Criteria	Items Evaluated	Result
Fever (≥38.0° C) or subjective fever for ≥24 hours	Fever (a) ≥2 days (b) ≥3 days (using denominator of 6,937 with documented fever duration)	a: n=6,672 (96%); b: n=6,242 (90%)
Laboratory evidence of inflammation: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, or neutrophils; or reduced lymphocytes or albumin	CRP ≥3 mg/dL	n=6,635 (94%)
Multisystem organ involvement, ≥2 of the following:		
• Cardiac (includes elevated troponin, elevated B-type natriuretic peptide [BNP] or N-terminal pro hormone BNP (proBNP), arrhythmia, coronary artery aneurysm, cardiac dysfunction, or shock)	(a) Cardiac involvement as defined by LVEF<55% OR coronary artery abnormality OR troponin documented as “high” (not including BNP and proBNP elevation) (b) Shock alone	a: n=4,381 (62%); b: n=3,003 (42%)
• Dermatologic (includes rash or mucocutaneous lesions)	Mucocutaneous involvement as defined by rash OR mucosal inflammation OR conjunctivitis/ conjunctival injection OR extremity findings	n=5,260 (74%)
• Gastrointestinal (includes elevated bilirubin, elevated liver enzymes, or diarrhea)	Gastrointestinal involvement as defined by abdominal pain OR vomiting OR diarrhea	n=6,316 (89%)
• Hematologic (includes elevated D-dimer, thrombophilia, or thrombocytopenia)	Hematologic involvement as defined by platelet count <150k/microliter OR platelets indicated as ‘low’ OR absolute lymphocyte count <1k/microliter	n=3,964 (56%)
• Neurologic (includes cerebrovascular accident, aseptic meningitis, encephalopathy, or headache)	(a) Neurologic involvement as defined by headache, altered mental status, meningitis, encephalopathy, cerebrovascular accident, encephalitis, OR cerebrospinal fluid pleocytosis (b) Neurologic involvement defined similarly but not including headache	a: n=3,760 (53%); b: n=1,104 (16%)
• Renal (includes acute kidney injury or renal failure)	Renal involvement as defined by acute kidney injury or receipt of renal replacement therapy	n=1,388 (20%)
• Respiratory (includes pneumonia, acute respiratory distress syndrome, or pleural effusion)	Respiratory involvement as defined by cough, shortness of breath, chest pain/tightness, acute respiratory distress syndrome, pleural effusion, OR atelectasis	n=4,483 (63%)
Example of potential combination of revised criteria:	Fever ≥2 days; CRP ≥3.0 mg/dL; ≥2 of cardiac (without BNP/proBNP elevation), shock, dermatologic, GI, and hematologic organ involvement; and SARS-CoV-2 laboratory testing	n=6,158 (87%)

Table 2. Evaluation of SARS-CoV-2 laboratory testing reported in MIS-C cases fulfilling the 2020 case definition and meeting criteria for evaluation<sup>1</sup>

All	NAAT OR Antigen positive	NAAT negative/not done <sup>2</sup> AND Antigen negative/not done <sup>2</sup>	Total
Antibody positive	2,524 (36%)	3,553 (50%)	6,077
Antibody negative/not done	870 (12%)	134 (2%)	1,004
Total	3,394	3,687	7,081

<sup>1</sup> Cases were to have a positive nucleic acid amplification test, antigen, or serology test, or exposure to a suspected/confirmed COVID-19 case within 4 weeks prior to symptom onset; N=7,081  
<sup>2</sup> Because of limitations in national MIS-C case reporting, negative laboratory results could not be distinguished from absence of a test performed

### UPDATED 2023 MIS-C SURVEILLANCE CASE DEFINITION (Approved in Council of State and Territorial Epidemiologists [CSTE] Position Statement on June 23, 2022; effective January 1, 2023)

**Confirmed:** Meets the clinical criteria and the laboratory criteria  
**Probable:** Meets the clinical criteria and the epidemiologic linkage criteria  
**Suspect:** Meets the vital records criteria

#### Clinical criteria

An illness characterized by all of the following, in the absence of a more likely alternative diagnosis:

- Subjective or documented fever (temperature ≥38.0C)
- Clinical severity requiring hospitalization or resulting in death
- Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL
- New onset manifestations in ≥2 of the following categories:
  - o Cardiac involvement indicated by:
    - LVEF <55%, OR
    - Coronary artery dilatation, aneurysm, or ectasia, OR
    - Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note
  - o Mucocutaneous involvement indicated by:
    - Rash, OR
    - Inflammation of the oral mucosa, OR
    - Conjunctivitis or conjunctival injection, OR
    - Extremity findings (e.g., erythema or edema of the hands or feet)
  - o Shock
  - o Gastrointestinal involvement indicated by:
    - Abdominal pain, OR Vomiting, OR Diarrhea
  - o Hematologic involvement indicated by:
    - Platelet count <150,000 cells/μL, OR
    - Absolute lymphocyte count (ALC) <1,000 cells/μL

#### Laboratory criteria

- Detection of SARS-CoV-2 RNA or SARS-CoV-2 specific antigen in a clinical specimen up to 60 days prior to or during hospitalization, or in a post-mortem specimen, OR
- Detection of SARS-CoV-2 specific antibodies in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization

#### Epidemiologic linkage criteria

Close contact with a confirmed/probable case of COVID-19 disease in the 60 days prior to hospitalization

#### Vital records criteria

A person whose death certificate lists MIS-C as an underlying cause of death or a significant condition contributing to death

