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Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: Current knowledge and implications for public health

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has caused widespread mortality and morbidity. Though children are largely spared from severe illness, a novel childhood hyperinflammatory syndrome presumed to be associated with and subsequent to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged with potentially severe outcomes. Multisystem inflammatory disorder in children (MIS-C) most commonly affects young, school-aged children and is characterized by persistent fever, systemic hyperinflammation, and multisystem organ dysfunction. While uncommon and generally treatable, MIS-C presents potentially life-altering medical sequelae, complicated by a dearth of information regarding its etiology, pathophysiology, and long-term outcomes. The severity of MIS-C may warrant the need for increased awareness and continued COVID-19 mitigation efforts, particularly until potential factors conferring a predisposition to MIS-C can be clarified through additional research. Well-informed guidelines will be critical as the school year progresses. In this article, current knowledge on MIS-C is reviewed and the potential implications of this novel syndrome are discussed from a public health perspective.

Contents

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused widespread morbidity and mortality, impacting nearly every nation in the world. Though the majority of infected children appear to be spared from severe illness, an unusual pediatric syndrome called multisystem inflammatory syndrome in children (MIS-C), is believed to be associated with prior SARS-CoV-2 infection and presents an additional challenge in this ongoing public health crisis.

By the end of June 2020, approximately 1000 MIS-C cases had been documented globally [1]. In the United States, where there is a high burden of SARS-CoV-2 community spread, 570 MIS-C cases were reported by the end of July 2020 and were predominantly geographically concentrated in COVID-19 hotspots, such as New York state [2]. Nonetheless, the incidence of MIS-C diagnoses subsequent to SARS-CoV-2 infection appears to be relatively low. In the U.S., rough estimates of incidence based on data from the surge in New York found the incidence of SARS-CoV-2 infection among those under 21 years of age to be 322 per 100,000 and MIS-C to be 2 per 100,000 persons among the same age group [3]. However, the total number of children who may be at risk for MIS-C remains unknown because there is a potentially high proportion of SARS-CoV-2 infections among children that remains undetected, given that the likelihood of paucisymptomatic or asymptomatic infection is higher among children than in adults [4,5].

Information about this rare, though potentially fatal, syndrome is rapidly evolving. In this review, we describe current information on case definitions, patient demographics, clinical features, and key laboratory findings, including articles published between May and August 2020 that reported on a minimum of 15 patients. We also briefly discuss public health implications related to MIS-C, which are particularly relevant as schools continue to adjust their institutional COVID-19 mitigation plans in response to local incidence rates and evolving knowledge.

Current knowledge about MIS-C

History of MIS-C

In April 2020, pediatricians in the United Kingdom first reported a cluster of children presenting with fever, cardiovascular shock, and hyperinflammation, exhibiting symptoms resembling those of Kawasaki Disease (KD), cytokine storm, or toxic shock syndrome [6]. The disorder was later termed "pediatric inflammatory multisystem syndrome temporarily associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", or PIMS-TS, by the Royal College of Paediatrics and Child Health (RCPCH) [7]. Soon after the RCPCH released their case definition, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) published their own respective case definitions of the syndrome and named it multisystem inflammatory syndrome in children [8,9] (Table A1).

MIS-C case definitions generally include pediatric age, persistent fever, multi-organ dysfunction, laboratory markers of significant inflammation, lack of an alternative diagnosis, and prior SARS-CoV-2 infection or exposure, though definitions vary. For example, both the U.S. CDC and the WHO MIS-C case definitions require evidence of prior SARS-CoV-2 infection or exposure, whereas the RCPCH does not. In contrast to the WHO, the CDC case definition permits a shorter duration of fever ($\geq$ 24 h versus $\geq$ 3 days) and severe illness requiring hospitalization. The rapid development and variation among case definitions may explain some of the variability in reported clinical features and severity of disease thus far, though the extent to which remains unclear, and it is likely that case definitions will evolve as more information becomes available.

While clinicians initially faced challenges differentiating between MIS-C and KD, key differences in demographic, clinical, and laboratory features have been delineated (further described in Section 2.6) [6,10,11]. Similar to KD, MIS-C patients typically present with persistent fever, mucocutaneous signs, and raised inflammatory markers. However, MIS-C tends to affect older children ($\geq$ 5 years old) and is distinguishable by more remarkable multi-organ involvement, particularly that of the gastrointestinal (GI) and cardiovascular systems.

Demographic characteristics of patients

Based on currently available literature, children who develop MIS-C are typically in their early to middle childhood years and often previously healthy. The median age across the included studies varied from 7 to 10 years old, with an age range spanning from 7 months to 20 years (Table 1). While some have hypothesized that being overweight may confer a greater risk of developing MIS-C, the majority of studies identified few to no comorbidities. In a case series of 186 patients, Feldstein et al. reported that 73% of MIS-C patients were previously healthy [12]. Among those who did have prior health conditions across studies, the most common comorbidities were being overweight (10–39%) and having a prior history of asthma (5–18%) [3,11,13–18].

While early reports suggested males may be overrepresented, similar to that in KD, a clear gender predilection has not yet been established in MIS-C. Reported distributions of male and female cases have been largely even thus far, with only a slight male preponderance in six studies [3,12,15,17,19,20].

With regard to race and ethnicity, many studies have indicated that African American, African/Afro- Caribbean, and Hispanic children may be disproportionately affected by MIS-C. Among European studies with available race/ethnicity data, African/Afro Caribbean children often accounted for the greatest proportion of cases, ranging from 38% to 62% of MIS-C patients [11,18,20,21]. In one of the largest published case series to date (n = 58), Whittaker et al. found that 38% of cases were of African/Afro Caribbean descent [11]. Among U.S. studies, African American and Hispanic children had a higher burden of MIS-C compared to other races reported. Across U.S. studies with available race/ethnicity data, the proportion of children who were African American ranged from 18% to 40%, and Hispanic from 24% to 45% [3,12,14,16,19].

Table 1
Overview of studies included in the review.[a]

Study	Geographical location	Timeline of patient enrollment	Number of patients (% Male)	Age, median (IQR), years	Number of positive patients/total number tested (%)	Most common clinical features	Imaging findings	Clinical course and outcomes
Belhadjer et al. (2020) [13]	France and Switzerland	Mar 22-Apr 30	35 (51%)	10 (NA)	RT-PCR: 14/35 (40%) Serology: 30/35 (86%) Overall[b]: 31/35 (89%)	Fever (100%), Asthenia (100%), Shock[c] (80%), Gastrointestinal symptoms (83%), Respiratory distress (65%), Adenopathy (60%), Rash (57%), Meningism (31%)	Depressed LVEF[d] (100%), Coronary artery dilation (17%), Pericardial effusion (9%), Arrhythmia (3%)	ICU admission (100%), Inotropic support (80%), Respiratory support (94%), Mortality (n = 0)
Belot et al. (2020) [23]	France	Mar 1-May 17	108 (49%)	8 (NA)	RT-PCR: 28/108 (26%) Serology: 42/108 (39%)	Kawasaki-like disease (61%), Macrophage activation syndrome (23%), Seritis (22%)	Not reported	ICU admission (67%), Myocarditis (70%), Mortality (n = 1)
Cheung et al. (2020) [14]	New York, United States	Apr 18-May 5	17 (47%)	8 (1.8–16)	RT-PCR: 8/17 (47%) Serology: 9/17 (53%) Overall: 17/17 (100%)	Fever (100%), Gastrointestinal symptoms (88%), Shock (76%), Rash (71%), Conjunctivitis (65%), Headache, stiff neck, or vision changes (47%), Cough (31%),	Abnormal chest radiograph (82%), Depressed LVEF (65%), Pericardial effusion (47%)	ICU admission (88%), Vasopressor support (66%), Hypoxia (53%), Coronary artery aneurysm (6%) Mortality (n = 0)
Dufort et al. (2020) [3]	New York, United States	Mar 1-May 10	99 (54%)	NA	RT-PCR: 50/98 (51%) Serology: 76/77 (99%)	Fever (100%), Gastrointestinal symptoms (80%), Rash (60%), Conjunctivitis (56%), Lower respiratory symptoms (40%), Kawasaki disease or atypical Kawasaki disease (36%), Hypotension (32%), Neurologic symptoms (30%), Shock (10%)	Abdominal abnormalities (77%), Cardiac abnormalities (60%), Ventricular dysfunction (52%), Inflammation of appendix or gallbladder (39%), Chest opacity (39%), Ascites, pleural effusions, or pelvic fluid (36%), Pericardial effusion (32%),	ICU admission (80%), Vasopressor support (62%), Mechanical ventilation (10%), Myocarditis (53%), Acute kidney injury (10%), Coronary artery aneurysm (9%), Mortality (n = 2)

							Mesenteric adenopathy (18%)	
Feldstein et al. (2020) [12]	26 states, United States	Mar 15-May 20	186 (62%)	8.3 (3.3-12.5)	Overall: 131/186 (70%)	Fever (100%), Gastrointestinal involvement (92%), Cardiovascular involvement (80%), Rash (59%), Conjunctivitis (55%), Shock (50%), Peripheral edema (37%)	Depressed LVEF (38%),	ICU admission (80%),
							Pericarditis or pericardial effusion (26%),	Vasoactive support (48%),
							Arrhythmia (12%)	Mechanical ventilation (20%),
								Respiratory insufficiency/failure (59%),
								Coronary artery aneurysm (8%),
								Mortality (n = 4)
Grimaud et al. (2020) [22]	Paris, France	Apr 15-Apr 27	20 (50%)	10 (NA)	RT-PCR: 10/20 (50%)	Fever (100%), Tachycardia (100%), Gastrointestinal symptoms (100%), Shock (100%), Rash (50%), Conjunctivitis (30%)	Depressed LVEF (100%),	ICU admission (100%),
					Serology: 15/15 (100%)		Pericardial effusion (27%)	Inotropic support (95%),
					Overall: 19/20 (95%)			Invasive mechanical ventilation (40%),
								Noninvasive mechanical ventilation (55%),
								Myocarditis (100%),
								Acute renal failure (70%),
								Mortality (n = 0)
Kaushik et al. (2020) [19]	New York City, New York, United States	Apr 23-May 23	33 (61%)	10 (6-13)	RT-PCR: 11/33 (33%)	Fever (93%), Nausea/vomiting (69%), Abdominal pain (63%), Hypotension (63%), Diarrhea (48%), Rash (42%)	Pericardial effusion (46%),	Vasoactive support (51%),
					Serology: 27/33 (81%)		Cardiomegaly (30%),	Invasive mechanical ventilation (15%),
							Pulmonary opacities (33%),	Noninvasive mechanical ventilation (36%),
							Depressed LVEF (63%)	Cardiac arrest (3%),
								Morality (n = 1)
Lee et al. (2020) [15]	Boston, Massachusetts, United States	Mar-June	28 (57%)	9 (NA)	RT-PCR: 17/28 (61%)	Fever (100%), Conjunctivitis (57%), Gastrointestinal symptoms (54%), Shock (54%), Rash (36%)	Depressed LVEF (39%),	ICU admission (61%),

Table 1 (*Continued*)

Study	Geographical location	Timeline of patient enrollment	Number of patients (% Male)	Age, median (IQR), years	Number of positive patients/total number tested (%)	Most common clinical features	Imaging findings	Clinical course and outcomes
					Serology: 18/19 (95%) Overall: 28/28 (100%)		Focal consolidation/opacity (38%), Pleural effusion (12%), Coronary dilation (7%)	Inotropic support (25%), Non-invasive ventilation (25%), Acute kidney injury (21%), Coronary artery aneurysm (14%), Mortality (n = 0)
Miller et al. (2020) [16]	New York, United States	Apr 18-May 22	44 (45%)	7.3 (NA)	RT-PCR: 15/44 (34%) Serology: 31/32 (97%)	Fever (100%), Gastrointestinal symptoms (84%), Poor appetite (75%), Rash (71%), Conjunctivitis (52%), Mucosal changes (52%) Shock (50%), Neurologic symptoms (30%)	Cardiac abnormalities (50%), Abnormal abdominal imaging (27%)	Vasopressor support (50%), Acute kidney injury (16%), Mortality (n = 0)
Moraleda et al. (2020) [17]	Spain	Mar 1-June 1	31 (58%)	7.6 (4.5-11.5)	RT-PCR: 17/31 (55%) Serology IgM: 10/17 (59%) Serology IgG: 19/21 (90%) Overall: 30/31 (97%)	Fever (97%), Gastrointestinal symptoms (87%), Rash or conjunctivitis (74%), Malaise (51%), Hypotension or shock (48%), Cough (36%), Shortness of breath (27%)	Myocardial dysfunction (48%), Valvular dysfunction (29%), Arrhythmia (23%), Pericardial effusion (19%), Coronary abnormalities (10%)	ICU admission (65%), Invasive mechanical ventilation (19%), Renal failure (13%), Coronary artery aneurysm (3%), Mortality (n = 1)
Pouletty et al. (2020) [18]	Paris, France	Apr 7-Apr 30	16 (50%)	10 (4.7-12.5)	RT-PCR: 11/16 (69%)	Fever (100%), Conjunctivitis (94%), Gastrointestinal symptoms (81%), Rash (81%), Peripheral edema (69%), Complete KD (62%), Neurological symptoms (56%), Lymphadenopathy (37%)	Cardiac abnormalities (68%),	ICU admission (44%),

					Serology: 7/8 (87%) Overall: 14/16 (88%)		Pericarditis (25%), Coronary dilation (19%)	Fluid resuscitation (44%), Inotropic support (38%), Myocarditis (44%), Acute renal failure (56%), Mortality (n = 0)
Ramcharan et al. (2020) [20]	Birmingham, England	Apr 10-May 9	15 (73%)	8.8 (6.4-11.2)	RT-PCR: 2/15 (13%) Serology: 12/15 (80%)	Cardiovascular involvement (100%), Gastrointestinal symptoms (87%), Myalgia/lethargy (27%)	Coronary artery abnormalities (93%), Depressed LVEF (80%), Pericardial effusion (53%)	ICU admission (67%), Respiratory support (53%), Vasoactive support (67%), Mortality (n = 0)
Toubiana et al. (2020) [21]	Paris, France	Apr 27-May 7	21 (43%)	7.9 (3.7-16.6)	RT-PCR: 8/21 (38%) Serology: 19/21 (90%)	Fever (100%), Gastrointestinal symptoms (95%), Conjunctivitis (81%), Rash (76%), Mucosal changes (76%), Neurological symptoms (29%)	Coronary artery abnormalities (38%), Pericardial effusion (48%), Pleural effusion (14%), Ascites (19%)	ICU admission (81%), Myocarditis (76%), Vasoactive support (71%), Mechanical ventilation (52%), Kidney failure (52%), Mortality (n = 0)
Whittaker et al. (2020) [11]	England and United States	Mar 23-May 16	58 (43%)	9 (5.7-14)	RT-PCR: 15/58 (26%) Serology: 40/46 (87%) Overall: 45/58 (78%)	Fever (100%), Abdominal pain/diarrhea (53%), Rash (52%), Shock (50%), Vomiting (45%), Conjunctivitis (45%), Mucosal changes (29%), Headache (26%)	Depressed LVEF (31%), Arrhythmia (7%)	Inotropic support (50%), Mechanical ventilation (40%), Intubation (43%), Acute kidney injury (22%), Coronary artery aneurysm (14%), Mortality (n = 1)

ICU, intensive care unit; NA, not available; RT-PCR, reverse transcription polymerase chain reaction.

[a] The denominator for percentages is the total number of MIS-C patients in the study, unless otherwise indicated.

[b] Positive for current or recent SARS-CoV-2 infection by RT-PCR or serology.

[c] Shock was defined by author.

[d] Depressed left ventricular ejection fraction of <50% or < 55%.

Clinical features

Clinical presentation

MIS-C has a wide spectrum of clinical signs and symptoms, though it most commonly presents with persistent fever, along with dermatologic, mucocutaneous, and GI features (Table 1). Fever was reported in 97–100% of patients at presentation [3,11–19,21,22]. Dermatologic and mucocutaneous findings such as rash, conjunctivitis, and lip redness and swelling were reported in the majority of patients, though they were more commonly found in children than in adolescents. Similar to KD and toxic shock syndrome, rash and conjunctivitis were frequently observed, with 36–81% of patients presenting with rash and 30–94% with conjunctivitis [3,11–19,21,22].

GI involvement was often the most prominent feature of MIS-C, with all but two studies reporting GI involvement in more than 80% of patients. GI symptoms including abdominal pain, vomiting, and diarrhea were described in 54–100% of patients at presentation and may precede other common symptoms associated with MIS-C, often mimicking common gastrointestinal infections or even inflammatory bowel disease [3,13–22]. For example, Miller et al. found that 29.5% of children hospitalized with a diagnosis of MIS-C had presented *within seven days prior to admission* at either an emergency room or urgent care center with GI symptoms similar to those of viral gastroenteritis without additional systemic symptoms [16].

Demonstrating the considerable spectrum of gastrointestinal pathology in MIS-C, abnormal abdominal features were also reported in four studies that performed abdominal imaging [3,15,16,21]. Of 44 patients who underwent abdominal ultrasound or computed tomography, Dufort et al. found evidence of abdominal abnormalities in 77% of patients, including ascites, pleural effusions, or pelvic fluid (n = 35), mesenteric adenopathy (n = 8), and enteritis or enterocolitis (n = 3) [3]. Similar abnormalities, including mesenteric adenitis, biliary sludge, and ascites, were reported by Miller et al. in over 80% of patients [16]. Both studies found evidence of bowel wall thickening.

Nervous and respiratory system involvement were also reported at MIS-C presentation. Neurological symptoms including headache, vision changes, confusion, and meningitis signs were reported in 12–56% of patients [3,14–19,21]. While COVID-19-like respiratory symptoms are generally not a part of MIS-C presentation, shortness of breath, cough, hypoxia, and respiratory distress have been documented [13,14,16,18,19].

Cardiac involvement

Studies to date have indicated that there can be potentially considerable cardiac involvement in MIS-C. With the exception of one study that did not perform imaging [23], all studies reported cardiac abnormalities as evidenced by echocardiography or electrocardiography and highlighted the prominence of myocardial dysfunction among patients.

Depressed left ventricular systolic function was commonly reported and described in 31–100% of patients who underwent imaging [3,11–15,19,20,22]. Belhadjer et al. described a cohort of 35 patients admitted to intensive care units (ICU) for severe heart failure associated with MIS-C, wherein left ventricular dysfunction was the main cardiac feature [13]. At admission, echocardiography revealed that 72% of patients had a depressed left ventricular ejection fraction (LVEF) between 30 and 50%, indicating mild to moderate dysfunction, while the remaining 28% had a depressed LVEF of <30%, indicating severe dysfunction. Seventy-one percent of patients made a full recovery, defined as LVEF > 60%, by day 7, with a median time to full recovery of two days (range 2–5 days). Similarly, 95% of patients described by Kaushik et al. recovered left ventricular function prior to discharge [19].

Myocarditis and pericarditis, or pericardial effusion, were common diagnoses among MIS-C cases [3,12–14,17–19,21–23]. Pouletty et al. reported myocarditis in 44% of patients and pericarditis in 25% [18]. Similarly, Dufort et al. found that 53% and 32% of MIS-C patients received a diagnosis of myocarditis and pericarditis, respectively, noting noticeably higher rates of myocarditis among adolescents [3]. Eighty-one percent of patients 13–20 years of age received a diagnosis of myocarditis, compared to 39% among those under six years of age.

Coronary artery abnormalities are among the more severe reported features of MIS-C and were described in the majority of studies reviewed. Ten studies reported evidence of coronary artery abnormalities, six of which included coronary artery aneurysms [3,11–15,17,18,20,21]. The extent of coronary involvement was profound. Ramcharan et al. and Toubiana et al. found coronary artery abnormalities in 93% and 47% of patients studied, respectively [20,21]. A small number of giant coronary artery aneurysms have also been observed in MIS-C. Out of 55 patients in a cohort of 58 who underwent echocardiography in the U.K., coronary artery aneurysms were found in 14% of patients, with giant coronary artery aneurysms in two [11]. Dufort et al. obtained echocardiograms for 93 hospitalized patients and found 9% had documented coronary artery aneurysms [3].

Laboratory findings

Laboratory evidence of systemic inflammation, myocardial dysfunction, and coagulation activation among patients has been consistently reported across the currently available literature. Per the case definitions of MIS-C, inflammatory markers, including C-reactive protein (CRP), ferritin, procalcitonin, and serum interleukin-6, are expected to be significantly elevated. Feldstein et al. found 171 out of 186 total subjects had elevations in at least four inflammatory biomarkers [12]. Troponin and N-terminal-pro B-type Natriuretic Peptide (NT-pro-BNP) were the most commonly reported cardiac markers and were highly elevated in the majority of patients. High levels of D-dimer and fibrinogen characterized coagulation dysfunction in most patients. In addition, laboratory evidence of lymphocytopenia, neutrophilia, hypoalbuminemia, anemia, and thrombocytopenia was also common.

The American Academy of Pediatrics, the American College of Rheumatology, and other professional societies have summarized common laboratory features of MIS-C and have provided interim clinical guidance on diagnostic evaluation and treatment [24,25].

Treatment and outcomes

While there are currently no standard clinical practice guidelines regarding treatment for MIS-C, current management and treatment plans have generally yielded favorable outcomes. Similar to standard KD treatment, intravenous immunoglobulin (IVIG) therapy was the most commonly reported treatment provided to patients (55–100%), followed by corticosteroids (10–96%) [3,11–20,22]. Often leading to rapid recovery within a few days, several studies support IVIG and corticosteroids as viable options for anti-inflammatory treatment.

A significant proportion of MIS-C patients are admitted to the ICU, often requiring cardiac or respiratory support. Across studies that reported ICU admission rates, the percentage of subjects admitted ranged from 44% to 100% (Table 1) [3,12,13,14,15,17,18,20,21,23]. The largest French and U.S. studies found 67% and 80% of cases required ICU support, respectively [12,23]. Dissimilar to COVID-19 cases, comorbidities do not seem to be associated with ICU admissions based on the current literature [18,20]. Mechanical ventilation use was noted in substantial proportion of patients, with 10%–62% of MIS-C patients requiring

invasive support in the ICU [3,11–13,17,19,22]. Low to moderate doses of vasoactive agents, including vasopressors and inotropes, were frequently administered to MIS-C patients admitted to the ICU due to shock resulting from myocardial involvement (e.g., acute myocarditis) and/or severe vasoplegia [3,12,14,16,19–21,23].

Eight studies noted significant renal complications among their patients. Among these, the proportion of patients with acute kidney injury or renal failure ranged from 10 to 70% [3,11,15–18,21,22]. In a case series of 20 patients, Grimaud et al. noted that out of 70% of patients with transient acute renal failure, none required renal replacement therapy [22].

Despite potentially severe clinical manifestations, outcomes of MIS-C are generally favorable and most cases tend to improve within a few days of treatment. Median reported lengths of ICU stay ranged from 4 to 7 days [3,12–15,19–21]. Moreover, mortality rates are relatively low, with the current estimates at approximately 2% [3,12]. While reported outcomes are encouraging, abnormal cardiac findings warrant further research, surveillance, and follow-up to gain a better understanding of the scope of MIS-C and to determine whether long-term complications may arise post convalescence.

MIS-C compared to KD

MIS-C shares multiple features with KD, such that a significant proportion of MIS-C patients reportedly meet complete KD criteria, prompting considerable discussion whether the two have different or shared etiologic and pathophysiologic pathways [14,18,21]. However, although many initially postulated that MIS-C was SARS-CoV-2-associated KD, it is now clear that the two syndromes appear to have key differences, including patient age distributions, racial/ethnic predilection, and clinical manifestations. (A detailed comparison of MIS-C with KD, KD shock syndrome, and toxic shock syndrome can be found elsewhere [11]). Briefly, comparing MIS-C to KD, the median age for those diagnosed with KD is approximately 1.5 years, which is substantially younger than what has been observed in MIS-C thus far [26]. Furthermore, KD appears to primarily affect those of East Asian ancestry, whereas MIS-C has been found to disproportionately affect those of African American, Hispanic, and Afro Caribbean descent and is seemingly rare among East Asian children [26]. When compared to children with KD, clinical features of MIS-C include much more significant gastrointestinal, myocardial, and multi-organ involvement [14,15]. Evidence of cardiovascular involvement, including myocarditis, ventricular dysfunction, and troponin elevations, is also much more prominent in MIS-C than in KD [11,14,15,21]. Cardiogenic shock requiring vasoactive or vasopressor support has been reported in a considerable proportion of MIS-C patients, compared to approximately 5% among KD patients [12]. Furthermore, laboratory features of MIS-C are also distinct from those in KD, more closely resembling those of macrophage activation syndrome and cytokine storm of toxic shock syndrome. Noticeably higher procalcitonin and CRP levels and lower platelet and lymphocyte counts are observed in MIS-C patients compared to KD patients [11,12,18,21]. Interestingly, one study noted that their immunologic findings in MIS-C patients seem to mimic the immunologic profiles of severe COVID-19 cases in adults [15].

Public health implications

The emergence of MIS-C serves as a reminder that children, though largely spared from the most severe outcomes associated with COVID-19, may still experience serious medical consequences related to SARS-CoV-2 infection. Though current evidence suggests MIS-C is rare among children and adolescents, comprehensive surveillance data are limited, and a few reports have suggested the low incidence observed thus far may, in part, be influenced by reduced exposure to SARS-CoV-2 due to schools not being in session or fully open for in-person instruction [27]. Because recent re-initiations of in-person education may increase extra-household contact frequency and duration for many children, additional vigilance is warranted to assess potential impact on pediatric incidence rates of both COVID-19 and MIS-C.

While causality (and the complete causal mechanism) is far from established, current findings support a temporal association between SARS-CoV-2 infection and MIS-C, with MIS-C typically occurring within two to four weeks after infection [3,11,12,18,23,28]. Noting this lag in time, and that MIS-C patients more often test positive for SARS-CoV-2 antibodies than the virus, some have proposed that MIS-C may be a post-infectious phenomenon related to antibody-mediated enhancement of disease rather than the result of acute viral infection [29]. Though several hypotheses are being explored [29,30], research studies are urgently needed to understand the underlying mechanisms of MIS-C. Furthermore, at the time of writing, some early literature on multisystem inflammatory syndrome in adults (MIS-A) was emerging. Future studies should seek to compare the pathophysiology of MIS-C to that of MIS-A as more information on both syndromes becomes available.

Currently, there is little evidence on risk factors associated with MIS-C development, though Afro-Caribbean, African American, and Hispanic children appear to be disproportionately affected, which may contribute to the persistent and pervasive racial/ethnic health disparities underscored by the COVID-19 crisis [31]. Though some have hypothesized that genetic predisposition may play a role in susceptibility to MIS-C [32], the over-representation of black and Hispanic racial/ethnic distribution among MIS-C patients could also be partly attributable to the higher rates of infection among these racial/ethnic minority groups [33,34]. Further compounding the problem, racial/ethnic minority groups are also generally more likely to be uninsured and to face other barriers to access to healthcare [31,35]. Provided the necessity of early detection, intervention, and critical care support among a substantial proportion of MIS-C cases, these barriers may hinder the receipt of proper treatment and clinical care for this largely treatable condition.

While more research is needed to establish risk and prognostic factors for MIS-C, some trends appear to be relatively consistent in the published literature thus far. MIS-C can develop in previously healthy children with no known comorbidities and usually presents within four weeks following SARS-CoV-2 infection, though symptoms consistent with MIS-C may appear before the resolution of COVID-19 symptoms in some cases [3,10]. Moreover, given that a large subset of SARS-CoV-2-infected children display mild to no symptoms, some children may develop MIS-C with little to no forewarning, and in some cases, caregivers may not even be aware that the child was previously infected with SARS-CoV-2. Therefore, it is important that caregivers are alerted to remain attentive to possible symptoms for several weeks following potential exposure to the virus or a positive SARS-CoV-2 molecular or antigen test. Early visible symptoms include prolonged fever, abominable pain, rash, and red eyes. As GI symptoms often precede other common symptoms of MIS-C, it is important to inform caregivers to watch for symptoms resembling those of common gastrointestinal infections.

Another cause for concern involves the prevalence of cardiac involvement and the potential rapid progression into shock or cardiorespiratory failure. A striking number of children exhibited features of cardiac involvement across studies, including cardiogenic shock, left ventricular dysfunction, coronary dilation, and aneurysms [3,6,13,17–22,33]. Despite being largely treatable and/or transient, the cardiac manifestations of MIS-C are vast and potentially life-threatening. Future research studies that follow patients over time are imperative to fill the gap in knowledge

related to potential long-term cardiac and other sequelae among MIS-C survivors.

Despite being a rare condition, the potential severity of MIS-C provides yet another incentive to implement effective preventative measures to mitigate the spread of SARS-CoV-2 infection and keep children safe within potentially high-contact environments, such as schools or childcare centers. Within the U.S. and across nations, a wide spectrum of school mitigation plans has been enacted, with some schools requiring face coverings and strictly enforcing social distancing and others flouting public health recommendations or simply lacking the resources needed to instate effective mitigation [36,37]. In the U.S., as schools return to in-person classes, the onus has fallen largely on school district leaders and school administrators to develop and maintain re-opening plans informed by public health best practices and to prioritize the safety of their students and the greater communities in which the students reside. MIS-C is a rare condition that simply adds to the gamut of other considerations that need to be weighed when planning for social reintegration and the ongoing safe operation of schools. Nevertheless, the associated critical outcomes merit heightened awareness, and parents, teachers, and school administrators should first and foremost be aware and conscientious of the signs and symptoms of both COVID-19 and MIS-C.

Conclusions

While seemingly rare and generally treatable, MIS-C is yet another challenge associated with the COVID-19 pandemic. Given the existing knowledge gaps, it remains challenging to predict which children may be at higher risk for MIS-C and, moreover, which will have poor outcomes. Because current studies support the idea that SARS-CoV-2 may act as a trigger or immunomodulatory factor in MIS-C pathogenesis [10], mitigating the transmission of SARS-CoV-2 not only serves to prevent COVID-19 but also presents a likely effective strategy for MIS-C prevention until future research can elucidate the etiology, pathophysiology, and potential long-term consequences associated with this rare condition.

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Competing interests

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Appendix A.

Table A1
RCPCH, U.S. CDC, and WHO case definitions of PIMS-TS and MIS-C.

RCPCH case definition[a]	U.S. CDC case definition[b]	WHO case definition[c]
1 A child presenting with persistent fever (>38.5 °C), 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 (see below). This may include children fulfilling full or partial criteria for Kawasaki disease.	1 Age <21 years	1 Age 0-19 years
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).	2 Clinical presentation including the following:	2 Fever for ≥3 days
3 SARS-CoV-2 PCR testing may be positive or negative	• Fever >38.0 °C for ≥24 hours, or report	a At least 2 of the following clinical features:
Clinical	• of subjective fever lasting ≥24	
		i Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs
• All: persistent fever	• Laboratory evidence of inflammation including, but not limited to, one or more of the following:	i Hypotension or shock
• Most: oxygen requirement, hypotension		
	○ Elevated CRP	1 Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities

Table A1 (*Continued*)

RCPCH case definition[a]	U.S. CDC case definition[b]	WHO case definition[c]
• Some: Abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting	○ Elevated ESR	1 Evidence of coagulopathy
Laboratory		
	○ Elevated fibrinogen	1 Acute gastrointestinal problems
• All: abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminemia, lymphopenia, neutrophilia in most	○ Elevated procalcitonin	i Elevated markers of inflammation such as ESR, CRP, or procalcitonin
• Some: acute kidney injury, anemia, coagulopathy, high IL-10 if available, high IL-6 if available, neutrophilia, proteinuria, raised CK, raised LDH, raised triglycerides, raised troponin, thrombocytopenia, transaminitis	○ Elevated D-dimer	i No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes
Imaging and ECG		
	○ Elevated ferritin	i Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19
• Echo and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilation		
	○ Elevated LDH	
• CXR: patchy symmetrical infiltrates, pleural effusion;		
	○ Elevated IL-6	
• Abdominal ultrasound: colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly		
	○ Neutrophilia	
• Chest CT: may demonstrate coronary artery abnormalities		
	○ Lymphocytopenia	
	○ Hypoalbuminemia	
	• Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal respiratory, hematologic, gastrointestinal, dermatologic, or neurological)	
	3 No alternative plausible diagnoses	
	4 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	

RCPCH, Royal College of Paediatrics and Child Health; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization; CRP, C-reactive protein; CK, creatinine kinase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; COVID-19, Coronavirus disease 2019; ECG, electrocardiogram; CXR, chest x-ray; CT, computerized tomography.

[a] https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance.

[b] https://www.cdc.gov/mis-c/hcp/.

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

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