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SYNTHESIS

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

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Introduction

Public Health Ontario (PHO) is actively monitoring and assessing relevant information related to Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). "What We Know So Far" documents provide a rapid review of the evidence on a specific aspect related to COVID-19. This document replaces *Pediatric Post-acute COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) – What We Know So Far* (April 5, 2021).[1] This rapid review concentrates on results from systematic reviews and meta-analyses where applicable, updating the evidence concerning post-acute COVID-19 syndrome (PACS) and MIS-C in children.

Key Findings

- This rapid review considered PACS as persistent symptoms or new sequelae present three or more weeks after SARS-CoV-2 infection, irrespective of disease severity (i.e., severe, mildly symptomatic or asymptomatic).
    - From eight controlled studies, the prevalence of PACS or specific PACS symptoms or sequelae was below 10%. Sequelae consistent with PACS that were more frequently reported in children with previous SARS-CoV-2 infection, compared to controls not infected with SARS-CoV-2, included smell dysfunction, shortness of breath and fatigue. Currently, it is unclear if and how PACS impacts quality of life measures in children.
    - Overall, there is inconclusive evidence demonstrating a causal link between SARS-CoV-2 infection and PACS in children and findings may change as more high quality research is conducted. In addition, studies found relatively high levels of non-specific symptoms in non-SARS-CoV-2-infected children, such as headache, cognitive difficulties, mental health conditions and sleep impairment.

- MIS-C is a rare systemic inflammatory vasculopathy of children that can occur following SARS-CoV-2 infection. The onset of MIS-C generally occurs 2–6 weeks after confirmed or suspected SARS-CoV-2 infection.
    - Symptoms of MIS-C from 17 systematic reviews included: abdominal pain; vomiting; rash (any type); hemodynamic shock or hypotension; conjunctivitis; diarrhea; other cardiac abnormalities (e.g., pericardial effusion, myocarditis); diarrhea; oral cavity changes (e.g., dry/cracked lips, strawberry tongue); and swelling in extremities.
- Prevention strategies that reduce the risk of SARS-CoV-2 transmission can be layered to mitigate the risks of children developing PACS or MIS-C. This layered approach includes ventilation, universal indoor masking in public settings, vaccination, masking directives in high-risk settings, and communication on the importance of wearing masks with good fit and filtration for personal and population-level protection. Those at highest risk of severe disease (e.g., those with immune compromise and those from racialized and low income populations), ineligible for vaccination (i.e., children less than 5 years) and those impacted by disruptions in educational settings (e.g., individuals who cannot attend due to being infected or symptomatic), can benefit from population-level interventions.

Background

There is ongoing research into what constitutes PACS and how to define the condition. There are also a number of names used to refer to persistent symptoms after the acute phase of a SARS-CoV-2 infection, including “long COVID,” “post-COVID syndrome,” “post-COVID-19 condition”, and “post-acute sequelae of SARS-CoV-2 infection”;[2] however, we will use PACS throughout this document. Nalbandian et al. (2021) described PACS as persistent symptoms and/or delayed symptoms of SARS-CoV-2 infection beyond 4 weeks from symptom-onset.[3] PACS has been defined elsewhere as signs and symptoms that develop during or after SARS-CoV-2 infection, continue for more than 12 weeks, and are not explained by an alternative diagnosis.[4-6] Stephenson et al. (2022) used the Delphi process to develop a research definition as follows: “Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time.”[7] The Ontario COVID-19 Science Advisory Table (2021) reported that while a consistent case definition has not been established, PACS encompasses many potential sequelae of infection with SARS-CoV-2 which may persist for weeks to months, and can develop after severe, mildly symptomatic or asymptomatic SARS-CoV-2 infections.[8] To ensure a broad assessment of PACS, we will consider PACS as persistent symptoms or sequelae present 3 weeks or more after SARS-CoV-2 infection.

MIS-C is a recognized illness associated SARS-CoV-2 infection. MIS-C has been described as a post-viral systemic inflammatory vasculopathy of children following SARS-CoV-2 infection, with similar clinical presentations to Kawasaki disease.[9,10] MIS-C generally occurs 2–6 weeks after confirmed or suspected SARS-CoV-2 infection and illness is attributed to an enhanced immune response, rather than active viral replication and acute infection.[11,12]

In order to plan for a potential increase in burden of disease related to PACS and MIS-C, and an associated increase in use of healthcare resources post-COVID-19, we need a better understanding of these conditions. Knowledge of the risk factors associated with the development of PACS and MIS-C may be able to assist with directing resources appropriately.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding PACS and MIS-C. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted (e.g., duplicate screening, quality assessment) in order to be timely.[13]

PHO Library Services conducted updated literature searches in MEDLINE (February 11, 2022), National Institutes of Health COVID-19 Portfolio (Preprints) (February 11, 2022), Embase (February 15, 2022) and Global Health/Scopus (February 15, 2022). The search was informed by the previous search strategy, with the addition of updated SARS-CoV-2 variant of concern (VOC) terms and COVID-19 vaccination terms to ensure up-to-date concepts were captured (search strategies available upon request). We searched PubMed on April 16, 2022 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed studies that described PACS or MIS-C were included. Studies did not have to specify if cases of SARS-CoV-2 were test-confirmed to be included, and did not need to specify if cases were symptomatic, asymptomatic, hospitalized or not hospitalized. We restricted the search to articles published after the previous search (March 1, 2021). This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate.

Where prevalence data were reported for multiple end-points after SARS-CoV-2 infection, we reported prevalence for the latest follow-up period. Pooled prevalence estimates for PACS, PACS sequelae, MIS-C or MIS-C signs and symptoms were extracted from systematic reviews and primary literature. We excluded systematic reviews that conducted their literature searches before 2021. Due to the substantial increase in available literature since the last version of this synthesis, and to limit the volume of primary studies included, we only included primary studies with at least 500 participants. Studies were restricted to those with patients less than or equal to 21 years of age. We did not scope out signs (e.g., diagnostic tests and biomarkers) in this review; however, we focused on describing symptoms of PACS and MIS-C.

This document does not report on the indirect impacts of pandemic public health measures on long-term sequelae; e.g., impact of social distancing on mental health or the consequences of deferred health care on chronic disease management. In addition, this synthesis does not address the management of patients with long-term sequelae, the underlying mechanisms for the emergence of sequelae, or sequelae related to treatment of SARS-CoV-2 infection (e.g., post-intensive care unit [ICU] admission, invasive mechanical ventilation, therapeutics). Finally, the impact of vaccination on PACS is not in scope for this synthesis; however, is addressed in PHO's *Impact of Vaccination on Post-Acute COVID-19 Syndrome (PACS) – What We Know So Far*.[14] For information on the adult population, please see PHO's *Post-Acute COVID-19 Syndrome (PACS) in Adults*.[15]

Prior to posting, PHO subject-matter experts review all knowledge products. As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of the respective literature searches.

Screening Results

We screened 7,263 articles identified from updated database searches: MEDLINE (n=2,893 articles), Embase and Global Health (n=3,223), Scopus (n=756), and National Institutes of Health COVID-19 Portfolio (Preprints) (n=391). After screening, full-text review, and re-assessment of the previously included evidence with updated inclusion criteria, we included 22 systematic reviews and meta-analyses (PACS: n=4; MIS-C: n=18), and 24 primary research articles (PACS: n=12; MIS-C: n=12).

For PACS studies, settings during the acute phase of COVID-19 illness usually included a mix of inpatient and outpatient settings (13/16), followed by outpatient only (2/16) and inpatient only (1/16). All MIS-C studies were conducted in inpatient settings. Due to scarce studies with large sample sizes for MIS-C risk factors, studies in this sub-section were exempt from the eligibility criteria for 500 or more participants. Two of the 22 included reviews were non-peer reviewed preprints.[16,17] Six of the 24 primary studies were non-peer-reviewed preprints.[18-23] Primary studies were conducted primarily the United States (US) (13/24) and Europe (10/24), one study included multiple countries.

Please refer to Appendix A (Table 1) and Appendix B (Table 5) for additional characteristics of included studies.

It is important to note the considerable heterogeneity across included studies. Studies used different follow-up periods and different time points to determine follow-up periods; e.g., time from hospital discharge, time from positive SARS-CoV-2 test, and time from symptom-onset in acute stage of disease. Reported symptoms, outcome measures/criteria, populations (e.g., severity of illness during acute SARS-CoV-2 infection) also varied widely across studies.

PACS in the Pediatric Population

Patient Characteristics and Prevalence of PACS

We included four systematic reviews and 12 primary research articles related to PACS in children. The pooled mean/median age of patients with PACS ranged from 10.2–17.7 years and the pooled mean/median proportion of female patients ranged from 46.9%–63.5%. Race or ethnicity of patients was not reported in any of the included systematic reviews, but in three of the 12 primary studies over 60% of patients were reported as white.[19,20,24] Two of the total 16 studies did not include a control group (non-SARS-CoV-2 infected).[25,26] Throughout this report, we use “case” to refer to patients with previous SARS-CoV-2 infection, and “control” to refer to patients without previous SARS-CoV-2 infection.

As noted above, the definition, diagnostic criteria and official name for this condition are not yet established. A meta-analysis was not appropriate due to the heterogeneity among studies. We report the prevalence difference range, which is the mean prevalence of an outcome (e.g., comorbidity, sequelae) among children with previous SARS-CoV-2 infection minus the study-matched mean prevalence of an outcome from children without previous SARS-CoV-2 infection. In addition, we provide the interquartile range (IQR) of the prevalence differences for any given outcome along with the number of studies used for estimates.

In eight controlled studies, the prevalence difference range of any comorbidity or pre-existing condition in patients with PACS was 0.0% to 5.8% (IQR: 0.6%–3.5%). Pre-existing neurological/mental health conditions were lower in children with PACS compared to controls (prevalence difference range: -2.6% to -0.4%, IQR: -2.1% to -1.0%, 3 studies); pre-existing asthma was slightly more prevalent in children with PACS compared to controls (prevalence difference range: 0.1%–2.1%, IQR: 0.1%–1.1%, 3 studies) (Appendix A, Table 2).

From the included studies, the association of previous COVID-19 infection in children and symptoms consistent with PACS was unclear, with several studies showing higher (or similar) prevalence of symptoms in controls. The prevalence difference range of having at least one PACS sequelae or symptoms was -2.4% to 13.2% (IQR: -0.6% to 8.0%, 8 studies).

In three controlled studies and one uncontrolled study with multiple follow-up periods, the prevalence of PACS decreased over time.[20,26-28] Behmood et al. (2022) reported in a meta-regression that as the number of months since diagnosis increased, the prevalence of headache, cognitive difficulties and abdominal pain decreased, but the prevalence of fatigue, myalgia, loss of smell and shortness of breath increased.[27] In a study of 6,630 patients and 21,640 controls in Denmark, Berg et al. (2022) reported that all sequelae decreased from 2 months through 12 months post-diagnosis; e.g., fatigue at 2 months was 11.1%, compared to 3.3% at 12 months.[28] In a study of 518 patients in Russia, Osmanov et al. (2022) reported that the prevalence of persistent symptoms decreased over time; e.g., prevalence of fatigue at discharge was 15.8%, compared to 8.8% at 6 months.[26]

Specific PACS Symptoms and Sequelae

Seven studies investigated specific symptoms and sequelae consistent with PACS in children with the use of non-SARS-CoV-2-infected controls.[16,18,22,24,27-29] The prevalence of specific PACS symptoms was relatively low, with some studies even showing similar or greater prevalence of symptoms in controls. For example, children with previous SARS-CoV-2 infection had approximately 4.8% to 12.1% greater prevalence of smell dysfunction compared to children without previous SARS-CoV-2 infection. In contrast, children with previous SARS-CoV-2 infection had approximately -5.9% to -0.6% lower prevalence of sleep impairment compared to children without previous SARS-CoV-2 infection. The prevalence difference range (and IQR) of PACS symptoms are reported below (see Appendix A, Table 3 and Table 4).

- **Smell dysfunction:** prevalence difference range: 0.2%–12.2%, IQR: 4.8%–12.1%, 5 studies
- **Shortness of breath:** prevalence difference range: 0.8%–13.0%, IQR: 1.0%–11.7%, 5 studies
- **Fatigue:** prevalence difference range: -2.4%–14.6%, IQR: 1.0%–8.9%, 6 studies
- **Joint pain:** prevalence difference range: 0.4%–1.9%, IQR: 1.1%–1.9%, 3 studies
- **Decreased appetite/weight loss:** prevalence difference range: 0.8%–2.3%, IQR: 0.9%–1.7%, 3 studies
- **Dizziness:** prevalence difference range: -1.5%–5.3%, IQR: 0.5%–4.9%, 5 studies
- **Nausea/vomiting/diarrhea:** prevalence difference range: -0.7%–1.8%, IQR: 0.5%–1.1%, 4 studies
- **Myalgia:** prevalence difference range: -0.1%–4.4%, IQR: 0.1%–3.6%, 4 studies

- **Chest pain:** prevalence difference range: -0.9%–3.5%, IQR: 0.1%–2.3%, 3 studies
- **Headache:** prevalence difference range: -3.1%–9.0%, IQR: -0.5%–6.4%, 6 studies
- **Cough:** prevalence difference range: -4.0%–1.7%, IQR: -0.6%–1.3%, 4 studies
- **Abdominal pain:** prevalence difference range: -3.8%–1.0%, IQR: -2.2%–0.8%, 4 studies
- **Cognitive difficulties:** prevalence difference range: -6.9%–3.2%, IQR: -2.4%–0.8%, 6 studies
- **Sleep impairment:** prevalence difference range: -10.9% to -0.3%, IQR: -5.9% to -0.6%, 3 studies

In a cross-sectional study of 24,315 adolescents (ages 15–18 years) in Denmark, Berg et al. (2022) reported that the following sequelae consistent with PACS had significantly higher odds ratios (OR, 95% confidence interval [CI]) in those with a positive SARS-CoV-2 test compared to age and sex-matched controls (test negative and untested): shortness of breath (2.7, 2.31–3.15), cough (1.6, 1.43–1.85), sore throat (1.6, 1.21–2.10), chest pain (1.4, 1.12–1.69), dizziness (1.4, 1.16–1.59), headache (1.2, 1.10–1.34), palpitations (1.2, 1.10–1.36) and loss of appetite (1.2, 1.02–1.29) (2 month follow-up period).[28] Children with SARS-CoV-2, compared to non-infected controls, had significantly lower odds of experiencing abdominal pain, rash, mood swings, dark circles under the eyes, cold hands or feet, chapped lips, discolored fingers and toes and extreme paleness. Given the higher prevalence of these symptoms in the control group, this highlights a situation where there is a high background level of signs and symptoms with other underlying causes.

Impact of PACS on Quality of Life (QoL) in Children

The impacts of PACS on QoL were investigated in five studies, which had inconsistent findings, with two studies reporting that children with PACS had better QoL scores than controls.[19,22,25,28,29] Borch et al. (2022) reported that those in the case group had a higher sense of well-being compared to healthy controls (WHO-score difference: 4, 95% CI: 3.5–4.8).[29] Berg et al. (2022) reported that children with SARS-CoV-2 infection had higher Pediatric Quality of Life (PedsQL) scores than controls for physical functioning, emotional functioning, social functioning, and school functioning experienced over the past month.[28] In a study of 3,227 test-positive individuals in England and 3,869 test-negative individuals, Nugawela et al. (2022) (preprint) reported that in test-positive patients (at a minimum of 3 months post COVID-19) there was increased risk of loneliness, problems with mobility, problems with performing daily activities and experiencing increased pain.[19] Overall, there was insufficient and inconsistent evidence to conclude the impact of PACS on QoL measures in children; therefore, further research is needed.

Risk Factors Associated with PACS in Children

Few studies assessed risk factors for the development of PACS in children, with inconsistent results reported among the included studies. While more research is needed, potential risk factors were female sex and increasing age (statistically significant findings in 4/6 studies each), along with the presence of comorbidities or increased number of comorbidities (3/6 studies).

In a systematic review and meta-regression of 23,141 patients with COVID-19, Behnood et al. (2022) reported that the presence of several persistent symptoms (e.g., fatigue, shortness of breath) was associated with female sex and increasing age.[27] In a study of 5,053 adolescents with a positive test in Massachusetts, US, Castro et al. (2022) (preprint) reported a lower risk (OR, 95%) of neurological sequelae 90–150 days after testing in males (0.7, 0.54–0.84) and a higher risk in those with more

comorbidities (Charleston comorbidity index 2+ compared to 0: 6.3, 2.53–14.3), Hispanic ethnicity (1.3, 1.00–1.73) and those with public insurance (1.4, 1.07–1.76).[20] In Russia, Osmanov et al. (2022) reported an increased risk with pre-existing allergic conditions (1.7, 1.03-2.63); when restricting to those >6 years, risk of PACS was higher in those that had severe acute COVID-19 (6.1, 1.37–43.9) compared to mild infection.[26] Osmanov et al. defined severe disease as having received non-invasive ventilation, invasive ventilation or admission to the paediatric intensive care unit (PICU) during hospital admission.

Two studies found that risk factors for persistent symptoms consistent with PACS were similar amongst SARS-CoV-2 cases and non-SARS-CoV-2-infected controls. In a national, cross-sectional study of 6,630 patients and 21,640 controls, Berg et al. (2022) reported that the risk of sequelae consistent with PACS after 2 months was higher in females in both the case group (OR: 2.7, 95% CI: 2.40–3.03) and the control group (OR: 2.6, 95% CI: 2.42–2.70).[28] In a national matched cohort study in England of 3,065 patients (tested positive) and 3,739 controls (tested negative), assessed 3-months after testing, Stephenson et al (2022) reported that factors associated with an increased risk of a child developing sequelae consistent with PACS were similar for cases and controls including; female sex, increasing age and presence of any comorbidities.[24]

Multisystem Inflammatory Syndrome in Children (MIS-C)

Case definitions for MIS-C vary (E.g., Canadian Pediatric Surveillance Program,[30] United States [US] Centers for Disease Control and Prevention);[31] for simplicity, we adapted the World Health Organization's MIS-C case definition:[32]

- Children and adolescents 0–19 years old with fever lasting more than 3 days
- Elevated markers of inflammation
- No other obvious microbial cause of inflammation
- Evidence of SARS-CoV-2 infection or contact with a patient with COVID-19
- AND two of the following: 1) rash, conjunctivitis or mucocutaneous inflammation signs; 2) hypotension or shock; 3) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities; 4) evidence of coagulopathy; 5) acute gastrointestinal problems

This section will not include assessments of PACS in those recovering from MIS-C; however, research is beginning to look at this question. In most studies, the prevalence of clinical and self-reported PACS sequelae is low.[33-37] For example, in a study of 89 patients recovering from MIS-C in Sweden, Kahn et al. (2021) reported that upon examination 2 months after diagnosis, children had few abnormal clinical findings and the most commonly self-reported symptom was fatigue (14%).[36]

We included 18 systematic reviews and 12 primary studies related to MIS-C. Unlike the studies related to PACS, the studies related to MIS-C did not include control groups of children who were not infected with SARS-CoV-2. A meta-analysis was not appropriate due to the heterogeneity among studies. Thus, to summarize the pooled mean/median prevalence estimates extracted from heterogeneous studies, we first reported the range of all identified pooled mean/median prevalence results (e.g., 5%–75%). Then, for each outcome we identified the interquartile range (IQR) of all prevalence estimates. We used this descriptive approach to demonstrate the wide range of results in the available literature related to this topic, along with a central range (i.e., IQR) to describe a more focused range of available results.

Patient Characteristics and Incidence of MIS-C

In 13 systematic reviews, the pooled mean/median age of patients with MIS-C ranged from 7.5 to 9.3 years. In 14 systematic reviews, the pooled mean/median prevalence of male patients with MIS-C ranged from 52.3%–62.6% (see Appendix B, Table 5).

In nine systematic reviews, the pooled mean/median prevalence of MIS-C by ethnic or racial background was (see Appendix B, Table 6):

- **Black:** range: 31%–37%, IQR: 31.5%–34.8%, 9 studies
- **Hispanic:** range: 19%–35%, IQR: 25.7%–34.3%, 7 studies
- **White:** range: 14%–29%, IQR: 18.9%–27.0%, 9 studies
- **Other/mixed/unknown:** range: 14%–25%, IQR: 9.0%–22.3%, 6 studies
- **Asian:** range: 5%–19%, IQR: 8.1%–13.8%, 9 studies

At least 20% of patients with MIS-C had at least one co-morbidity (range: 20%–48%, IQR: 25.0%–32.0%, 8 studies). In 12 systematic reviews, the pooled mean/median prevalence of the most commonly reported co-morbidities were (see Appendix B, Table 5):

- **Obesity/overweight:** range: 8%–57%, IQR: 18.0%–30.8%, 9 studies
- **Chronic lung conditions:** range: 4%–27%, IQR: 13.2%–20.2%, 7 studies

MIS-C is a relatively rare condition, with incidence typically below 5 cases per 100,000 population.[38-43] 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 (Dufort et al. 2021).[40] 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).[38]

Clinical Manifestations

Greater than 50% of patients with MIS-C experienced symptoms involving the gastrointestinal and cardiovascular systems. In 14 systematic reviews, the pooled mean/median prevalence of MIS-C according to organ system involvement was (see Appendix B, Table 7):

- **Gastrointestinal:** range: 59%–89%, IQR: 75.3%–85.7%, 11 studies
- **Cardiovascular:** range: 38%–82%, IQR: 52.2%–72.7%, 7 studies
- **Respiratory:** range: 10%–50%, IQR: 38.8%–43.0%, 8 studies
- **Neurological:** range: 19%–41%, IQR: 22.9%–36.0%, 10 studies

The most commonly reported signs and symptoms in MIS-C patients through disease course were abdominal pain, vomiting, rash (any type), conjunctivitis, diarrhea, oral cavity changes (e.g., dry and cracked lips, mucosal rash, strawberry tongue) and swelling in extremities. Additional symptoms reported in less than 20% of patients included shortness of breath, cough, headache, lymphadenopathy, myalgia and sore throat. In 15 systematic reviews, the pooled mean/median prevalence of the most commonly reported signs and symptoms were (see Appendix B, Table 8):

- **Abdominal pain:** range: 36%–81%; IQR: 58.4%–70.1%, 5 studies
- **Vomiting:** range: 25%–76%, IQR: 57.4%–67.2%, 7 studies
- **Rash:** range: 19%–68%, IQR: 56.2%–59.9%, 13 studies
- **Conjunctivitis:** range: 40%–63%, IQR: 50.3%–54.7%, 10 studies
- **Diarrhea:** range: 27%–58%, IQR: 41.0%–56.1%, 6 studies
- **Oral cavity changes:** range: 5%–44%, IQR: 23.0%–42.3%, 5 studies
- **Swelling in extremities:** range: 13%–59%, IQR: 22.7%–36.0%, 7 studies

Since fever is typically an inclusion criterion for MIS-C diagnosis, almost all patients had objective fever. As expected, clinical phenotypes affecting the cardiovascular system were common in patients with MIS-C. In 17 systematic reviews, the pooled mean/median prevalence of the most commonly reported clinical findings were (see Appendix B, Table 9):

- **Fever:** range: 91%–100%, IQR: 97.1%–100%, 12 studies
- **Hemodynamic shock or hypotension:** range: 21%–66%, IQR: 50.6%–61.0%, 13 studies
- **Decreased left ventricular ejection fraction:** range: 32%–65%, IQR: 40.7%–56.4%, 11 studies
- **Myocarditis:** range: 16%–65%, IQR: 39.3%–59.0%, 9 studies
- **Pericardial effusion:** range: 14%–49%, IQR: 20.5%–33.4%, 7 studies

While the prevalence of intensive care unit (ICU) admissions and those requiring invasive mechanical ventilation were relatively high in patients with MIS-C, deaths from MIS-C were rare. In 15 systematic reviews, the pooled mean/median prevalence of disease severity measures were (see Appendix B, Table 10):

- **ICU admission:** range: 67%–79%, IQR: 70.3%–76.0%, 12 studies
- **Invasive mechanical ventilation:** range: 18%–50%, IQR: 24.3%–32.3%, 12 studies
- **Death:** range: 1.0%–2.8%, IQR: 1.6%–2.0%, 13 studies

For clinical parameters, the four primary studies (>1,000 patients) we included were largely in agreement with the findings from the systematic reviews; however, there were some notable exceptions. The pooled mean/median prevalence range of oral cavity changes was lower in primary studies (23%–29% in 2/2 studies that included this parameter), compared to 40%–49% in 3/5 systematic reviews. The prevalence of myocarditis was lower in primary studies (15%–18% in 4/4 studies), compared to 50%–69% in 5/9

systematic reviews. In addition, prevalence of disease severity measures were lower in primary studies: ICU admission (58%–60% in 3/3 primary studies versus 70%–79% in 9/12 systematic reviews) and invasive mechanical ventilation (9.3%–9.4% in 2/2 primary studies versus 18%–50% in 12/12 systematic reviews).

Risk Factors Associated with Developing MIS-C

In part due to the low incidence of MIS-C, the majority of studies on risk factors associated with MIS-C have relatively small sample sizes (i.e., 2/10 studies with >1,000 patients) and concentrated on age, sex and ethnic background as potential risk factors. Having a comorbidity did not increase the risk of developing MIS-C; however, comorbidities increase the severity of MIS-C (i.e., ICU admission, death).[44,45] While outside the scope of this rapid review, studies have shown that the risk of developing MIS-C has decreased over the course of the pandemic defined by dominant VOC (higher to lower relative risk: Alpha > Delta > Omicron).[46,47]

In one systematic review and nine primary studies, the primary risk factor associated with developing MIS-C was Black race (9 out of 10 studies with significant findings) (see Appendix B, Table 11). In a study of 1,382 children with MIS-C and 1,090,302 children with COVID-19, Stierman et al. (2021) examined observed (O) and expected (E) numbers of patients with MIS-C by race.[48] The numbers of Black (O/E: 2.1, 95% CI 1.84–2.37) children were higher than expected, compared to lower than expected numbers for white children (O/E: 0.7; 95% CI: 0.65-0.72). 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.[49] Compared to those with severe COVID-19, the risk of MIS-C was higher in those 6–12 years old (versus those <6 years; adjusted risk ratio [aRR]: 1.5; 95% CI: 1.33–1.72) and Black patients (versus white; aRR: 1.4; 95% CI: 1.17–1.76). In a study of 223 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 Hispanic (IRR: 2.1; 95% CI: 1.7–2.7) children had higher hospitalization rates when compared to white children.

Limitations

The expected limitations associated with systematic reviews apply to our rapid review as well. First, we did not include non-English studies and we possibly missed additional articles of interest in other languages. Second, we did not check systematic reviews for overlap of included primary studies; therefore, primary studies may have appeared in more than one review. Thirdly, the high levels of heterogeneity in systematic reviews and meta-analyses made it difficult to compare findings between studies, and likely the result of primary studies being mostly observational in nature with variable follow-up periods.

There was no consistent definition of "PACS", and we accepted authors' definitions of post-acute symptoms and sequelae. In most studies, it was not possible to determine the proportion of cases that had PACS symptoms or sequelae (but who had completely recovered), in contrast to those with ongoing symptoms from a lack of complete recovery from infection. Few studies examined PACS symptoms over multiple follow-up periods, making it difficult to understand how long specific PACS symptoms last; however, sequelae tended to decrease in prevalence as time from diagnosis increased. Studies used different follow-up periods and used different time points for determining follow-up periods; e.g., time from hospital discharge, time from negative test, and time from symptom-onset in acute stage of disease. In addition, as the follow-up period increased, the sample size of patients decreased; therefore, we likely over-represent relatively short-term sequelae. Among systematic reviews and meta-analyses, along with primary studies, there was no standardization of symptom definitions and diagnostic criteria (e.g., validated self-reported questionnaires versus clinical assessments). Included studies were likely biased towards studies where patients were tested by RT-PCR for SARS-CoV-2 infection. A bias towards positive test subjects means underrepresentation of those without access to testing, those with asymptomatic infection or mild infection, and those with barriers to care. Most studies used subjective assessments of symptoms, which may be affected by recall bias.

It remains unclear the extent to which some persistent neuropsychiatric symptoms in children are due to public health measures (e.g. 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.[51] In studies where subjects were recruited online for symptom reporting potentially led to selection bias, where the symptoms reported for children are non-specific and occur in children at a relatively high prevalence in the non-COVID-19 population. 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 a systematic review of PACS in children (21 studies and 81,896 patients), Hirt et al. (2022) (preprint) called into question the validity of included studies with respect to the reported PACS outcomes.[17] The concerns with included studies were due primarily to a critical risk of confounding bias in studies (21/21 studies) and serious/critical risk of selection bias (19/21 studies). The authors noted that only two studies demonstrated a potential causal relationship between SARS-CoV-2 infection in children and development of PACS; i.e., Blomberg et al. (2022) (patients 16–30 years; not included in our review)[52] and Roessler et al. (2021) (preprint).[18]

The findings presented in this review may not be generalizable to all pediatric patients with COVID-19.

Conclusions and Public Health Implications

PACS in children is generally characterized by smell dysfunction, fatigue and shortness of breath. The prevalence of PACS in children (less than 10%) is lower compared to the estimates for the adult population,[15] which may reflect the relatively milder nature of disease in children. These findings are highly heterogeneous and subject to a high degree of bias; therefore, readers should use caution when interpreting these results. In contrast to PACS, 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 children.

Since the majority of PACS studies in children concentrated on white children, more research is needed with racialized communities. Johnson et al. (2020) recognized that racialized communities are more impacted by COVID-19, case prevalence and economic hardship.[53] While Black race was identified as a risk factor for developing MIS-C, it is unclear whether biological or social factors, or both underpin this risk. 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."[10] A media article dated March 30, 2021, noted that about 50% of Toronto's population belongs to a racialized group, yet they represented 77% of all COVID-19 cases.[54] 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 aligns with the findings from this review.

Prevention strategies that reduce the risk of SARS-CoV-2 transmission can be layered to further mitigate the risks of children developing PACS or MIS-C. This layered approach includes ventilation, universal indoor masking in public settings, vaccination, masking directives in high-risk settings, and communication on the importance of wearing masks with good fit and filtration for personal and population-level protection. Those at highest risk of severe disease (e.g., those with immune compromise and those from racialized and low income populations), ineligible for vaccination (i.e., children less than 5 years) and those impacted by disruptions in educational settings (e.g., when individuals cannot attend due to being infected or symptomatic), can benefit from population-level interventions.

Further research is needed to characterize PACS and MIS-C in children, especially for identifying future healthcare resource requirements and to tailor care for higher risk groups for complications. Care for patients with PACS may place added stresses on healthcare and social support systems (e.g., parents and guardians unable to work due to a child's PACS or MIS-C), including increased emergency department visits, outpatient care, inpatient care and rehabilitation therapy involving multidisciplinary teams.[55-58] However, in a register-based cohort study of 706,855 children (10,279 tested positive, 275,859 tested negative) in Norway, Magnusson et al. (2022) reported that there was no difference in the percentage of test-positive children using primary care compared to test-negative patients (up to 9 months after testing).[59] Further longitudinal, standardized, case-control and large prospective cohort studies are needed to characterize PACS and MIS-C in children. Some of the research needs include:[51,59-64]

- Refining and developing a standardized definition of PACS and PACS prevalence under this definition
- Developing standardized definitions of PACS symptoms and respective diagnostic criteria
- Including more children from racialized communities in studies of PACS and MIS-C
- Further research into the risk factors associated with developing PACS or MIS-C
- Determining baseline, pre-infection comorbidities among case patients and non-case subjects; contributing to separation of sequelae due to COVID-19 or other etiologies
- Determining if SARS-CoV-2 is persisting in children, and if this is contributing to PACS
- Determining the duration of PACS and MIS-C symptoms and sequelae
- Determining the biological and physiological processes contributing to PACS and MIS-C
- Determining if PACS and MIS-C differ among variants of concern (VOCs), as most studies were performed previous to the emergence of Delta and Omicron
- Determining if vaccination status has an impact on development and severity of PACS and MIS-C

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

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Appendix A. Summary Demographics and PACS Sequelae in Patients Recovering from COVID-19

Table A1. Study population and characteristics of children with sequelae consistent with PACS from included systematic reviews (n=4) (bold) and primary studies (n=12)

First author	Country	Study period (date of last search for reviews)	Acute illness setting	Mean % sequelae consistent with PACS (Controls)	Sample size (N)*	Mean % female patients**	Mean patient age (years)**	Mean % white patients**	Min follow-up (days)	Included control group
Behnood[27]	NA	July 31, 2021	Mixed	NA (NA)	23,141	NA	NA	NA	30	Yes
Borel[25]	NA	Sept 1, 2021	Mixed	NA (NA)	11,951	NA	NA	NA	NA	No
Hirt[17] (preprint)	NA	Jan 22, 2021	Mixed	13 (NA)	81,896	NA	NA	NA	60	Yes
Lopez-Leon[16] (preprint)	NA	Feb 10, 2021	Mixed	25.2 (NA)	80,071	NA	NA	NA	30	Yes
Barrett[65]	US	Mar 2020 to June 2021	Mixed	NA (NA)	80,893/ 439,439	50.1/50.1	12.3/12.7	NA	30	Yes
Berg[28]	Denmark	July to Sept 2021	Mixed	61.9 (57.0)	34,900	58.4	17.7	NA	90	Yes
Borch[29]	Denmark	Jan 2020 to Mar 2021	Mixed	25.4 (22.9)	30,117	NA	2.7/12.0	NA	90	Yes
Castro[20] (preprint)	US	Mar 2020 to Apr 2021	Mixed	7.2 (9.6)	5,058	49.8	12.4	62.6	90	Yes
Dumont[22] (preprint)	Switzerland	June to July 2021	Mixed	2.4 (3.3)	660	46.9	10.2	NA	21	Yes
Kildegaard[66]	Denmark	Feb 2020 to Oct 2021	Mixed	0.12 (0.0053)	656,938	48.9	11	NA	30	Yes
Miller[21] (preprint)	England and Wales	June 2020 to Feb 2021	Outpatient	4.6 (1.7)	4,678	48.7	NA	NA	90	Yes
Molteni[67]	UK	Sept 2020 to Jan 2021	Outpatient	1.8 (NA)	3,468	50.2	13	NA	60	Yes

First author	Country	Study period (date of last search for reviews)	Acute illness setting	Mean % sequelae consistent with PACS (Controls)	Sample size (N)*	Mean % female patients**	Mean patient age (years)**	Mean % white patients**	Min follow-up (days)	Included control group
Nugawela[19] (preprint)	England	Jan to Mar 2021	Mixed	39.6 (30.6)	7,096	62.9	NA	73.0	90	Yes
Osmanov [26]	Russia	Jan to Aug, 2020	Inpatient	25.3 (NA)	518	52.1	10.4	NA	210	No
Roessler[18] (preprint)	Germany	Jan 2020 to Feb 2021	Mixed	NA (NA)	11,950	48.1	NA	NA	90	Yes
Stephenson[24]	UK	Jan to Mar, 2021	Mixed	66.5 (53.3)	6,804	63.5	NA	72.8	90	Yes

Abbreviations: NA, not applicable. *Total patients includes controls. **Data presented in reference to case patients only.

Table A2. Pooled mean/median prevalence (%) of comorbidities or pre-existing conditions in children with sequelae consistent with PACS (primary studies, n=8). Values in brackets are for controls.

First author	Any comorbidity or pre-existing condition	BMI ≥25	Allergies	Neurological and mental health	Asthma	Eczema
Borch[29]	5.0 (5.0)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Berg[28]	NA (NA)	15.7 (16.1)	21.8 (22.9)	8.0 (9.5)	9.5 (7.4)	0.8 (6.2)
Castro [20] (preprint)	20.2 (14.4)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Kildegaard[66]	23.2 (22.1)	NA (NA	NA (NA)	6.9 (6.1)	5.5 (5.4)	NA (NA)
Miller[21] (preprint)	4.4 (NA)	NA (NA)	NA (NA)	NA (NA)	8.2 (NA)	NA (NA)
Osmanov [26]	44.7 (NA)	4.9 (NA)	13 (NA)	8.8 (NA)	2.3 (NA)	8.8 (NA)
Roessler[18] (preprint)	NA (NA)	0.1 (0.1)	NA (NA)	NA (NA)	1.1 (1.0)	NA (NA)
Stephenson[24]	NA (NA)	NA (NA)	NA (NA)	9.1 (9.7)	NA (NA)	NA (NA)

Abbreviations: NA, not applicable

Table A3: Pooled mean/median prevalence (%) of neurological, mental health, respiratory and cardiovascular sequelae consistent with PACS (systematic reviews, n=2 [bold]; primary studies, n=6). Values in brackets are for controls.

First Author	Smell Dysfunction	Cognitive impairment	Headache	Sleep impairment	Dyspnea	Cough	Chest pain
Behnood[27]	13.7 (1.5)	11.0 (17.9)	20.1 (23.2)	19.5 (30.4)	20.8 (9.1)	4.0 (2.3)	NA (NA)
Lopez-Leon[16] (preprint)	5.6 (NA)	6.3(NA)	7.8 (NA)	8.4 (NA)	7.6 (NA)	3.8 (NA)	4.6 (NA)
Berg[28]	NA (NA)	8.3 (8.1)	6.2 (5.9)	NA (NA)	2.1 (1.1)	NA (NA)	0.0 (0.9)
Borch[29]	10.3 (0.1)	6.1 (9.2)	6.9 (6.0)	NA (NA)	4.1 (1.2)	2.7 (6.7)	1.4 (0.4)
Castro[20] (preprint)	0.5 (0.3)	2.3 (2.5)	2.4 (3.1)	0.6 (1.5)	NA (NA)	NA (NA)	NA (NA)
Dumont[22] (preprint)	4.8 (0.0)	1.9 (0.9)	11.1 (2.9)	1.0 (1.3)	1.0 (0.2)	5.3 (4.2)	NA (NA)
Osmanov[26]	4.7 (NA)	0.4 (NA)	3.5 (NA)	5.2 (NA)	1.4 (NA)	1 (NA)	0.6 (NA)
StephensonB[24]	13.5 (1.4)	6.5 (3.3)	23.2 (14.2)	NA (NA)	23.4 (10.4)	3.2 (2.6)	7.0 (3.5)

Abbreviations: NA, not applicable

Table A4. Pooled mean/median prevalence (%) of other-organ-system sequelae consistent with PACS (systematic reviews, n=2 [bold]; primary studies, n=6). Values in brackets are for controls.

Author	Abdominal pain	Fatigue	Joint pain	Muscle pain	Decreased appetite or weight loss	Diarrhea/ vomiting/ nausea	Dizziness
Behnood[27]	6.2 (10.0)	36.0 (26.2)	NA (NA)	6.8 (10.4)	NA (NA)	3.0 (2.1)	12.7 (7.8)
Lopez-Leon[16] (preprint)	2.9 (NA)	9.7 (NA)	3.8 (NA)	3.8 (NA)	6.1 (NA)	1.7 (NA)	4.4 (NA)
Berg[28]	0.0 (1.7)	7.9 (10.3)	2.1 (1.9)	2.1 (1.9)	3.7 (2.9)	NA (NA)	2.1 (3.6)
Borch[29]	NA (NA)	10.6 (4.3)	1.5 (1.8)	2.2 (2.3)	NA (NA)	1.6 (2.3)	3.4 (1.2)
Castro[20] (preprint)	NA (NA)	1.1 (1.6)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Dumont[22] (preprint)	2.9 (2.2)	11.5 (6.2)	1.4 (0.4)	4.8 (1.5)	3.4 (2.4)	2.9 (1.1)	0.5 (0.0)
Osmanov[26]	2 (NA)	10.7 (NA)	1.2 (NA)	0.8 (NA)	2.4 (NA)	2.0 (NA)	1.0 (NA)
StephensonB[24]	3.9 (2.9)	39.0 (24.4)	NA (NA)	5.4 (2.2)	9.7 (7.4)	3.0 (2.1)	13.7 (8.4)

Abbreviations: NA, not applicable

Appendix B. Summary demographics and clinical manifestations of patients with MIS-C

Table A5. Study population and characteristics of children with MIS-C from included systematic reviews (n=18) (bold) and primary studies (n=5)

Author	Last search/end of study period	Number included studies	Sample size	Mean/median male %	Mean/ median age	Evidence of SARS-CoV-2 exposure (%)	One comorbidity (%)	Obesity (%)	Chronic lung disease (%)
Ahmed[68]	Jul 2020	39	662	52.3	9.3	84.7	48.0	50.8	26.5
Aronoff[69]	Jul 2020	16	505	NA	9	85.3	NA	NA	NA
Baradaran[70]	Jul 2020	16	600	53.7	NA	At least 77.3	NA	28.2	13.1
Dhar[71]	Jul 2020	25	833	56.7	8.9	At least 65.8	NA	28.6	14.9
Haghighi Aski[72]	Oct 2020	21	916	NA	9	At least 37.8	NA	NA	NA
Henrina[73]	Oct 2020	26	1,228	53.5	8.6	At least 81.2	31.7	17.0	NA
Hoste[74]	Aug 2020	68	953	58.9	8.4	At least 71.4	NA	25.3	4.1
Kaushik[75]	Jul 2020	16	655	55	8	At least 54%	23.3	56.9	25.5
Kornitzer[76]	Mar 2021	54	543	59.7	NA	NA	NA	NA	NA
Lo[77]	Mar 2021	32	1,458	56.4	NA	At least 82.2	NA	NA	NA
Nepal[78]	Feb 2021	15	785	NA	NA	NA	NA	NA	NA
Radia[79]	Jun 2020	35	783	55	8.6	59%	20	7.7	NA
Rodriguez-Gonzalez[80]	Jul 2020	16	688	56.8	9	NA	25.6	NA	NA
Santos[81]	Jul 2021	98	2,275	56.8	8.9	At least 84%	33.0	NA	NA
Sharma[82]	Jun 2021	14	780	57.9	9.1	NA	NA	30.8	13.3
Sood[83]	Oct 2020	17	992	62.6	7.5	At least 48%	NA	NA	NA
Williams[84]	Jul 2020	18	833	57	9	85	29	NA	NA
Yasuhara[85]	Aug 2020	27	917	56.8	9.3	NA	30.7	18.0	14.4
Abrams[86] (US)	Jun 2020	NA	1,080	56	8	100	NA	26	NA

Author	Last search/end of study period	Number included studies	Sample size	Mean/median male %	Mean/ median age	Evidence of SARS-CoV-2 exposure (%)	One comorbidity (%)	Obesity (%)	Chronic lung disease (%)
Belay[38] (US)	Jan 2021	NA	1,733	57.6	9	At least 84.2	NA	NA	NA
Bowen[44] (US)	Mar 2021	NA	2,818	59.0	NA	100	38.5	28.4	9.2
Miller[87] (US)	Jul 2021	NA	4,470	59.9	9	97.7	37.8	25.1	9.6

Abbreviations: NA, not applicable

Table A6. Mean/median pooled prevalence (%) of ethnic and racial demographics of children with MIS-C from included systematic reviews (n=9) (bold) and primary studies (n=4)

Author	Black	White	Asian	Hispanic	Other and mixed races
Ahmed[68]	34.8	27.6	8.1	19.3	10.2
Baradaran[70]	31	23	10	34	NR
Dhar[71]	34.2	21.5	16.6	34.8	NR
Henrina[73]	31.1	16.3	6.0	22.1	24.5
Hoste[74]	37.0	29.2	8.7	29.2	22.3
Santos[81]	32	19	5	33	24.5
Sharma[82]	34.1	13.5	13.8	NR	NR
Williams[84]	35	27	10	NA	14
Yasuhara[85]	31.5	18.9	18.7	34.6	19.0
Abrams[88]	36	14	NA	41	9
Belay[38]	33.9	20.2	1.3	37.4	NA
Bowen[44]	28.8	27.7	2.3	37.0	4.2
Miller[87]	31.1	28.9	2.4	30.6	7.0

Abbreviations: NA, not applicable

Table A7. Mean/median pooled prevalence (%) of organ system involvement in children with MIS-C from included systematic reviews (n=14)

Author	Gastrointestinal	Cardiovascular	Respiratory	Neurological
Aronoff[69]	79.1	NA	42.9	NA
Baradaran[70]	80.3	NA	38.8	33 .0
Dhar[71]	84.3	NA	NA	22.9
Haghighi Aski[72]	NA	38.0	21.0	NA
Hoste[74]	85.6	79.3	50.3	NA
Kaushik[75]	70	51	NA	22
Lo[77]	76.7	NA	NA	36.8
Nepal[78]	NA	NA	NA	27.1
Radia[79]	71	82	9.6	NA
Santos[81]	82	66	39	28
Sharma[82]	89.2	NA	NA	40.8
Sood[83]	59.3	53.3	46.3	19.1
Williams[84]	86	NA	43	32
Yasuhara[85]	87.3	55.3	40.7	36.0

Abbreviations: NA, not applicable

Table A8. Mean pooled prevalence (%) of signs and symptoms in children with MIS-C from included systematic reviews (n=14) (bold) and primary studies (n=4)

Author	Rash	Swollen cervical lymph nodes	Conjunctivitis	Abdominal pain	Diarrhea	Vomiting	Dyspnea	Cough	Sore throat	Headache	Muscle pain	Swollen extremities	Oral cavity changes
Ahmed[68]	56.2	13.9	51.8	NA	NA	68.3	18.3	13.0	8.9	19.5	13.4	19.3	4.7
Aronoff[69]	60.2	30.3	52.2	NA	NA	NA	NA	41.7	14.3	NA	NA	29.6	43.5
Baradaran[70]	59.9	23.6	NA	NA	NA	NA	NA	NA	NA	NA	23.1	26.1	NA
Hoste[74]	54.9	NA	49.8	58.4	50.4	57.5	26.7	NA	NA	NA	NA	NA	NA
Kaushik[75]	58	4	40	NA	NA	NA	NA	NA	NA	NA	NA	13	23
Kornitzer[76]	19.2	NA	NA	NA	53.2	57.3	11.2	13.6	3.1	13.8	9.8	NA	NA
Lo[77]	57.1	NA	48.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nepal[78]	NA	NA	NA	NA	NA	NA	NA	NA	NA	27	NA	NA	NA
Radia[79]	42	NA	NA	36	27	25	NA	4.5	4	NA	NA	NA	NA
Santos[81]	59	NA	54	68	58	66	29	41	20	28	NA	59	NA
Sharma[82]	64.4	NA	62.5	81.1	37.8	75.7	NA	NA	NA	NA	NA	NA	NA
Sood[83]	68.3	NA	54.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Williams[84]	58	24	52	NA	NA	NA	NA	NA	NA	NA	NA	39	42
Yasuhara[85]	59.0	25.2	57.0	70.1	57.0	60.0	37.6	35.2	18.5	NA	14.2	32.9	42.3
Abrams[86]	54	NA	49	64	53	63	27	30	NA	NA	NA	NA	29
Belay[38]	55.6	NA	53.6	66.5	53.7	64.3	27.4	28.3	NA	NA	NA	NA	NA
Bowen[44]	55.7	NA	55.8	NA	NA	NA	NA	29.0	NA	NA	NA	NA	NA
Miller[87]	55.2	11.3	55.4	68.5	53.8	66.6	28.0	29.4	NA	44.8	29.8	NA	22.6

Abbreviations: NA, not applicable

Table A9. Mean pooled prevalence (%) of clinical findings in children with MIS-C from included systematic reviews (n=17) (bold) and primary studies (n=4)

Author	Fever	Pericardial effusion	Coronary artery dilation abnormalities	Hemodynamic shock or hypotension	Myocarditis	Acute kidney injury	Decreased left ventricular ejection fraction
Ahmed[68]	100	NA	8.1	NA	NA	16.3	45.1
Aronoff[69]	100	NA	NA	NA	NA	11.9	51
Baradaran[70]	97.3	49.1	19.9	55.2	56.9	31.1	65.3
Dhar[71]	NA	31.0	17.2	NA	61.8	22.7	45.0
Haghighi Aski[72]	NA	NA	20.0	NA	59	NA	38.0
Henrina[73]	NA	14.0	8.1	50.6	15.5	NA	59.0
Hoste[74]	99.4	22.3	11.6	59.9	41.4	NA	40.4
Kaushik[75]	NA	NA	23.4	28	23	NA	32
Kornitzer[76]	97.6	NA	NA	21.4	NA	NA	NA
Lo[77]	96.4	NA	NA	61.5	NA	NA	NA
Radia[79]	100	NA	NA	61	NA	NA	NA
Rodriguez-Gonzalez[80]	NA	NA	15.0	53.2	NA	NA	NA
Santos[81]	100	NA	NA	60	NA	NA	NA
Sharma[82]	100	NA	NA	59.8	NA	NA	NA
Sood[83]	91.4	18.7	23.1	49.0	39.3	NA	41
Williams[84]	96	35	16	65	65	35	61
Yasuhara[85]	99.3	31.7	21.4	65.8	55.3	NA	53.8
Abrams[86]	NA	NA	17	36	18	NA	NA
Belay[38]	NA	23.4	16.5	50.8	17.3	NA	NA
Bowen[44]	NA	NA	15.8	45.0	15.0	19.0	NA
Miller[87]	100	22.1	16.7	51.7	14.6	19.0	25.7

Abbreviations: NA, not applicable

Table A10. Mean/median pooled prevalence (%) of disease severity measures in children with MIS-C from included systematic reviews (n=15) (bold) and primary studies (n=4)

Author	Intensive care unit admission	Invasive mechanical ventilation	Death
Ahmed[68]	71.0	22.2	1.7
Aronoff[69]	NA	26.1	1.4
Baradaran[70]	76	32.0	NA
Dhar[71]	NA	27.8	1.6
Henrina[73]	75.5	27.3	2.0
Hoste[74]	73.3	NA	1.9
Kaushik[75]	NA	NA	1.7
Kornitzer[76]	67.2	NA	NA
Radia[79]	68	18	1.5
Rodriguez-Gonzalez[80]	75.6	22.0	1.8
Santos[81]	76	50	1
Sharma[82]	71.5	49.2	2.8
Sood[83]	67.8	30.1	2.2
Williams[84]	76	25	2
Yasuhara[85]	79.1	33.0	1.9
Abrams[86]	60	NA	2
Belay[38]	58.2	NA	1.4
Bowen[44]	57.8	9.3	1.2
Miller[87]	NA	9.4	NA

Abbreviations: NA, not applicable

Table A11. Studies reporting on significant risk factors contributing to development of MIS-C in children from included systematic review (n=1) (bold) and primary studies (n=9)

Author	Country	Sample size	Significant risk factors for developing MIS-C
Dhar[71]	Multiple	833	Male sex
Abrams[86]	US	1,080	Black, 6–12 years
DeBiasi[89]	US	63	Black
Feldstein[49]	US	539	Black, 6–12 years
Feldstein[90]	US	186	Black, 6–12 years
Lee[50]	US	223	Black, Hispanic
Martin[23] (preprint)	US	498	Black, male sex, ≤12 years
Middleburg[91]	Multiple	73	Black, Asian
Payne[43]	US	248	Black, Hispanic, Asian, 6–10 years
Stierman[48]	US	1,382	Black

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