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SYNTHESIS

04/05/21

# Pediatric Post-acute COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) – What We Know So Far

## Introduction

Public Health Ontario (PHO) is actively monitoring and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence on a specific aspect related to COVID-19.

## Updates to Latest Version

This rapid review replaces *COVID-19 – What We Know So Far About…Kawasaki Disease-Like Illness* (May 30, 2020).[1] This updated rapid review draws primarily upon systematic reviews and meta-analyses, and primary research where applicable, updating evidence on post-acute COVID-19 in children and multisystem inflammatory syndrome in children (MIS-C). Previously, we did not present any findings on post-acute COVID-19 in children and, while the literature remains sparse, we now report initial findings.

## Key Findings

- Post-acute COVID-19 is a syndrome with persistent or delayed symptoms lasting or appearing more than 3 weeks since illness-onset. There were limited primary studies on post-acute COVID-19 in the pediatric population; therefore, the results were highly heterogeneous.
- Fatigue, headache, insomnia, trouble concentrating and cough were the most common manifestations of post-acute COVID-19 in children.
- No studies examined risk factors for developing post-acute COVID-19 in pediatric patients.
- MIS-C is a post-viral hyperinflammatory condition affecting multiple organ systems. We investigated MIS-C separately from post-acute COVID-19 in children, focusing on systematic reviews and meta-analyses.
- The most common symptoms in patients with MIS-C were persistent fever, gastrointestinal symptoms, cardiovascular symptoms, conjunctivitis, rash, oral cavity changes and swelling in arms and legs. The most common clinical phenotype was hemodynamic shock/hypotension (50%–75%), followed by depressed left ventricular ejection fraction (LVEF) (40–70%), pleural effusion or infiltrates (30%–40%) and myocarditis (40%–60%). 80% of patients required

admission to a pediatric intensive care unit (PICU), with death occurring in 1.4%–2.2% of patients.

- The risk of developing MIS-C was higher among Black children and those aged 6–12 years.

# Background

For the purposes of this What We Know So Far, post-acute COVID-19 includes patients with persistent or delayed symptoms that develop, or last, more than 3 weeks after symptom-onset. The 3-week period is in line with evidence that viable virus is rarely detected past 10 days in mild to moderate COVID-19, and rarely past 20 days in severe cases.[2] Another term used to describe this condition is "long COVID".[3,4] Others have divided the post-acute phase of the disease into firstly, sub-acute or ongoing stage with symptoms persisting; secondly, delayed 3–4 weeks after symptom-onset (or after discharge from inpatient care); and lastly, a chronic phase with symptoms persisting/delayed more than 12 weeks since symptom-onset.[5-8] There are no agreed-upon definitions for these time points after initial infection.[7,9,10]

Given the low disease severity, high rate of asymptomatic infection, and lower incidence of disease in children, we expect few reports on the prevalence of post-acute symptoms in the literature. In a recent systematic review and meta-analysis of 37 articles and 2,874 pediatric patients, Qi et al. (2021) reported that the prevalence of asymptomatic infection in children was 27.7% (95% confidence interval [CI]: 19.7–36.4), and fever (48.5%; 95% CI: 41.4–55.6) and cough (40.6%; 95% CI: 33.9–47.5) were the most common symptoms.[11] In PHO's umbrella review of children with COVID-19, most children (80%–89%) experienced mild to moderate disease and approximately 10%–19% of children were asymptomatic; fever (50%–59%) and cough (40%–49%) were the most common clinical manifestations.[12] In Ontario, the cumulative rate of infection among children is approximately two times lower (1,223.8 per 100,000) than adults (2,330.0 per 100,000).[13] In addition, for Ontario, the proportion of asymptomatic cases was higher among children (27.2%) compared to adults 18–64 years (14.4%) and ≥65 years (22.9%). Further research and the emergence of variants of concern (VOCs) may change the context for post-acute COVID-19 in children.

Since MIS-C is not true sequelae, we will report on MIS-C separately from post-acute COVID-19. MIS-C is a newly recognized illness associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. McMurray et al. (2020) described MIS-C as a post-viral systemic inflammatory vasculopathy of children following SARS-CoV-2 infection, with similar clinical presentations to Kawasaki disease.[14,15] MIS-C generally occurs 2–6 weeks after exposure to SARS-CoV-2 and illness attributed to an enhanced immune response, rather than active viral replication and acute infection.[16,17] Anderson et al. (2020) (preprint) reported that patients with MIS-C had higher IgG titres against the Spike protein-receptor binding domain and full-length spike protein compared to children with severe COVID-19.[18]

In Ontario, MIS-C is reportable to public health as a complication of COVID-19. Case definitions for MIS-C vary (E.g., Canadian Pediatric Surveillance Program, United States [US] Centers for Disease Control and Prevention); for simplicity, we adapted the World Health Organization's MIS-C case definition:[19-21]

1. Children and adolescents 0–19 years of age with fever lasting more than 3 days

2. Elevated markers of inflammation (E.g., elevated erythrocyte sedimentation rate [ESR]), C-reactive protein [CRP], procalcitonin)

3. No other obvious microbial cause of inflammation (E.g., bacterial sepsis, staphylococcal or streptococcal shock syndromes)

4. Evidence of COVID-19 (E.g., reverse transcription polymerase chain reaction [RT-PCR], antigen test or serology positive), likely contact with a patient with COVID-19

5. **AND** two of the following:

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

    b) Hypotension or shock

    c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (E.g., echocardiogram findings, elevated troponin, N-terminal proB-type natriuretic peptide [NT-proBNP])

    d) Evidence of coagulopathy (E.g., prothrombin time [PT], partial thromboplastin time [PTT], elevated D-dimer)

    e) Acute gastrointestinal problems (E.g., diarrhoea, vomiting, abdominal pain)

In order to plan for a potential increased use of healthcare resources, it would be useful to characterize the syndromes as well as understand the symptoms of post-acute symptoms of children. Understanding risk factors that can contribute to post-acute COVID-19 or MIS-C can be used to monitor patients at risk of further morbidity. The purpose of this document is to examine what is known about the persistent and delayed symptoms of post-acute COVID-19 in children and MIS-C, along with the associated risk factors.

# Methods

In considering feasibility, scope and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding the persistent and delayed symptoms of post-acute COVID-19 and MIS-C. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted in order to be timely (E.g., quality assessment).[22]

We conducted literature searches in MEDLINE (March 1, 2021), National Institutes of Health COVID-19 Portfolio (Preprints) (March 5, 2021), Embase (March 2, 2021) and Global Health/Scopus (March 4, 2021) (search strategies available upon request). We searched PubMed and Google Scholar on March 30, 2021 for additional articles of interest. English-language peer-reviewed and non-peer-reviewed records that described persistent or delayed symptoms in post-acute COVID-19 in children or MIS-C were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate. We reviewed citations from included articles to identify additional research.

Prior to publishing, PHO subject-matter experts review all What We Know So Far documents. As the scientific evidence expands, the information provided in this document is only current as of the date of respective literature searches.

This document does not report on indirect impacts of pandemic public health measures on long-term sequelae; for example, the impact of social distancing on mental health or the consequences of deferred health care on chronic disease management (see PHO's *Negative Impacts of Community-based Public Health Measures on Children, Adolescents and Families During the COVID-19 Pandemic: Update*).[23] In addition, this review does not address the management of pediatric patients with long-term sequelae; the underlying mechanisms for the emergence of sequelae; or sequelae related to treatment (E.g., from post-PICU stay).

# Results

We screened 2,705 articles identified from database searches: MEDLINE (n=1,523 articles), Global Health and Scopus (n=663), Embase (n=398), and National Institutes of Health COVID-19 Portfolio (Preprints) (n=121). After screening and full-text review, we included 14 systematic reviews and meta-analyses and 18 primary research articles.

## Post-acute COVID-19 and Persistent or Delayed Symptoms

**Main findings:** Fatigue, neuropsychiatric symptoms (E.g., headache, insomnia, trouble concentrating) and cough were the most commonly reported persistent/delayed symptoms in children over 3 weeks since illness-onset.

Post-acute COVID-19 in children is poorly understood; however, we anticipate more research to develop. For this section, we included studies that reported on complications or pathological findings during the acute-phase of illness that may have contributed to the development of long-term sequelae. We did not review any studies that investigated the risk factors associated with post-acute COVID-19 (non-MIS-C patients). While disease severity and duration of hospitalization is associated with persistent symptoms in adults, it is unclear if similar findings are expected for children and it is not appropriate to extrapolate results from adults to the pediatric population (see PHO's *Persistent Symptoms and Post-acute COVID-19 in Adults – What We Know So Far*).[24]

Five primary research articles were included.[25-29]

- In a survey of 3,489 children with COVID-19 in the United Kingdom (UK), 9.8% (95% CI: 7.3–13.1; versus control: 2.0%; 95% CI: 1.8–2.9) of children 2–11 years old experienced persistent or delayed symptoms five weeks after initial symptom-onset (or from date of first positive test if asymptomatic); 13.0% (95% CI: 10.3–16.6; control: 1.7%; 95% CI: 1.0–2.8) for children 12–16 years.[25] The sample size for patients 2–11 years was 1,809 and for those 12–16 years was 1,680. This article does not specify symptoms by age group; however, commonly reported persistent symptoms were fatigue (11.8%; control: 0.8%), cough (10.9% vs. 0.5%) and headache (10.1% vs. 1.0%). The control group consisted of those who tested negative and were matched one-to-one to cases by sex, age and month of enrollment.

- In a case series of 1,695 pediatric patients with COVID-19 and MIS-C in the US, LaRovere et al. (2021) reported 22% of patients had new neurological impairment, especially in those with neurological comorbidities.[26] Approximately 5% of patients that survived had acquired a neurological deficit and 4% of all patients with neurological involvement required rehabilitation therapy after discharge. The median age of patients was 9.1 years (interquartile range [IQR]: 2.4–15.3).

- In a cross-sectional study of 129 children, Buonsenso et al. (2021) (preprint) followed-up with patients 162.5 ± 113.7 days after initial diagnosis.[29] Parents or caregivers of children completed a questionnaire and were then interviewed by two pediatricians. Persistent or delayed symptoms were not reported in 41.9% of patients, 35.7% of patients reported one or two symptoms, and 22.5% reported three or more symptoms. The most commonly reported persistent symptoms were fatigue (same or more as before infection; 86.8%), insomnia (18.6%), nasal congestion/runny nose (12.4%), trouble concentrating (10.1%), myalgias (10.1%), weight loss (7.7%), joint pain/swelling (6.9%), skin rash (6.9%), constipation (6.2%), chest tightness (6.2%) and persistent cough (5.4%). The mean age of patients was 11.0 ± 4.4 years. The most common comorbidities among patients included neurological conditions (10.1%), skin conditions (4.7%), asthma (3.9%), and allergic rhinitis (3.1%). In the post-acute phase, 2.3% developed MIS-C, 2.3% had new-onset asthma, and 1.6% had myocarditis (based on physician diagnoses).

- In a study of 50 hospitalized children with COVID-19 (mild disease, n=21; MIS-C, n=18; severe disease, n=11), Diorio et al. (2020) reported that 89% (17/19) showed evidence of thrombotic microangiopathy.[27] Complement-mediated thrombotic microangiopathy (TMA) was reported if patients met 5 out of 7 criteria (E.g., elevated lactate dehydrogenase [LDH], thrombocytopenia, anemia, elevated soluble C5b9, hypertension). The median age of patients with mild disease was 13 years (IQR: 5–17), 9 years (IQR: 7–13) for MIS-C, and 15 years (IQR: 14–17) for severe disease.

- In a study of 25 children in Italy that recovered from COVID-19, Denina et al. (2020) reported on findings from a follow-up examination performed (physician-diagnosed symptoms) an average of 35 days post-discharge (IQR: 19–46).[28] Twenty-one (84%) patients had mild to moderate disease in the acute phase, of which one patient had pre-existing cystic fibrosis and one had congenital heart disease. At follow-up, some patients showed elevated ferritin, ESR, D-dimer, creatinine and fibrinogen. Twenty percent of patients had interstitial patterns on lung ultrasound (B-lines), along with consolidation (8%). The mean age of patients was 7.8 years (IQR: 0.4–15).

## Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is relatively rare; for example, in New York City, the incidence of COVID-19 in those under 21 years old was 322 per 100,000 population and the incidence of MIS-C was 2 per 100,000.[16] In a cross-sectional analysis of 1,733 patients in the US, Belay et al. (2021) reported that the overall incidence of MIS-C was 2.1 per 100,000 and varied by state (range: 0.2–6.3).[30] In a meta-analysis of 71 articles and 11,671 pediatric patients, Wang et al. (2021) reported that 6.2% (95% CI: 2.8–10.7) of patients developed MIS-C.[31] The high prevalence was likely the result of the meta-analyses drawing primarily upon hospitalized patients for the estimate of MIS-C prevalence.

For summary demographic and clinical findings in patients with MIS-C, we reported on data from 12 systematic reviews and meta-analyses.[32-43] Please refer to Appendix A for additional details on systematic reviews and meta-analyses (E.g., patient age, sex, clinical findings). For additional context, we included 6 primary research articles and 2 systematic reviews and meta-analyses (we did not extract data from these two systematic reviews as they concentrated on laboratory biomarkers).[14,16,18,31,44-47]

## DEMOGRAPHICS

**Main findings:** The median or mean age of patients with MIS-C was between 7 and 9.5 years old, with the distribution of cases slightly skewed towards males. A higher proportion of patients were of Black and Latino ethnic backgrounds (50%–75%).

**Age and sex:** The median or mean age of patients ranged from 7.0–9.5 years and more than half of patients were male (51%–65%). The age of patients with MIS-C was higher, compared to children with Kawasaki disease or non-MIS-C hospitalized patients with COVID-19 (median age: <5 years).

**Race or ethnic background:** Most patients were Black (30%–40%), followed by Latino (20%–35%), white (20%–30%), mixed/unknown/other (10%–20%) and Asian (10%–20%). Authors did not explicitly address indigenous people in their study metrics.

**Comorbidities:** The two most commonly reported comorbidities were obesity (10%–50%) and asthma (5%–15%). Most patients (70%–75%) were previously healthy and reported no comorbidities. Other comorbidities included in studies, but representing less than 5% of all patients, included glucose-6-phosphate dehydrogenase deficiency, acute leukemia, chronic lung disease, cardiovascular disease, immunodeficiency and diabetes. Note that these comorbidities were not assessed as risk factors for developing post-acute COVID-19.

## DIAGNOSTICS, EPIDEMIOLOGY AND OUTCOMES

**Main findings:** Exposure to SARS-CoV-2 was identified through positive serology in 55%–85% of patients, compared to positive RT-PCR (30%–40%). Seventy to eighty percent of patients required admission to a PICU. Deaths among patients with MIS-C were rare and occurred in 1.4%–2.2% of patients.

**Laboratory diagnostics and epidemiological investigations:** Patients were diagnosed with SARS-CoV-2 infection either through serology (IgG) or RT-PCR. The mean IgG positivity reported in the systematic reviews ranged from 55%–85%. RT-PCR positivity ranged from 30%–40%. Prevalence of patients with history of contact with a case ranged from 30%–40%. Anderson et al. (2020) (preprint) reported that children with MIS-C have higher SARS-CoV-2 Spike protein IgG titres compared to those with acute severe disease, suggestive of a delay in onset of illness in patients with MIS-C.[18] The high percentage of patients with positive serology suggests that illness is due to "antibody-dependent enhancement of acquired immune response", rather than viral replication as seen in patients with acute infection.[32]

**Outcomes:** Invasive mechanical ventilation was needed for 20%–35% of patients and 70%–80% of patients were admitted to a PICU. The duration of hospitalization was approximately 3–12 days and PICU admission was 4–8 days.[16,33,36,45,48] Death in patients with MIS-C was rare in the studies reviewed, with death reported in 1.4%–2.2% of patients. For comparison, in a recent meta-analysis of 67 articles and 11,309 pediatric patients with COVID-19 (including cases with MIS-C), Wang et al. (2021) reported that the fatality rate was 0.3% (95% CI: 0.19–0.39).[31]

## CLINICAL MANIFESTATIONS

**Main findings:** Patients with MIS-C experienced persistent fever with gastrointestinal and cardiovascular symptoms, with conjunctivitis, rash, oral cavity changes and swelling in extremities. The most common clinical phenotype was hemodynamic shock/hypotension (50%–75%), followed by depressed LVEF (40%–70%), pleural effusion/infiltrates (30%–40%) and myocarditis (40%–60%).

**Organ system involvement:** The gastrointestinal system was the organ system most impacted in patients with MIS-C (60%–90%), followed by cardiovascular (40%–80%), neurological (20%–35%), respiratory (10%–50%) and renal (19%). Most systematic reviews and meta-analyses did not specifically report on mucocutaneous (conjunctivitis) and dermatological (E.g., rash) system involvement; however, authors reported these as individual signs and symptoms.

Systematic reviews and primary research articles varied in how they reported laboratory findings; thus, we could not present prevalence estimates and just report on markers with abnormal levels. Inflammatory and cytokine biomarkers were usually elevated in patients with MIS-C, especially CRP, D-dimer, ESR, ferritin, fibrinogen, interleukin-6 (IL-6), LDH and procalcitonin.[34] Elevated cardiac and coagulopathy biomarkers were platelets, B-type natriuretic peptide (BNP), NT-proBNP, PT, PTT and troponin. Additional abnormalities were decreased albumin, hemoglobin, lymphocytes and sodium; elevated biomarkers were alanine transaminase and neutrophils.

- In a meta-analysis of 787 patients, Zhao et al. (2021) reported that, compared to patients with severe COVID-19, patients with MIS-C had lower LDH and platelets, and higher ESR.[46]

- In a systematic review and meta-analysis of 16 articles, Rodriguez-Gonzalez et al. (2020) reported on the cardiac manifestations of MIS-C in 688 pediatric patients (mean age: 9 years).[40] The authors reported that 5.5% of patients had persistent cardiac symptoms, including mild myocardial dysfunction or coronary artery alterations.

- In a case series of patients with MIS-C (n=539) and severe COVID-19 (n=577) in the US, Feldstein et al. (2021) reported that within 48 hours of hospital admission, patients with MIS-C (compared to severe COVID-19 cases) had a higher risk for an elevated neutrophil to lymphocyte ratio >5 (adjusted risk ratio [aRR]: 1.59; 95% CI: 1.40–1.80), decreased platelets (aRR: 1.58; 95% CI: 1.43–1.75), and elevated CRP (aRR: 1.70; 95% CI: 1.52–1.92).[47]

**Individual signs and symptoms:** Since objective or subjective fever was in the case definition, almost all patients were febrile (90%–100%). The next most commonly reported symptom was tachycardia (75%–80%), followed by conjunctivitis (50%–65%), rash (40%–70%), changes to the oral cavity (40%–60%), abdominal pain (35%–70%), peripheral extremity changes (swelling) (30%–45%), vomiting (25%–70%), diarrhea (25%–60%), lymphadenopathy (25%–40%) and shortness of breath (25%–40%).

**Clinical phenotypes:** The most common clinical phenotype was hemodynamic shock/hypotension (50%–75%), followed by depressed LVEF (40%–70%), pleural effusion or infiltrates (30%–40%), myocarditis (40–60%), pericardial effusion (20%–50%), acute kidney injury (10%–40%) and coronary artery dilation/vessel abnormality/aneurysm (10%–25%).

- In a case series of patients with MIS-C (n=539) and severe COVID-19 (n=577) in the US, Feldstein et al. (2021) reported that 91.0% (95% CI: 86.0–94.7) of children with depressed LVEF (34.2% of patients) recovered within 30 days and 79.1% (95% CI: 67.1–89.1) of children with coronary artery aneurysm (13.4%) recovered within 30 days.[47] The median age of patients was 9.7 years. Compared to patients with severe COVID-19, patients with MIS-C had a higher risk of cardiorespiratory involvement (vs. respiratory without cardiovascular; aRR: 2.99; 95% CI: 2.55–3.50), cardiovascular without respiratory involvement (aRR: 2.49; 95% CI: 2.05–3.02), and mucocutaneous without respiratory or cardiovascular involvement (aRR: 2.29; 95% CI: 1.84–2.85).

- Aronoff et al. (2020) reported that although 11.9% of 505 patients had acute kidney injury, none required long-term dialysis.[38]

- Zou et al. (2021) recommended long-term follow-up of patients that had arterial dilation to monitor for aneurysms.[42]

### RISK FACTORS ASSOCIATED WITH MIS-C

**Main findings:** The risk of MIS-C was higher among Black children and those aged 6–12 years.

Given that the mechanisms underlying the pathophysiology of MIS-C are poorly understood, so are the factors that increase the risk of developing MIS-C. For this section, we examined five primary research articles.[47,49-52]

- In a retrospective surveillance study of 1,080 patients with MIS-C in the US, Abrams et al. (2021) reported that the risk of PICU admission was higher in 6–12 years olds (vs. <6 years; adjusted odds ratio [aOR]: 1.9; 95% CI: 1.4–2.6), 13–20 year olds (vs. <6 years; aOR: 2.6; 95% CI: 1.8–3.8) and Black patients (vs. white; aOR: 1.6; 95% CI: 1.0–2.4).[49] The median age of patients was 8 years (IQR: 4–12).

- In a case series of patients with MIS-C (n=539) and severe COVID-19 (n=577) in the US, Feldstein et al. (2021) reported on risk factors associated with developing MIS-C.[47] Compared to those with severe COVID-19, the risk of MIS-C was higher in those 6–12 years old (vs. those <6 years; aRR: 1.51; 95% CI: 1.33–1.72) and Black patients (vs. white; aRR: 1.43; 95% CI: 1.17–1.76). The median age of patients was 9.7 years.

- In a study of 233 patients in New York City, Lee et al. (2020) reported that compared to white children, there was a higher incidence of MIS-C among Black (incidence rate ratio [IRR]: 3.2; 95% CI: 2.0–4.9) and Hispanic (IRR: 1.7; 95% CI: 1.1–2.7) children.[50] There was no increased risk when comparing Asian (IRR: 0.9; 95% CI: 0.4–1.7) and white children. Black (IRR: 1.7; 95% CI: 1.3–2.2) and Latino (IRR: 2.1; 95% CI: 1.7–2.7) children had higher hospitalization rates when compared to white children.[50] The median age of patients was 7 years (IQR: 3–12).

- In a study of 95 patients with MIS-C and 314 patients with non-MIS-C COVID-19 in South America, Antúnez-Montes et al. (2021) reported that the risk of MIS-C was higher as age increased (undefined; $p<0.0001$) and higher in those of low socioeconomic status ($p<0.0001$).[51] The median age of patents was 3.0 years (IQR: 0.6–9.0).

- In a retrospective cohort study of 44 pediatric patients with MIS-C in New York, Cantor et al. (2020) reported that patients with acute hepatitis had higher rates of shock, respiratory support and longer hospitalization duration (all $p<0.05$), compared to non-acute hepatitis.[52]

## Limitations

We did not check systematic reviews for overlap among reviews in the studies that they included. Further, we did not check if our included primary studies were included in the systematic reviews. Thus, there is likely some duplication of findings.

One limitation is that symptoms at baseline or before COVID-19 are unknown, except where comorbidities were reported. Without pre-COVID-19 clinical assessments, it is difficult to attribute post-

acute symptoms solely to COVID-19. As highlighted in the Background, there was no consistent definition of persistent symptoms. In most studies, we could not determine the proportion of cases with persistent symptoms that had completely recovered; in contrast to those with ongoing symptoms from a lack of complete recovery from infection.

It remains unclear the extent to which some persistent neuropsychiatric symptoms in children are due to public health interventions (lockdowns, physical distancing) rather than infection itself; further case-control studies would help clarify the contribution of public health interventions and infection to persistent symptoms. Most studies used subjective assessments of symptoms, which may be limited by recall bias. A child's ability to articulate symptoms is often difficult and researchers often have to rely on parental surveys. In addition, PICU admission, invasive mechanical ventilation, corticosteroids, and other medical treatments may contribute to persistent symptoms in recovering patients, and these symptoms may not necessarily be due to the infection. In addition, the majority of patients studied were hospitalized and likely had more severe disease, leading to higher prevalence of persistent symptoms. The findings presented in this review may not be generalizable to all pediatric COVID-19 patients.

# Implications

Currently, there is little information on the long-term sequelae in survivors of MIS-C or on post-acute COVID-19 in children, representing a significant knowledge gap.[53] This evidence is needed to understand and characterize post-acute COVID-19 better in order to understand future healthcare resource requirements and to target higher risk groups for complications. Care for post-acute COVID-19 patients may place added stresses on healthcare and social support systems (parents and guardians unable to work due to a child's post-acute COVID-19 or MIS-C), including increased emergency department visits, outpatient care, inpatient care and rehabilitation therapy involving multidisciplinary teams.[54-57]

Johnson et al. (2020) recognized that racialized communities are more impacted by COVID-19, case prevalence and economic hardship.[58] In post-acute COVID-19, the authors suggest that more resources should be provided to ethnic and racialized communities, given these communities experience more adverse outcomes from post-intensive care syndrome (persistent neuropsychiatric and cognitive symptoms). Rubens et al. (2021) noted "racial and ethnic differences may reflect vulnerabilities to viral transmission related to occupational exposures, housing arrangements, or need to use public transportation. These factors, in addition to limitations in healthcare access and systemic inequities, contribute to the disparities highlighted by the COVID-19 pandemic."[15] A media article dated March 30, 2021, noted that about 50% of Toronto's population belongs to a racialized group, yet they represent 77% of all COVID-19 cases.[59] The authors reported that at The Hospital for Sick Children in Toronto, they have cared for approximately 130 patients with MIS-C, with only 20% of these patients being white. The over-representation of racialized groups in MIS-C patients in Toronto is in agreement with the findings from this review.

# Conclusions

Post-acute COVID-19 in children is generally characterized by neuropsychiatric symptoms such as fatigue, attention problems and insomnia; however, this is based on a few heterogeneous studies. Given the mild nature of disease in children, post-acute COVID-19 in children is likely less prevalent compared to adults. In contrast, the clinical aspects of MIS-C are better described, with most patients experiencing gastrointestinal, cardiovascular, mucocutaneous and dermatological symptoms. Risk of developing MIS-C is higher in racialized communities, especially in Black and Latino children aged 6 to 12 years.

Currently, there are a number of longitudinal studies underway to better characterise post-acute COVID-19, leading to better guidance on managing patients with persistent symptoms. For example, in a viewpoint article, del Rio et al. (2020) stated "Longer-ranging longitudinal observational studies and clinical trials will be critical to elucidate the durability and depth of health consequences attributable to COVID-19 and how these may compare with other serious illnesses."[9] In addition to longitudinal studies, research should focus on comparing symptoms present before and after infection in children, as well as distinguishing persistent symptoms, from chronic symptoms, from delayed symptoms. To better plan and prepare health and social services for recovering children, there is a need to study the factors contributing to increased risk of developing persistent symptoms, including how post-acute COVID-19 and MIS-C affects racialized communities.

On February 23, 2021, the National Institutes of Health announced a study of the causes of long-COVID, in which they hope to improve prevention and treatment of persistent symptoms.[60] On March 2, 2021, the National Institutes of Health in the US announced a new research effort called the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID).[61] Funk et al. (2021) have developed the Paediatric Emergency Research Networks (PERN) Study Protocol, which aims to study the long-term sequelae of 12,500 children with COVID-19, at 14 and 90 days after discharge.[62]

PHO will continue to monitor the scientific evidence on pediatric post-acute COVID-19 and MIS-C, updating this document as necessary.

## Appendix A. Demographics and clinical findings from included systematic reviews and meta-analyses

| Study variable[a] | Sood | Hoste | Yasuhara | Haghighi Aski | Radia | Rodriguez-Gonzalez | Ahmed | Baradaran | Aronoff | Abrams | Tang | Zou |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Studies included** | 17 | 68 | 27 | 21 | 35 | 16 | 39 | 16 | 16 | 8 | 24 | 7 |
| **Sample size, n** | 992 | 953 | 917 | 916 | 783 | 688 | 662 | 600 | 505 | 440 | 207 | 182 |
| **Age (years), mean or median** | 7.5 (6-9)[b] | 8.4 (5-12.6)[b] | 9.3 (8.4-10.1)[b] | na | 8.6 (7–10)[b] | 9 | 9.3±0.5[c] | na | 9 | 7.3-10[d] | 7.3-11[d] | 9.0 (8-10)[b] |
| **Male, %** | 62.6 (56.1-69.0) | 58.9 | 56.8 (52.1-61.5) | na | 55 | 56.8 (53.1-60.5) | 52.3 | 53.7 (49-59) | na | 59 | na | na |
| **Race, %** | Na | na | na | na | na | na | na | na | na | na | na | na |
| Black | Na | 37.0 | 31.5 (24.8-38.1) | na | na | na | 34.8 | 31 (25-38) | na | na | na | na |
| White | Na | 29.2 | 18.9 (14.3-23.6) | na | na | na | 27.6 | 23 (15-32) | na | na | na | na |
| Asian | Na | 8.7 | 18.7 (8.6-28.9) | na | na | na | 8.1 | 10 (4-26) | na | na | na | na |
| Latino | Na | 29.2 | 34.6 (28.3-40.9) | na | na | na | 19.3 | 34 (27-42) | na | na | na | na |
| Mixed, unknown, other | Na | 22.3 | 19.0 (10.0-28.0) | na | na | na | 10.2 | na | na | na | na | na |
| **Comorbidity, %** | Na | na | na | na | na | na | na | na | na | na | na | na |
| Obesity | Na | 25.3 | 18.0 (11.0-24.9) | na | 7.7 | Na | 50.8 | 28 (21-36) | na | na | na | na |
| Asthma | na | 4.1 | 14.4 (11.2-17.5) | na | na | Na | na | 13 (8-20) | na | na | na | na |
| **Outcomes** | na | na | na | na | na | Na | na | na | na | na | na | na |
| Hospital stay duration, days | na | 8 (7-12) | na | na | na | Na | 7.9±0.6 | na | na | na | na | 10.7 (8.9-12.5) |
| PICU stay duration, days | na | 4 (3.75-8) | na | na | na | Na | na | na | na | na | na | na |
| PICU admission, % | 67.8 (56.4-79.2) | 73.3 | 79.1 (71.6-86.7) | na | 68 | 75.6 (72.2-78.7) | 71.0 | 76 (68-82.7) | na | na | 72 (54-90) | 74 (52-91) |

| Study variable[a] | Sood | Hoste | Yasuhara | Haghighi Aski | Radia | Rodriguez-Gonzalez | Ahmed | Baradaran | Aronoff | Abrams | Tang | Zou |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Invasive mechanical ventilation, % | 30.1 (20.6-39.7) | na | 33.0 (24.5-41.5) | na | 18 | 22.0 (19.0-25.3) | na | na | 26.1 | na | na | na |
| Death, % | 2.2 | 1.9 | 1.9 (1.0-2.8) | na | 1.5 | 1.8 (1.0-3.1) | 1.7 | na | 1.4 | na | 2 | na |
| **SARS-CoV-2 Diagnostics, %** | na | na | na | na | na | Na | na | na | na | na | na | na |
| RT-PCR positive | 30.3 (24.4-36.3) | 37.5 | na | 37.7 (32.2-43.7) | na | Na | na | 36.8 (30.7-43.4) | 39.2 | na | 36 (26-46) | na |
| Serology positive | 57.3 (42.4-72.3) | 63.6 | na | na | na | Na | na | 77.3 (62.7-87.3) | 60.2 | na | 86 (78-95) | na |
| Close contact with a case | 41.8 (24.6-58.9) | 28.1 | na | na | na | Na | na | 38 (17.2-64.7) | 32.9 | na | na | na |
| **Organ system involvement, %** | na | na | na | na | na | Na | na | na | na | na | na | na |
| Gastrointestinal | 59.3 (48.0-70.6) | 85.6 | 87.3 (82.9-91.6) | | 71 | Na | na | 80 (71-87) | 79.1 | na | 84 (77-90) | 90 (71-100) |
| Cardiovascular | 53.3 (42.8-63.9) | 79.3 | 55.3 (42.4-68.2) | 38.0 (34.6-41.5) | 82 | Na | na | na | na | na | na | na |
| Respiratory | 46.3 (34.7-57.9) | 50.3 | 40.7 (23.1-58.4) | na | 9.6 | Na | na | 38.8 (28-50) | 42.9 | na | 25 (14-36) | 9 (0-29) |
| Renal | 18.7 (15.9-21.4) | na | na | na | na | Na | na | na | na | na | na | na |
| Neurological | 19.1 (10.2-28.1) | na | 36.0 (22.8-49.2) | na | na | Na | na | 33 (25-42) | na | na | 34 (26-42) | na |
| **Symptoms, %** | na | na | na | na | na | Na | na | na | na | na | na | na |
| Fever | 91.4 (83.9-98.9) | 99.4 | 99.3 (98.8-99.9) | na | 100 | Na | 100 | 97.3 (95-99) | na | na | 100 | na |
| Rash | 68.3 (60.0-76.6) | 54.9 | 59.0 (52.8-65.2) | na | 42 | Na | na | 59.9 (53-66) | 60.2 | na | 65 (57-74) | na |

| Study variable[a] | Sood | Hoste | Yasuhara | Haghighi Aski | Radia | Rodriguez-Gonzalez | Ahmed | Baradaran | Aronoff | Abrams | Tang | Zou |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Conjunctivitis | 54.9 (43.2-66.7) | 49.8 | 57.0 (47.3-66.6) | na | na | Na | 51.8 | 54 (46-62) | 52.2 | na | 64 (47-82) | na |
| Abdominal pain | na | 58.4 | 70.1 (58.4-81.7) | na | 34 | Na | na | na | na | na | na | na |
| Diarrhea | na | 50.4 | 57.0 (49.3-64.7) | na | 27 | Na | na | na | na | na | na | na |
| Vomiting | na | 57.5 | 60.0 (52.6-67.4) | na | 25 | Na | 68.3 | na | na | na | na | na |
| Tachycardia | na | 76.7 | na | na | 82 | Na | na | na | 100 | na | na | na |
| Dyspnea | na | 26.7 | 37.6 (22.2-53.0) | na | na | Na | na | na | na | na | na | na |
| Cough | na | na | 35.2 (22.2-48.1) | na | 4.5 | Na | na | na | 41.7 | na | na | na |
| Sore throat | na | na | 18.5 (10.6-26.3) | na | 4 | Na | na | na | 14.3 | na | na | na |
| Peripheral extremity changes | na | na | 32.9 (20.6-45.1) | na | na | Na | na | na | 29.6 | na | 44 (16-72) | na |
| Mouth changes | na | na | 42.3 (31.7-53.0) | na | na | Na | na | na | 43.5 | na | 59 (43-76) | na |
| Lymphadenopathy | na | na | 25.2 (15.0-35.3) | na | na | Na | na | 23.6 (12.5-40) | 30.3 | na | 37 (21-54) | na |
| Muscle pain | na | na | 14.2 (8.3-20.0) | na | na | Na | na | 23 (14-35.6) | na | na | na | na |
| **Clinical phenotypes, %** | na | na | na | na | na | Na | na | na | na | na | na | na |
| Pericardial effusion | 18.7 (9.1-28.4) | 22.3 | 31.7 (23.5-40.0) | na | na | Na | na | 49.1 (39.5-58.9) | na | na | 34 (17-52) | na |
| Pleural effusion, infiltrates | 30.1 (5.5-54.6) | 35.5 | 38.3 (29.7-46.9) | na | na | Na | na | na | na | na | na | na |
| Coronary artery dilation, vessel abnormalities | 23.1 (12.2-34.1) | 11.6 | na | 20.0 (17.2-23.1) | na | 15.0 (12.4-17.8) | na | 19.9 (12.6-30) | na | na | 23 (8-39) | 17 (9-28) |

| Study variable[a] | Sood | Hoste | Yasuhara | Haghighi Aski | Radia | Rodriguez-Gonzalez | Ahmed | Baradaran | Aronoff | Abrams | Tang | Zou |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hemodynamic shock, hypotension | 49.0 (45.3-52.6) | 59.9 | 65.8 (51.1-80.4) | na | 61 | 53.2 (48.7-57.8) | na | 55 (29-78) | 72.7 | na | 60 (47-73) | 74 (57-88) |
| Aneurysms | 17.8 | 10.3 | 21.4 (12.8-30.1) | na | na | Na | na | na | na | na | 10 (4-16) | na |
| Myocarditis | 39.3 (28.1-50.5) | 41.4 | 55.3 (42.4-68.2) | na | na | Na | na | 56.9 (40.3-72.2) | na | na | 61 (29-93) | na |
| Acute kidney injury | na | na | na | na | na | Na | na | 31 (12-59) | 11.9 | na | 42 (22-62) | 13 (0-37) |
| Left ventricular ejection fraction (mild-moderate) | 41 | 40.4 | 53.8 (37.0-70.5) | 38.0 (34.6-41.5) | na | Na | na | 65.3 (56.9-72.9) | 51.0 | na | 54 (39-69) | 70 (44-91) |

Abbreviations: na, not applicable; PICU, pediatric intensive care unit

[a]Unless otherwise noted, value ranges in brackets represent 95% confidence intervals

[b]Median with interquartile range

[c]Mean plus/minus standard deviation

[d]Median range among studies

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# Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Pediatric post-acute COVID-19 and multisystem inflammatory syndrome in children (MIS-C) – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2021.

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