

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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# **Multisystem Inflammatory Syndrome in Children in NYS**

## **Supplementary Appendix**

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## Figure S1 New York State Department of Health Interim MIS-C Case Definition

**Clinical Criteria:** A patient aged < 21 years with:

- A minimum one-day history of subjective OR objective Fever ( $\geq 100.4$  °F/38.0 °C); **AND**
- Hospitalization; **AND**
- **Either:**
  - **One or more of following:**
    - Hypotension or shock (cardiogenic or vasogenic)
    - Features of severe cardiac illness including but not limited to myocarditis, pericarditis, or valvulitis, significantly elevated troponin/proBNP, or coronary artery abnormalities
    - Other severe end-organ involvement, including but not limited to neurological or renal disease (excluding severe respiratory disease alone)

**OR**

- **Two or more of the following:**
  - Maculopapular rash
  - Bilateral non-purulent conjunctivitis
  - Mucocutaneous inflammatory signs (mouth, hands, or feet)
  - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain); **AND**
- Absence of a more likely diagnosis of the illness, e.g., bacterial sepsis or other viral infection.

### **Laboratory Criteria:**

- **General Laboratory Criteria:** Two or more of the following markers of inflammation:
  - Neutrophilia, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein, erythrocyte sedimentation rate (ESR), fibrinogen, D-dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6 (IL-6), OR elevated procalcitonin
- **Virologic Laboratory Criteria:** One of the following SARS-CoV-2 laboratory results
  - Detection of SARS-CoV-2 RNA in a clinical specimen using a molecular amplification detection test (e.g., RT-PCR) (or detection of SARS-CoV-2 antigen in a clinical specimen), at the time of presentation with this clinical picture or within the prior 4 weeks.
  - Detection of specific antibody in serum, plasma, or whole blood indicative of a new or recent infection.

### **Epidemiological Criteria:**

One or more of the following exposures in the 6 weeks prior to the onset of symptoms:

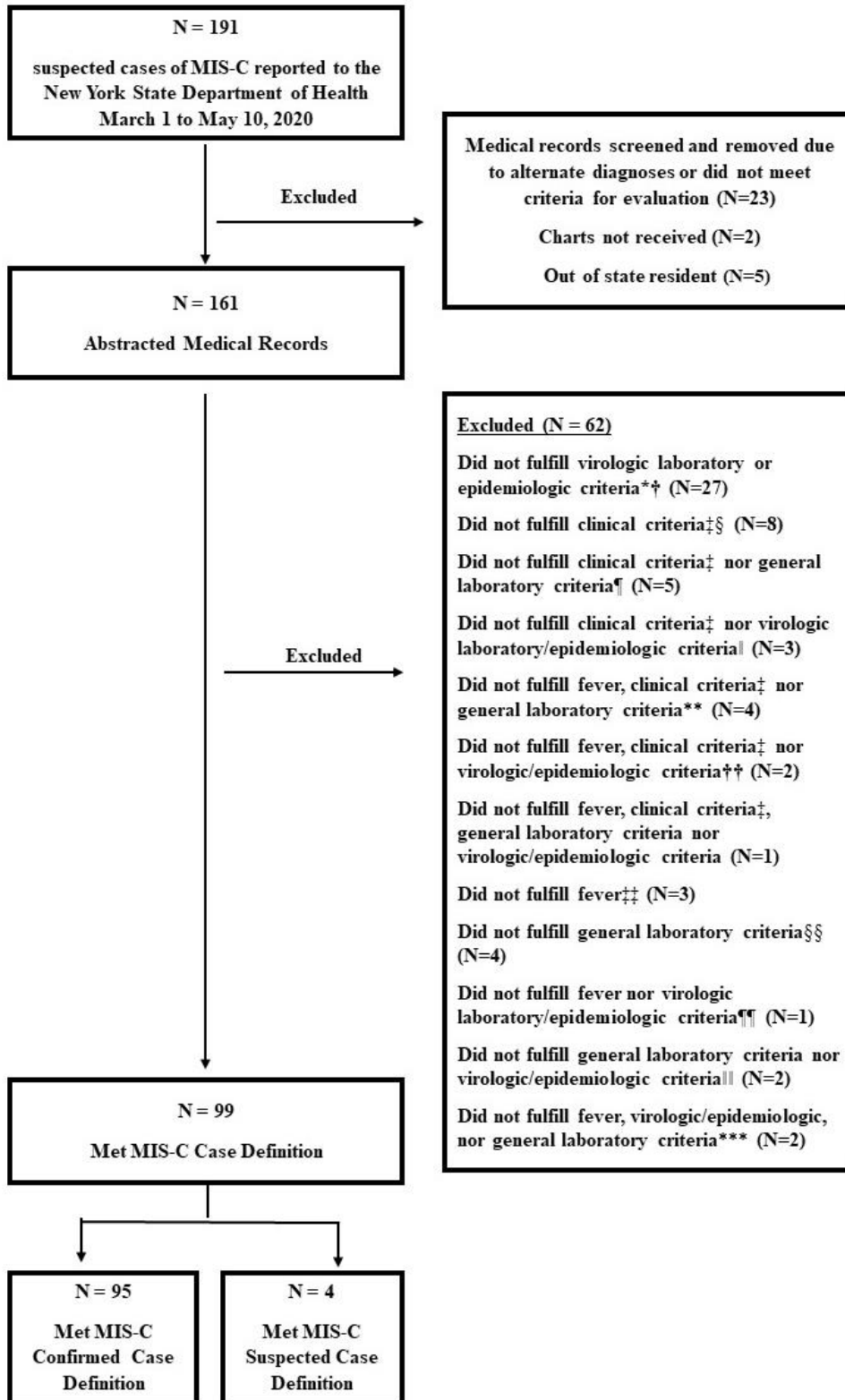
- Close contact with a person with laboratory confirmed SARS-CoV-2 infection
- Close contact with a person with illness clinically compatible with COVID-19 disease who had close contact with a person with laboratory confirmed SARS-CoV-2 infection\*
- Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2\*

Confirmed cases meet clinical and laboratory criteria  
Suspected cases meet clinical and epidemiologic criteria

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\* These criteria were not used for this evaluation

**Figure S2** Flow Diagram for selection of Multisystem Inflammatory Syndrome in Children associated with Covid-19 (MIS-C) cases in New York State (NYS)



\* Among patients missing SARS-CoV-2 virologic/epidemiologic criteria, 12 had negative molecular and concurrent or subsequent serologic testing, 6 had negative molecular testing and no serologic testing was performed, 2 had negative subsequent serologic testing and no molecular testing was performed, 2 had no molecular or serologic testing, 4 were negative by molecular testing and positive by serology >10 days after admission, and 1 had no molecular testing and was serology positive > 10 days after admission.

† Two patients also had alternative diagnoses of systemic lupus erythematosus flare (in 1) and phlegmon in neck (in 1).

‡ Clinical criteria defined as: Hypotension or shock, severe cardiac or other severe end-organ illness (excluding respiratory alone) OR two or more signs or symptoms listed in the case definition.

§ All patients also had alternative diagnoses of peritonsillar abscess (in 1), acute Covid-19 (in 2) and asthma exacerbation in the setting of acute Covid-19 (in 3).

¶ Four patients also had alternative diagnoses of acute Covid-19 (in 2), acute Covid-19 and pneumonia (in 1) and acute viral syndrome or Covid-19 (in 1).

|| All patients also had alternative diagnoses of sickle cell disease pain crisis/acute chest/pneumonia (in 1), pelvic abscess secondary to a ruptured appendix (in 1), and viral pharyngitis (in 1).

\*\* All patients also had alternative diagnoses of reactive airway disease in the setting of metapneumovirus infection (in 1), acute inflammatory bowel disease (in 1), cardiac arrest of unknown origin (in 1), and premature rupture of membranes in a pregnant patient (in 1).

†† One patient also had an alternative diagnosis of acute Covid-19 with acute respiratory distress syndrome.

‡‡ Two patients also had alternative diagnoses of acute Covid-19 (in 1) and cardiac arrest of unknown origin (in 1).

§§ One patient also had an alternative diagnosis of reactive airway disease.

¶¶ This patient also had an alternative diagnosis of multifocal localizing pneumonia, myocarditis, and markedly elevated mycoplasma IgG.

|| Subsequent SARS-CoV-2 serologic testing was negative for both patients.

\*\*\* Both patients also had alternative diagnoses of viral myocarditis in the absence of other systemic inflammatory signs (in 1) and cellulitis (in 1).

**Table S1** Demographic, Clinical and Laboratory Characteristics of Patients Fulfilling and Not Fulfilling New York State Multisystem Inflammatory Syndrome in Children Associated with Covid-19 (MIS-C) Interim Case Definition\*

<b>Characteristic</b>	<b>Met MIS-C Case Definition no./total no. (%)</b>	<b>Missing Virologic and Epidemiologic Criteria no./total no. (%)</b>	<b>Missing Other Criteria no./total no. (%)</b>
	N=99	N=27	N=35
Male sex	53/99 (54)	17/27 (63)	22/35 (63)
Age			
0-5 yr	31/99 (31)	18/27 (67)	18/35 (51)
6-12 yr	42/99 (42)	6/27 (22)	3/35 (9)
13-20 yr	26/99 (26)	3/27 (11)	14/35 (40)
Positivity for SARS-CoV-2			
On RT-PCR assay	50/98 (51)	0/22	22/33 (67)
On serologic assay for IgG antibodies	76/77 (99)	0/19	4/9 (44)
Race†			
White	29/78 (37)	13/24 (54)	17/22 (77)
Black	31/78 (40)	4/24 (17)	4/22 (18)
Asian	4/78 (5)	6/24 (25)	1/22 (5)
Other‡	14/78 (18)	1/24 (4)	0/22
Ethnic group †			
Hispanic	31/86 (36)	4/23 (17)	17/32 (53)
Not Hispanic	54/85 (64)	19/23 (83)	15/32 (47)
Coexisting conditions§			
Any	36/99 (36)	7/27 (25.9)	13/35 (37.1)
Chronic lung disease¶	14/99 (14)	2/7 (28.6)	8/18 (44.4)
Obesity	29/99 (29)	3/27 (11.1)	8/35 (22.9)
Symptoms at admission			
Constitutional: fever or chills	99/99 (100)	24/27 (89)	18/35 (51)
Cardiovascular: chest pain	11/99 (11)	1/27 (4)	5/35 (14)
Any gastrointestinal	79/99 (80)	16/27 (59)	12/35 (34)
Any dermatologic	61/99 (62)	16/27 (59)	7/35 (20)
Any gastrointestinal and any dermatologic	48/99 (48)	10/27 (37)	1/35 (3)
Any mucocutaneous	60/99 (61)	19/27 (70)	3/35 (9)
Any gastrointestinal and any mucocutaneous	48/99 (48)	11/27 (41)	1/35 (3)
Any neurologic	30/99 (30)	2/27 (7)	5/35 (14)
Any musculoskeletal	20/99 (20)	4/27 (15)	5/35 (14)
Upper respiratory	27/99 (27)	7/27 (26)	9/35 (26)
Lower respiratory	40/99 (40)	10/27 (30)	15/35 (43)
Cough	31/99 (31)	7/27 (26)	12/35 (34)
Shortness of breath	19/99 (19)	3/27 (11)	10/35 (29)
Wheezing	1/99 (1)	0/27	2/35 (6)



Characteristic	Met MIS-C Case Definition no./total no. (%)	Missing Virologic and Epidemiologic Criteria no./total no. (%)	Missing Other Criteria no./total no. (%)
<b>Vital signs</b>			
Median heart rate (IQR) – beats/min	133 (120–148)	142 (118–156)	132 (92–149)
Tachycardial	96/99 (97)	22/26 (85)	17/31 (55)
Median respiratory rate (IQR) – breaths/min	27 (23–36)	28 (22–34)	28 (20–42)
Tachypnea**	77/99 (78)	13/26 (50)	16/31 (52)
Hypotension††	32/99 (32)	0/25	3/29 (10)
Median temperature (IQR) - °C	38.3 (37.5–39.3)	38.3 (37.5–39.0)	37.4 (36.9–38.6)
Temperature ≥38.0°C‡‡	62/99 (63)	17/26 (65)	11/31 (35)
Median oxygen saturation (IQR) - %	98 (97–100)	99 (98–100)	98 (97–99)
Oxygen saturation <92%	4/99 (4)	3/27 (11)	10/35 (39)
<b>Laboratory values §§</b>			
Median white- cell count (IQR) - x 10 <sup>-3</sup> /ul	10.4 (6.7–14.5)	10.4 (6.5–18.8)	9.8 (7.2–14.9)
Median lymphocyte level (IQR) - %	10.0 (5.0–16.0)	14.0 (8.4–25.8)	25.9 (14.5–43.5)
Lymphopenia ¶¶	59/89 (66)	16/23 (70)	10/32 (31)
Median neutrophil level (IQR) - %	82.0 (76.0–89.0)	75.0 (67.0–82.0)	65.0 (33.0–78.5)
Neutropenia	0/89	0/25	3/32 (9)
Median platelet count (IQR) – x 10 <sup>9</sup> /l	155 (105–233)	251 (154–476)	251 (164–340)
Platelet count <80 x10 <sup>9</sup> /l	10/95 (11)	3/23 (13)	2/29 (7)
Elevated proBNP level***	74/82 (90)	4/5 (80)	5/8 (63)
Elevated troponin level	63/89 (71)	3/10 (30)	5/14 (36)
Median procalcitonin level (IQR) - ng/dl	6.2 (2.2–19.7)	0.8 (0.7–1.0)	0.2 (0.1–0.4)
Elevated procalcitonin level†††	60/65 (92)	5/6 (83)	2/13 (15)
<b>C-reactive protein level</b>			
Median (IQR) – mg/dl	21.9 (15.0–30.0)	27.4 (8.3–60.5)	8.4 (4.3–18.8)
Distribution			
≥3.0 mg/dl	98/98 (100)	24/27 (89)	23/28 (82)
>5.0 mg/dl	97/98 (99)	24/27 (89)	18/38 (64)
>10.0 mg/dl	85/98 (87)	19/27 (70)	11/28 (39)
>20.0 mg/dl	59/98 (60)	18/27 (67)	5/28 (18)
Median fibrinogen level (IQR) – mg/dl	624 (506–764)	615 (465–872)	517 (362–673)
Fibrinogen level >400 mg/dL	57/66 (86)	4/5 (80)	7/12 (58)
Median D-dimer level (IQR) – mg/liter	2.4 (1.2–3.7)	2.3 (0.8–3.9)	1.0 (0.5–2.4)
D-Dimer level >0.55 mg/L	86/94 (91)	9/11 (82)	13/18 (72)
Median ferritin level (IQR) - ng/ml‡‡‡	522 (305–820)	397 (188–675)	438 (123–763)
Ferritin level >300 ng/ml	62/83 (75)	6/10 (60)	8/14 (57)
Median albumin level (IQR) – g/dl	3.1 (2.5–3.6)	3.3 (2.6–3.6)	3.6 (2.9–4.1)
Albumin level ≤3.0g/dl	45/94 (48)	11/25 (44)	8/30 (27)
Median LDH level (IQR) – U/liter	313 (267–380)	412 (230–643)	401 (255–436)
LDH level ≥500 U/liter	6/69 (9)	3/8 (38)	3/16 (19)

Characteristic	Met MIS-C Case Definition no./total no. (%)	Missing Virologic and Epidemiologic Criteria no./total no. (%)	Missing Other Criteria no./total no. (%)
Median interleukin-6 level (IQR) pg/ml	116.3 (37.0–315.0)	--	36.3 (13.1–59.5)
Interleukin-6 level $\geq$ 5.0 pg/ml	33/34 (97)	0/0	2/2 (100)
Median ESR (IQR) – mm/hr	61.5 (43.0–77.5)	70 (51–89)	42 (2–71)
ESR $\geq$ 40 mm/hr	40/52 (77)	17/22 (77)	6/11 (55)
Median time from symptom onset to hospital admission (IQR) – days	4 (3–6)	5 (3–7)	2 (0–6)
ICU admission	79/99 (80)	7/27 (26)	13/35 (37)
Median time to ICU entry (IQR) – days	0.0 (0.0–1.0)	0.5 (0.0–3.0)	0.0 (0.0–0.0)
Median length of stay (IQR) – days			
Overall	6.0 (4.0–9.0)	4.0 (3.0–5.0)	5.0 (2.0–13.0)
Among those discharged	6.0 (4.0–8.0)	4.0 (3.0–5.0)	3.0 (2.0–9.0)
Therapy			
BiPAP or CPAP§§§	7/99 (7)	0/27	3/35 (9)
High-flow nasal cannula§§§	16/99 (16)	1/27 (4)	4/35 (11)
Mechanical ventilation§§§	10/99 (10)	1/27 (4)	5/35 (14)
ECMO	4/99 (4)	0/27	1/35 (3)
Vasopressor support	61/99 (62)	4/27 (15)	7/35 (20)
Systemic glucocorticoids	63/99 (64)	9/27 (33)	14/35 (40)
IVIG	69/99 (70)	22/27 (81)	6/35 (17)
Systemic glucocorticoids and IVIG	48/99 (48)	7/27 (26)	3/35 (9)
Diagnoses			
Kawasaki’s disease or atypical Kawasaki’s disease	36/99 (36)	17/27 (63)	3/35 (9)
Myocarditis	52/99 (53)	2/27 (7)	6/35 (17)
Shock	10/99 (10)	0/27	0/35
Coronary-artery aneurysm	9/99 (9)	1/27 (4)	2/35 (6)
Acute kidney injury	10/99 (10)	1/27 (4)	1/35 (4)

\* IQR denotes interquartile range, RT-PCR reverse transcriptase–polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, ESR denotes erythrocyte sedimentation rate, LDH lactate dehydrogenase, proBNP pro–brain natriuretic peptide, BiPAP denotes bilevel positive airway pressure, CPAP continuous positive airway pressure, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, and IVIG intravenous immune globulin.

† Race and ethnic group were determined by medical record review.

‡ American Indian/Alaska Native or multiracial or other racial-ethnic group.

§ Among patients with confirmed MIS-C, one patient each had congenital heart disease, psoriatic arthritis and adult-onset Stills on methotrexate. Among those excluded for missing virologic/epidemiologic criteria, two patients both had chronic neurologic disease. Among those excluded for missing other criteria, one patient had sickle cell disease, four patients had chronic neurologic disease, one patient had history of cancer, and one patient had chronic gastrointestinal disease.

¶ Among those with MIS-C, a total of 12 patients had asthma or reactive airway disease, 1 had oxygen dependence, and one was a former 25-week-premature infant; among those excluded for missing virologic/epidemiologic criteria, a total of 2 patients had asthma or reactive airway disease; and among those excluded for missing other criteria, a total of 6 patients had asthma/reactive airway disease and two had oxygen dependence.

|| An elevated heart rate was coded as more than 160 beats per minute for an age of 0 to younger than 3 months, more than 150 for 3 months to younger than 6 months, more than 130 for 6 to younger than 12 months, more than 125 for 1 to younger than 3 years, more than 115 for 3 to younger than 6 years, more than 100 for older than 6 years.<sup>1</sup>

\*\* An elevated respiratory rate was coded as more than 60 breaths per minute for an age of 0 to younger than 3 months, more than 45 for 3 to younger than 6 months, more than 40 for 6 to younger than 12 months, more than 30 for 1 to younger than 3

years, more than 25 for 3 to younger than 6 years, more than 22 for 6 to younger than 12 years, and more than 18 for older than 12 years.<sup>1</sup>

†† Hypotension was defined as a systolic blood pressure of less than 60 mm Hg for an age of younger than 1 month, less than 70 mm Hg for 1 month to younger than 1 year, [ $70 + (2 \times \text{the age in years})$ ] mm Hg for 1 to 10 years, and less than 90 mm Hg for older than 10 years.<sup>1</sup>

‡‡ Patients were considered to have fever if there was either subjective or objective fever.

§§ The normal ranges for selected variables are as follows: fibrinogen level, 200 to 400 mg per deciliter; d-dimer level, 0.20 to 0.55 mg per liter; albumin level, 3.4 to 5.4 g per deciliter; and erythrocyte sedimentation rate (ESR), 0 to 10 mm per hour.

¶¶ Lymphopenia was defined as a lymphocyte level of less than 2.5% for an age of younger than 1 month, less than 4.0% for 1 to younger than 12 months, less than 3.0% for 1 to younger than 2 years, less than 2.0% for 2 to younger than 4 years, less than 1.5% for 4 to younger than 10 years, less than 1.2% for 10 to younger than 16 years, and less than 1.0% for 16 years or older.<sup>1</sup>

|| Neutropenia was classified as a neutrophil level of less than 1.0% for an age of younger than 6 months, less than 1.5% for 6 months to younger than 10 years, and less than 1.8% for 10 years or older.<sup>1</sup>

\*\*\* An elevated proBNP level (excluding children <1 month of age) was classified as more than 1121 pg per milliliter for an age of 1 month to younger than 1 year, more than 675 pg per milliliter for 1 to younger than 2 years, more than 391 pg per milliliter for 2 to younger than 14 years, and more than 363 pg per milliliter for 14 years or older.<sup>2</sup>

††† An elevated procalcitonin level was classified as more than 0.5 ng per deciliter.<sup>3</sup>

‡‡‡ The ferritin level was measured for children older than 2 months.

§§§ Therapies were not mutually exclusive; among those with MIS-C, 2 patients received both BiPAP or CPAP and mechanical ventilation, and 3 patients received both high flow nasal cannula and mechanical ventilation; among those excluded for missing other criteria, 1 patient received both BiPAP or CPAP and mechanical ventilation, 2 patients received both high flow nasal cannula and mechanical ventilation, and 2 patients received both BiPAP or CPAP and high flow nasal cannula.

**Table S2 Admission Systolic and Diastolic Blood Pressure by Age Group**

Age	Systolic blood pressure (mmHg) median (IQR)	Diastolic blood pressure (mmHg) median (IQR)
0-3 months (n/N=1/1)	99.0 (99.0, 99.0)	64.0 (64.0, 64.0)
3-6 months (n/N=0/0)	--	--
6-12 months (n/N=0/0)	--	--
1-3 years (n/N=5/5)	94.0 (93.0, 99.0)	58.0 (53.0, 60.0)
3-6 years (n/N=25/25)	92.0 (87.0, 97.0)	53.0 (45.0, 59.0)
6-12 years (n/N=36/36)	91.5 (84.5, 98.5)	56.0 (44.5, 61.5)
>12 years (n/N=32/32)	93.0 (81.0, 100.5)	53.5 (48.0, 65.5)

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