Call for a universal PIMS-TS/MIS-C case definition

In April 2020, reports emerged of a new paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Numerous clinical uncertainties of PIMS-TS are still contested regularly in clinical practise today. These include distinguishing PIMS-TS from other common causes of childhood febrile illness and its pathogenesis. Disparity in clinical guidance exacerbates this uncertainty. This letter calls for a universal PIMS-TS case definition, which could improve coherency in clinical practise and research.

The first case definition released by the Royal College of Paediatrics and Child Health in May 2020[1] is broad and takes a cautionary approach to SARS-CoV-2 testing. Case definitions from the WHO[2] and the Centers for Disease Control and Prevention (CDC)[3] quickly followed with one notable difference: requirement of evidence of SARS-CoV-2 infection or previous exposure (table 1). Further research is needed to compare the diagnostic accuracy of the three definitions, contributing to the development of one cohesive definition.

For a universal recommendation to be made, consensus should be reached on the inclusion of SARS-CoV-2 testing in a PIMS-TS definition. This letter argues that the WHO and CDC definitions might not capture the true spectrum of patients with PIMS-TS that we see today. In May 2020, confirmation of a SARS-CoV-2 infection might have aided clinicians in differentiating PIMS-TS from similar febrile illnesses. However, nearly 2 years into the COVID-19 pandemic, with millions of people infected globally, a history of a SARS-CoV-2 infection or exposure is a non-specific marker for PIMS-TS, as a large proportion of the population will now be antibody positive. In a UK cohort of hospitalised patients with PIMS-TS (n=58),[4] there was no meaningful difference in clinical features of patients with or without evidence of SARS-CoV-2 infection (either PCR or antibody). Moreover, SARS-CoV-2 testing is not universally available and is therefore not a feasible option for resource-limited settings. It also remains unclear whether SARS-CoV-2 simply triggers a severe phenotype of other febrile illnesses.

Furthermore, the WHO and CDC definitions assume causality. To establish a causative link, the Bradford Hill criteria can be applied; consistency, temporality, plausibility and coherence are fulfilled. There is a clear temporal association, supported by literature, however robust research is needed to determine whether a higher viral load leads to higher severity, to help establish causality.

Conversely, evidence of another microbial cause should not exclude a PIMS-TS diagnosis, as patients may also have underlying bacteraemia. Ultimately, the development of a multi-omics signature of PIMS-TS would improve the diagnostic accuracy for patients with infectious and inflammatory disease in a COVID-19 era. However, it should be noted that treatment often commences before such laboratory data are available. Therefore, robust and cohesive clinical guidelines are vital.

This letter proposes that a positive SARS-CoV-2 test should not be included in a PIMS-TS case definition. This letter also supports the dynamic process of developing an international case definition to streamline clinical practise and research output in an area where considerable clinical uncertainty remains.

Table 1 Three case definitions of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2[1–3]

Country (organisation)	Case definition
WHO	► 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; (b) hypotension or shock; (c) features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities; (d) evidence of coagulopathy; (e) acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain) AND ► Elevated markers of inflammation such as ESR, CRP 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
US (CDC)	► An individual aged <21 years presenting with fever, laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalisation, 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 COVID-19 exposure within the 4 weeks prior to the onset of symptoms
UK (RCPCH)	► A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) 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 ► 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) ► SARS-CoV-2 PCR testing may be positive or negative

CDC, Centers for Disease Prevention and Control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RCPCH, Royal College of Paediatrics and Child Health; RT-PCR, reverse transcription polymerase chain reaction.

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