Supplementary Material

Supplementary Table 1. World Health Organization (WHO), Brighton Collaboration, and Royal College of Paediatrics and Child Health (RCPCH) case definitions for Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (PIMS-TS).

WHO	**Brighton Collaboration**	**RCPCH**
Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 (MIS-C) [a]	Multisystem inflammatory syndrome in children and adults (MIS-C/A) [b]	Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (PIMS-TS) [c]
Children and adolescents 0–19 years of age with fever ≥3 days AND two of the following: 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, PTT, elevated D-dimer) 5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	Level 1 – Definitive case Age <21 years (MIS-C) or ≥21 years (MIS-A) AND fever ≥3 consecutive days AND 2 or more of the following clinical features: - Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet) - Gastrointestinal (abdominal pain, vomiting, diarrhea) - Shock/hypotension - Neurologic (altered mental status, headache, weakness, paresthesias, lethargy) AND laboratory evidence of inflammation including any of the following: elevated CRP, ESR, ferritin, or procalcitonin AND 2 or more measures of disease activity: - Elevated BNP or NT-proBNP or troponin - Neutrophilia, lymphopenia, or thrombocytopenia - Evidence of cardiac involvement by echocardiography or physical stigmata of heart failure - EKG changes consistent with myocarditis or myo-pericarditis AND laboratory confirmed SARS-CoV-2 infection, personal history of confirmed COVID-19 within 12 weeks, close contact with known COVID-19 case within 12 weeks, OR following SARS-CoV-2 vaccination	1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease. 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice). 3. SARS-CoV-2 PCR testing may be positive or negative.

	Level 2 – Probable case Level 2a Same criteria as Level 1 except: 1 measure of disease activity AND within 12 weeks of a personal history of known or strongly suspected COVID-19, within 12 weeks of close contact with a person with known or strongly suspected COVID-19, OR following SARS-CoV-2 vaccination Level 2b Same criteria as Level 1 except: Fever lasting 1–2 days and can be subjective Level 3 – Possible case Level 3a Age <21 years (MIS-C) or ≥21 years (MIS-A) AND fever ≥3 consecutive days AND 2 or more of the following clinical features: - Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet) - Gastrointestinal (abdominal pain, vomiting, diarrhea) - Shock/hypotension - Neurologic (altered mental status, headache, weakness, paresthesias, lethargy) - Physical stigmata of heart failure AND no laboratory markers of inflammation or measures of disease activity available AND within 12 weeks of a personal history of known or strongly suspected COVID-19, within 12 weeks of close contact with a person with known or strongly suspected COVID-19, or following SARS-CoV-2 vaccination Level 3b Same criteria as Level 2a except fever lasting 1–2 days and can be subjective	

	Level 4 – Insufficient evidence Reported MIS-C/A with insufficient evidence to meet Level 1–3 in the case definition Level 5 – Not a case of MIS-C/A Sufficient clinical and laboratory evidence exists to ascertain that a case is NOT MIS-C/A. An alternative diagnosis has been ascertained.	

[a] https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

[b] https://brightoncollaboration.us/multisystem-inflammatory-syndrome-in-children-and-adults-mis-c-a-case-definition/

[c] https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

Supplementary Material

Supplementary Table 2. Side-by-side comparison of criteria included in the 2020 CDC MIS-C case definition and in the CSTE/CDC MIS-C surveillance case definition.

Criterion	2020 CDC MIS-C Case Definition	CSTE/CDC MIS-C Surveillance Case Definition
Patient age	<21 years	<21 years
Hospitalization	Clinically severe illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
No alternative diagnosis	No alternative plausible diagnoses	Absence of a more likely alternative diagnosis
Fever	Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours	Subjective or documented fever (temperature ≥38.0°C)
Laboratory evidence of systemic inflammation	Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin	C-reactive protein ≥3.0 mg/dL (30 mg/L)
Evidence of SARS-CoV-2 infection or exposure	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.	• Detection of SARS-CoV-2 RNA in a clinical specimen up to 60 days prior to or during hospitalization, or in a post-mortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction [PCR]), OR • Detection of 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, OR • Close contact with a confirmed or probable case of COVID-19 disease in the 60 days prior to hospitalization
Multisystem involvement	Multisystem (≥2) organ involvement: • Cardiac (e.g., shock, elevated troponin, BNP, abnormal echocardiogram, arrhythmia) • Renal (e.g., acute kidney injury, renal failure)	New onset manifestations in at least two of the following categories: • Cardiac involvement indicated by: ○ Left ventricular ejection fraction <55%, OR

	• Respiratory (e.g., pneumonia, ARDS, pulmonary embolism) • Hematologic (e.g., elevated D-dimer, thrombophilia, thrombocytopenia) • Gastrointestinal (e.g., elevated bilirubin, elevated liver enzymes, diarrhea) • Dermatologic (e.g., rash, mucocutaneous lesions) • Neurological (e.g., CVA, aseptic meningitis, encephalopathy)	○ Coronary artery dilatation, aneurysm, or ectasia, OR ○ Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note • Mucocutaneous involvement indicated by: ○ Rash, OR ○ Inflammation of the oral mucosa (e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue), OR ○ Conjunctivitis or conjunctival injection (redness of the eyes), OR ○ Extremity findings (e.g., erythema [redness] or edema [swelling] of the hands or feet) • Shock • Gastrointestinal involvement indicated by: ○ Abdominal pain, OR ○ Vomiting, OR ○ Diarrhea • Hematologic involvement indicated by: ○ Platelet count <150,000 cells/µL, OR ○ Absolute lymphocyte count (ALC) <1,000 cells/µL