**Appendix online only**

**Case definitions for multisystem inflammatory syndrome in children (MIS-C) from the US Centers for Disease Control, the New York State Department of Health, the UK Royal College of Paediatrics and Child Health, and the World Health Organization**

**US Centers for Disease Control and Prevention case definition for Multisystem Inflammatory Syndrome in Children (MIS-C)**

An individual aged <21 years presenting with feveri, laboratory evidence of inflammationii, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**

No alternative plausible diagnoses; **AND**

Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

i Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

ii 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

Additional comments

Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C

Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

**New York State Department of Health case definition for pediatric multi-system inflammatory syndrome (PMIS) temporally associated with COVID-19**

**Clinical Criteria:** An individual aged < 21 years with:

* A minimum one-day history of subjective OR objective fever (≥ 100.4° F/38° C); AND
* Hospitalization; AND
* Either:
  + One or more of the following:
    - Hypotension or shock (cardiogenic or vasogenic)
    - Features of severe cardiac illness including but not limited to myocarditis, pericarditis, or valvulitis, significantly elevated troponin/pro-BNP, 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
* The 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 (CRP), 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 results1
  + 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 SARS-CoV-2 antibody in serum, plasma, or whole blood indicative of a new or recent infection.

**Epidemiologic Criteria:**

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

* Close contact with an individual with laboratory-confirmed SARS-CoV-2 infection.1
* Close contact with an individual with illness clinically compatible with COVID-19 disease who had close contact with an individual with laboratory-confirmed SARS-CoV-2 infection.1
* Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2.

CASE CLASSIFICATIONS:

*Confirmed:* Meets clinical, general laboratory, and virologic laboratory criteria

*Suspect:* Meets clinical, general laboratory, and epidemiologic criteria

1 Based on the use of an FDA authorized test

**UK Royal College of Paediatrics and Child Health case definition for paediatric multisystem inflammatory syndrome temporally associated with COVID-19**

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 (see listed in Appendix 1). 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

**Appendix 1**

**Clinical and laboratory features**

**Clinical**

**All:**

• Persistent fever >38.5°C

**Most:**

• Oxygen requirement

• Hypotension

**Some:**

• Abdominal pain

• Confusion

• Conjunctivitis

• Cough

• Diarrhoea

• Headache

• Lymphadenopathy

• Mucus membrane changes

• Neck swelling

• Rash

• Resp symptoms

• Sore throat

• Swollen hands and feet

• Syncope

• Vomiting

**Imaging and ECG**

• Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation

• CXR – patchy symmetrical infiltrates, pleural effusion

• Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly

• CT chest – as for CXR – may demonstrate coronary artery abnormalities if with contrast

**Laboratory**

**All:**

• Abnormal Fibrinogen

• Absence of potential causative organisms (other than SARS-CoV-2)

• High CRP

• High D-Dimers

• High ferritin

• Hypoalbuminaemia

• Lymphopenia

• Neutrophilia in most – normal neutrophils in some

**Some:**

• Acute kidney injury

• Anaemia

• Coagulopathy

• High IL-10 (if available)\*

• High IL-6 (if available)\*

• Neutrophilia

• Proteinuria

• Raised CK

• Raised LDH

• Raised triglycerides

• Raised troponin

• Thrombocytopenia

• Transaminitis

\*These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

**World Health Organization case definition for multisystem inflammatory syndrome in children and adolescents with COVID-19**

Children and adolescents 0–19 years of age with fever > 3 days

**AND** two of the following:

a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).

b) Hypotension or shock.

c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),

d) Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).

e) 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.