Public Health Ontario | Santé publique Ontario

SYNTHESIS

# **(ARCHIVED)** Coronavirus Disease 2019 and the Pediatric Population: An Umbrella Review

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## Introduction

Public Health Ontario's (PHO) knowledge syntheses provide an overview of the published and grey literature reports related to Coronavirus Disease 2019 (COVID-19). For this systematic, umbrella review (a review of systematic reviews and meta-analyses), PHO Library information specialists searched several databases (e.g., MEDLINE, Embase) for systematic reviews related to clinical and epidemiological aspects of COVID-19 in the pediatric population (0–19 years old).

The goal of this umbrella review is to summarize evidence to date on COVID-19 and children, providing a summary of where systematic reviews show consistency or where they are contradictory with respect to the evidence. PHO subject matter experts review all PHO knowledge syntheses before posting.

For the purpose of clear communication, PHO uses the term COVID-19 to refer to both the virus and the disease. 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 posting.

## Key Findings

- Forty-eight systematic reviews were included in our final synthesis. We scored 85.4% (41/48) of systematic reviews as having a critically low or low methodological quality; therefore, caution must be used when interpreting results. The systematic reviews were in agreement for clinical manifestations, disease severity, viral shedding and exposure settings; however, high variability was found in the evidence for computed tomography findings, laboratory findings, co-infections and comorbidities.
- A single systematic review and meta-analysis described that children and adolescents younger than 20 years old were at lower risk of infection compared to adults 20 years old and over. Most children (80%–89%) in systematic reviews were exposed to COVID-19 through family members.

- Fever (50%–59% of all pediatric patients) and cough (40%–49%) were the most common clinical manifestations in children, followed by rhinorrhea/nasal congestion and sore throat/pharyngeal erythema (10%–19% each). Symptoms reported in less than 10% of patients included myalgia, fatigue, diarrhea, vomiting, nausea, headache and dizziness.
- Most children (80%–89%) experienced mild to moderate disease severity and approximately 10% to 19% of children in the systematic reviews were asymptomatic. Mortality rates in children were less than 0.4%.
- Detection of virus in respiratory samples lasted an average of 9 to 11 days from symptom-onset; however, virus detection in fecal samples lasted an average of 16 to 24 days.

# Background

During the early stages of the pandemic, the global numbers of reported COVID-19 cases in children were low. Initially, reports likely underestimated the true prevalence of COVID-19 across age groups, since testing policies often prioritized recent travelers, healthcare workers and those with severe symptoms. Further, in many jurisdictions, the first wave community-based public health measures that were implemented resulted in closures of settings where children may be exposed, such as schools. Therefore, we expected that early estimates of prevalence in children could increase, as children were re-introduced to settings that may put them at risk of exposure and where there was expansion of testing capacity and groups prioritized for testing.

As the pandemic has progressed, the prevalence of COVID-19 in the pediatric population has increased. For example, the prevalence of COVID-19 children 0–19 years old in the Unites States of America (USA) increased from 7.4% in May to 15.5% in August, 2020.[1] Children now comprise a larger proportion of all COVID-19 cases and with schools re-opened in many jurisdictions, understanding of the clinical and epidemiological characteristics in this population is advancing.

Researchers published the first paper on COVID-19 in children on February 5, 2020 and the first systematic review on COVID-19 in children on April 22, 2020; since then, the volume of literature has increased exponentially.[2,3] A quick search for "COVID + child" in PubMed (October 1, 2020) yields 4,948 articles, of which 751 articles are categorized as reviews, systematic reviews or meta-analyses. With this volume of research from various settings, a consensus on clinical and epidemiological aspects of COVID-19 in children can be difficult to reach.

The goal of this umbrella review is to summarize evidence to date on a broad array of topics concerning COVID-19 and the pediatric population (for this umbrella review, the pediatric population was defined as those 0–19 years old). We chose an umbrella review because it provides healthcare decision makers with current evidence on COVID-19 and demonstrates where systematic reviews show consistency on a research question, or where the evidence is contradictory or highly variable.

We concentrate our umbrella review on the following research questions:

1. What is the prevalence of COVID-19 in children?
2. What is the prevalence of COVID-19 by age group, sex and race?
3. What are the clinical manifestations of COVID-19 in children?
4. How severe is COVID-19 in children?

5. What are the laboratory findings in children with COVID-19?
6. What are the imaging findings in children with COVID-19?
7. What co-infections are associated with COVID-19 in children?
8. What comorbidities are associated with COVID-19 in children?
9. How long is viral shedding (respiratory and gastrointestinal) in children with COVID-19?
10. How are children exposed to COVID-19?

We organized our umbrella review by section for each research question. We present prevalence measures of variables, with an assessment of agreement among systematic reviews and propose reasons underlying disagreements or variability. In addition, we discuss findings in the context of sentinel primary literature. Where applicable, we discuss findings in terms of age within the pediatric population, race, comparison to adults and studies comparing COVID-19 to other pathogens.

## COVID-19 in Children: Global, Canada and Ontario Context

As of October 1, 2020, children with COVID-19 represented from 8.2% (Belgium, less than 19 years)[4] to 13.7% (Italy, less than 19 years)[5] of all infections. We examined the prevalence of children with COVID-19 in other countries with varied definitions of the pediatric population: Ireland (4.6%, less than 15 years)[6], Germany (6.6%, less than 15 years)[7], USA (8.5%, less than 18 years)[8], European Union + United Kingdom (UK) (8.8%, less than 19 years)[9] and Australia (13.5%, less than 20 years)[10] (countries reported represent a convenience sample of readily available data).

In Canada as of October 1, 2020, children represented 10.9% of all cases.[11] The prevalence of pediatric COVID-19 ranged from 8.0% in New Brunswick to 17.7% in Alberta (Table 1). The prevalence of COVID-19 in Canada was higher in 10–19 year olds (7.7%) compared to 0–9 year olds (4.4%).

**Table 1. Summary of COVID-19 prevalence in children by age group and Canadian province or territory (as of October 1, 2020)**

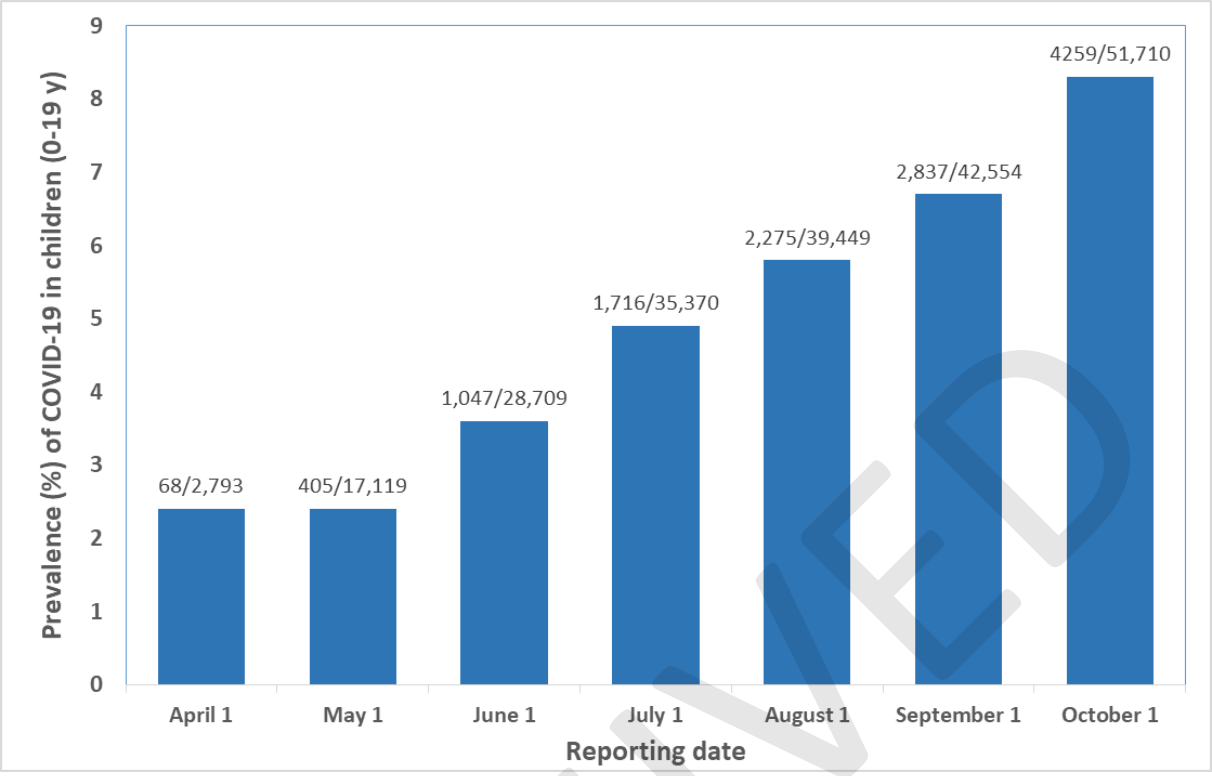
| Province or territory | Prevalence (%) by age group (x/n)* 0–9 years | Prevalence (%) by age group (x/n)* 10–19 years | Prevalence (%) by age group (x/n)* 0–19 years |
|---|---|---|---|
| British Columbia[12] | 3.3 (303/9,220) | 5.8 (533/9,220) | 9.1 (836/9,220) |
| Alberta[13] | 7.3 (1,329/18,235) | 10.4 (1,895/18,235) | 17.7 (3,224/18,235) |
| Saskatchewan[14] | NA | NA | 17.2 (331/1,927) |
| Manitoba[15] | 5.1 (103/2,029) | 11.6 (236/2,029) | 16.7 (339/2,029) |
| Ontario[16] | NA | NA | 8.3 (4,259/51,710) |
| Quebec[17] | 3.8 (2,858/75,221) | 7.2 (5,416/75,221) | 11.0 (8,274/75,221) |

| Province or territory | Prevalence (%) by age group (x/n)* 0–9 years | Prevalence (%) by age group (x/n)* 10–19 years | Prevalence (%) by age group (x/n)* 0–19 years |
|---|---|---|---|
| New Brunswick[18] | 5.0 (10/200) | 3.0 (6/200) | 8.0 (16/200) |
| Nova Scotia[19] | NA | NA | 10.0 (109/1,089) |
| Prince Edward Island[20] | NA | NA | 8.5 (5/59) |
| Newfoundland and Labrador[21] | NA | NA | 9.2 (25/272) |
| Yukon[22] | NA | NA | NA |
| North West Territories[23] | NA | NA | NA |
| Nunavut[24] | 0 (0/0) | 0 (0/0) | 0 (0/0) |
| **Total** | **4.4% (4,603/104,895)** | **7.7 (8,086/104,895)** | **10.9% (17,417/159,955)** |

*x, total pediatric patients; n, total COVID-19 patients (all ages); NA, not available for pediatric patients

In Ontario, the proportion of all cases involving the pediatric population has increased since the start of the pandemic from 2.4% (68/2,793) on April 1 to 8.3% (4,259/51,710) on October 1, 2020 (Figure 1).[16] In Ontario, seroprevalence in children remained relatively stable from March to April (0.0%, 0/182), May (0.92%, 2/218) and June (0.92%, 9/978).[25]

**Figure 1. Prevalence of COVID-19 in Ontario children, by reporting date from April 1 to October 1, 2020[16]**




# Methods

## Search strategy

Our umbrella review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[26]

PHO Library Services performed three literature searches:

1. MEDLINE (January 1 to September 11, 2020)
2. Supplementary databases (Embase [January 1 to September 16, 2020], Cumulated Index to Nursing and Allied Health Literature [CINAHL, January 1 to September 17, 2020], Cochrane Database of Systematic Reviews [CDSR, January 1 to September 17, 2020])
3. National Institutes of Health iSearch COVID-19 Portfolio (Preprints, January 1 to September 21, 2020)

In addition to database searches, we manually searched PubMed and Google Scholar (up to September 25, 2020) using the following key words: COVID-19, child and review. We provide the search strategy for MEDLINE in Appendix A (including a search strategy for the primary literature); other search strategies are available upon request. The search was limited to publication type (i.e., review, systematic review and meta-analysis) and we excluded animal studies, non-English language and non-research publications (e.g., comment, editorial, letter, news).

## Systematic Review Screening and Selection

Two authors independently reviewed all titles and abstracts identified in searches and resolved disagreements on study inclusion by consensus. Included systematic reviews and meta-analyses must have presented a detailed literature search and pooled means, averages and/or prevalence estimates of variables of interest. We excluded reviews that were primarily narrative and any reviews that did not report on measures addressing our research questions.

Complications related to COVID-19 in children were out of scope for this umbrella review (not abstracted from systematic reviews); however, we highlight complications when discussing disease severity. In addition, this review does not address the negative impacts of the pandemic context and related public health measures on children, such as mental health, physical activity and child welfare.

## Data Extraction and Synthesis

Data were extracted from each included study by one author and then fact-checked by one of three co-authors.

Data extracted from each review included:

1. First author and end date of literature search
2. Number of included studies and total patients
3. Age and sex of patients
4. Type of review and types of included studies
5. Prevalence data of interest (cases by age, sex and race; clinical manifestation; disease severity classification; laboratory findings; imaging findings; co-infections; comorbidities; viral shedding; and exposure setting)
6. Synthesis methodology and analysis
7. Number of databases searched
8. Assessment of methodological quality
9. Research questions addressed by each systematic review
10. Overall quality assessment score

The goal of an umbrella review is not to re-synthesize existing literature or to perform additional meta-analyses; rather, we want to determine whether included systematic reviews were in agreement with respect to each research question. We present summary figures for each research question, where needed, to highlight consensus or variability among reviews.

Primary literature was included to compare our findings and to highlight topics not addressed directly in systematic reviews (e.g., COVID-19 prevalence by race). We selected primary studies based on authors' experience with the literature and through suggestions from subject matter experts.

## Quality Assessment

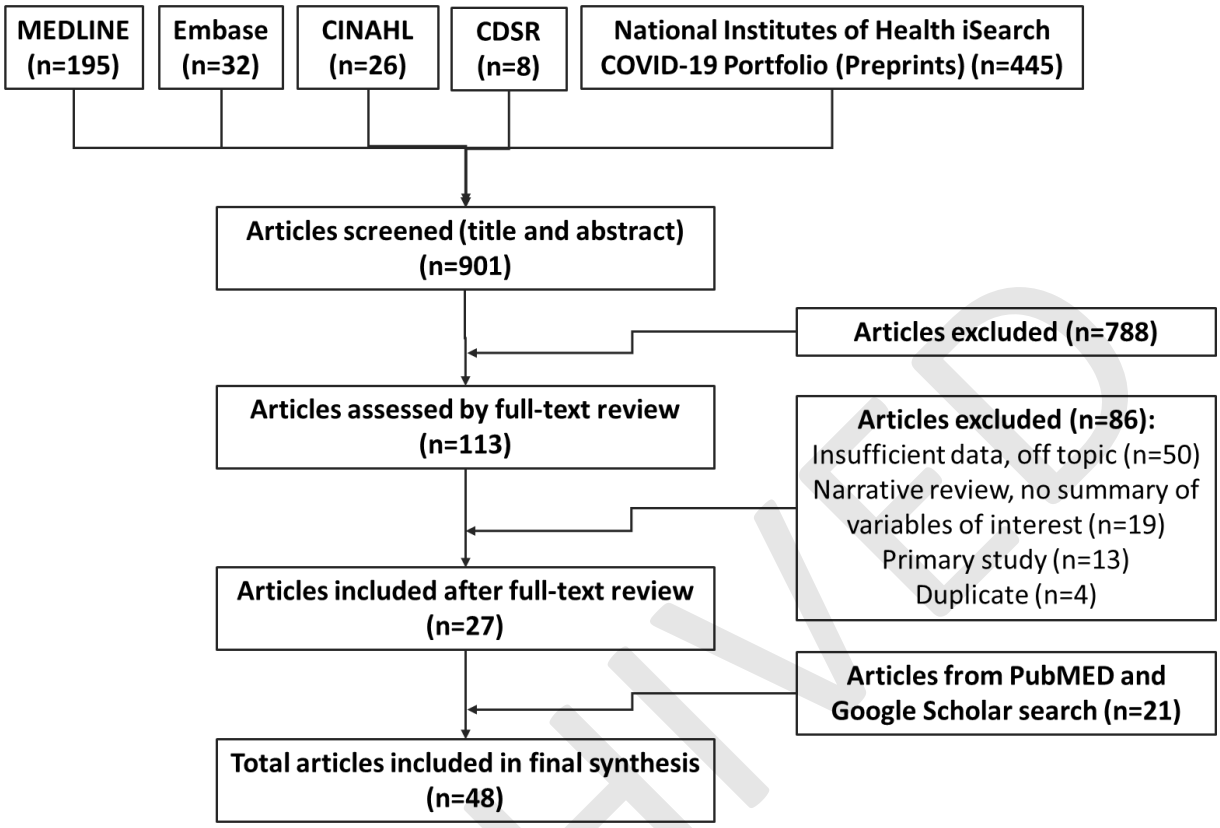
We used the Assessment of Multiple Systematic Reviews (AMSTAR) tool to assess the methodological quality of each systematic review and meta-analysis included in the umbrella review.[27] The AMSTAR tool included 16 questions for each article, resulting in a quality grade for the article (i.e., critically low, low, moderate, or high). Three authors assessed 20 articles each, meaning that approximately 28% of papers were assessed at least twice. Papers assessed twice were discussed amongst the reviewers in order to improve consistent use of the AMSTAR tool between them.

# Description of Included Systematic Reviews

## Systematic Review Selection

Our search strategy identified 706 articles, of which 113 were included for full-text review after screening titles and abstracts (Appendix B and Figure 2). After full text review, 27 studies were included in the final synthesis. A further 21 reviews were included after searching PubMed and Google Scholar; most of these were published shortly after the database searches were performed. The final number of included studies in the umbrella review was 48.

**Figure 2. Database Search and Article Selection process**




## Systematic Review Characteristics

Reviews included a range from 3 to 49 primary studies, with 10 to 7,780 total patients. The final literature search date for included primary studies varied in systematic reviews, from a high of 18 in April, followed by May (12), March (8), June (4), July (3) and August (3). The number of systematic reviews used to address each research question varied: prevalence and seroprevalence in children (n=1 study); prevalence and seroprevalence by age (8); clinical manifestations (0–19 years, n=29; less than 1 year, n=9); disease severity (35); laboratory findings (21); imaging findings (26); co-infections (9); comorbidities (14); viral shedding (5); and exposure setting (13).

## Systematic Review Quality

Using the AMSTAR tool to assess methodological quality, we scored 85.4% (41/48) of the reviews as critically low or of low quality. A relatively low quality score for most systematic reviews is not unexpected given the speed at which they have been published, and which may reflect efforts to rapidly synthesize and share information with healthcare providers and public health officials.

# COVID-19 Prevalence and Seroprevalence

In a systematic review of children and adults, Chen et al. reported that the seroprevalence of COVID-19 in 0–19 year olds was 1.9% (95% CI: 0.5–3.3), which is 20% lower than the seroprevalence in 20–49 year olds (3.6%; 95% CI: 1.9–5.4) (risk ratio [RR]: 0.8; 95% CI: 0.7–0.8).[28] In population-wide random screening

in Iceland, 0% (0/848) of children less than 10 years old were positive for COVID-19, while 0.8% (100/12,232) of 10–18 year olds were positive (performed early in pandemic before April 4, 2020).[29] For targeted testing, 6.7% of cases were less than 10 years old and 13.7% were 10 years old and over.

## COVID-19 Prevalence by Pediatric Age Group

Eight systematic reviews of the pediatric population reported on the prevalence of COVID-19 in children by age group (Table 2).[30-37] Most pediatric patients were 1–9/10 [slash represents variable cut-offs in studies] years old (systematic reviews with n greater than 1,000: ≈50%–67%), followed by children 10/11–19 years old (≈29%–38%) and infants less than 1 year (≈12–18%). The prevalence of COVID-19 in school-aged children (5/6–19 years old) varied from approximately 52% to 63% of all pediatric cases. There was no agreement among the systematic reviews with respect to increasing COVID-19 prevalence with age (as was the case with seroprevalence and surveillance data as presented in previous section). The mean age of patients ranged from 6.4 to 10.0 years (when n greater than 1,000) (Appendix B). The high variability in results was likely due to testing policies early in the pandemic; in which testing of children was not a priority compared to high risk individuals.

In a systematic review and meta-analysis, Viner et al. did not find a difference in risk of infection among those less than 10 years old and those 10–19 years old (includes household and non-household contact tracing studies).[38] However, children and adolescents less than 20 years old were less likely to be infected compared to adults (odds ratio [OR]: 0.56; 95% CI: 0.37–0.85).

## COVID-19 Prevalence by Gender and Race

In most systematic reviews, the percent of male patients ranged from 50% to 59% (Table 6, Appendix B). Several reviews noted no significant difference in the proportion of male and female patients.[31,37,39,40] Zheng et al. reported that susceptibility in male children was not different than females (OR: 1.15; 95% CI: 0.63–2.08).[40] In Canada, 49.5% of all pediatric patients (n=16,553) were male.

We are not aware of any systematic reviews that examined COVID-19 prevalence by race; however, the primary literature from the USA shows Black and Hispanic children have been disproportionately impacted by COVID-19. In a USA study of hospitalized pediatric patients (n=526), 45.8% were Hispanic/Latino, followed by Black (29.7%) and Caucasian (14.1%).[41] In a study of school-aged children (5–17 years; n=277,285) in the USA, most patients were Hispanic/Latino (41.7%), followed by Caucasian (32.4%) and Black (17.3%).[42]

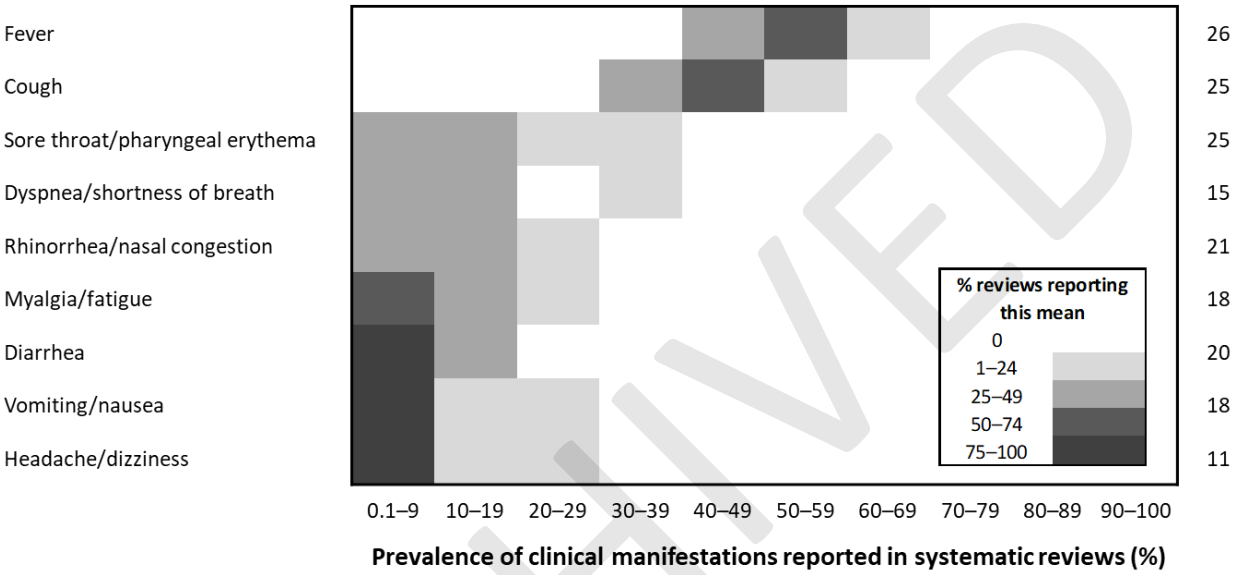
# Clinical Manifestations of COVID-19 in Children

Twenty-nine systematic reviews examined the clinical spectrum of COVID-19 in children (Table 3).[30-37,39,40,43-61] The clinical manifestations reported occurred over the entire course of disease or period of observation. No systematic reviews examined presenting symptoms, the timing, or course of signs or symptoms. In addition, none of the systematic reviews examined the number of signs and symptoms experienced by patients, singly or in combination. Overall, there was agreement among systematic reviews in terms of the prevalence of clinical manifestations in children.

The most common clinical signs and symptoms in children 0–19 years old were fever (50%–59%) and cough (40%–49%), followed by sore throat/pharyngeal erythema (10%–19%), dyspnea/shortness of breath (10%–19%) and rhinorrhea/nasal congestion (10%–19%) (Figure 3). Symptoms reported in less than 10% of patients included myalgia, fatigue, diarrhea, vomiting, nausea, headache and dizziness.

Clinical manifestations reported in fewer than ten of the systematic reviews were considered rare, e.g., poor eating, conjunctivitis, tachycardia and rash (Table 3). Variability in results could be in part due to definitions of clinical manifestations in primary studies. For example, fever was likely defined differently by settings (different countries, healthcare vs. non-healthcare) and in some cases, may be self-reported. In addition, eliciting information on subjective symptoms in small children can be difficult.

**Figure 3. Clinical manifestations of COVID-19 in children (0–19 years), by prevalence of clinical manifestation reported in systematic reviews (n=11–26, left axis)**




The results of this umbrella review are in agreement with symptoms reported for children (less than 10 years, n=6,659; 10–18 years, n=15,555) in the European Union + United Kingdom as of October 1, 2020.[9] Fever was the most commonly reported symptom (less than 10 years, 59% vs. 10–18 years, 38%), followed by cough (42% vs. 48%), runny nose (30% vs. 33%), sore throat (11% vs. 28%), diarrhea (10% vs. 6%), headache (6% vs. 14%), pain (5% vs. 8%), general weakness (4% vs. 7%), shortness of breath (3% vs. 4%) and muscular pain (1% vs. 5%).

Chilblains, acral lesions of the hands and feet, have been associated with COVID-19 in children; however, chilblains were not specifically highlighted in the systematic reviews examined.[62] In addition, none of the 48 systematic reviews reported the presence of olfactory or gustatory dysfunction for pediatric populations, although these can be common symptoms in adults.[63]

In a review of cases in China, Pei et al. reported children had a lower prevalence of fever compared to adults (57.1% vs. 72.0%, p=0.016).[64] In a systematic review and meta-analysis, Rokkas reported the prevalence of gastrointestinal symptoms in children was 9.6% (95% CI: 6.3–14.3), which was similar to adults at 9.7% (95% CI: 6.2–14.9).[49]

In a retrospective cohort study in the USA, Song et al. reported signs and symptoms in hospitalized children with COVID-19 and seasonal influenza. Patients with COVID-19, compared to patients with seasonal influenza, had a higher risk of fever (76% vs. 55%; OR: 2.6; 95% CI: 1.4–5.1), diarrhea/vomiting (26% vs. 12%; OR: 2.5; 95% CI: 1.2–5.0), headache (11% vs. 3%; OR: 3.9; 95% CI: 1.3–11.5), body

aches/myalgias (22% vs. 7%; OR: 3.9; 95% CI: 1.8–8.5) and chest pain (11% vs. 3%; OR: 3.9; 95% CI: 1.3–11.5).[65]

Chang et al. compared clinical aspects of COVID-19 and severe acute respiratory syndrome (SARS) in pediatric patients, where asymptomatic infection was more common in COVID-19 patients (26% vs. 0%, p<0.001), and the prevalence of fever (59% vs. 98%, p<0.01) and cough (46% vs. 60%, p=0.02) were higher in SARS patients.[60]

Swann et al. performed a prospective multicenter observational cohort study of 651 pediatric patients with COVID-19, examining clinical manifestations by age group (less than 1, 1–4, 5–9, 10–14, 15–19 years).[66] The prevalence of clinical manifestations such as fever and runny nose were generally higher in those 0–10 years old, compared to those over 10 years old. Clinical manifestations more prevalent in those older than 10 years included headache, sore throat, abdominal pain and nausea/vomiting.

## Clinical Manifestations in Infants (Less than 1 Year)

Nine systematic reviews reported on clinical manifestations in infants (less than one year, exclusively or as a sub-cohort) (Table 4).[34,36,47,67-72] Clinical manifestations in infants were similar to those reported for older children, with fever and cough being the most common findings. There was less agreement in the prevalence of symptoms in infants, likely due to the low numbers of patients. The most common clinical signs and symptoms reported in infants less than one year were fever (approximately 16%–73%), cough (8%–38%), rhinorrhea/congestion (6%–50%), gastrointestinal symptoms (9%–33%), and other respiratory symptoms (3%–41%).

# Severity of COVID-19 in Children

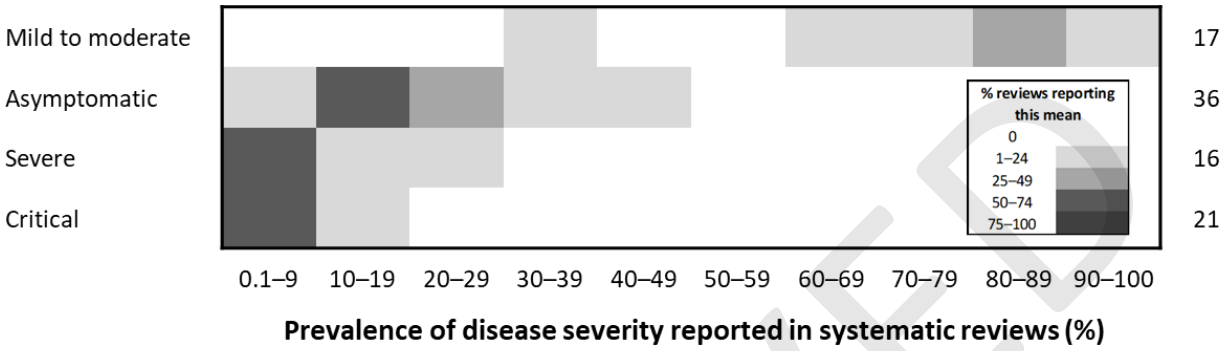
Thirty-five reviews reported on disease severity, where most COVID-19 infections were considered mild to moderate (80%–89%) or asymptomatic (10%–19%) (Figure 4, Table 5).[30-37,39,40,44-48,50,52-56,58-61,67-76] Overall, systematic reviews were in agreement for different classifications of disease severity. For consistency, we will use the following classifications of disease severity, modified from Shen et al.[77] and Dong et al.[78]; however, it is not always clear in systematic reviews whether researchers used the same classification system, and not all studies reported on all classification categories:

- **Asymptomatic infection:** A COVID-19-positive patient without clinical signs and symptoms, with normal chest radiography or computed tomography (CT).
- **Mild to moderate infection:** Patient with or without fever, but with cough or other clinical signs and symptoms. Patients do not exhibit hypoxia and may or may not have abnormal chest radiography or CT findings.
- **Severe infection:** Patients with fever, tachypnea, oxygen saturation lower than 92%, altered level of consciousness (e.g., lethargy) and dehydration.
- **Critical infection:** Patients admitted to intensive care unit (ICU) experiencing acute respiratory distress syndrome (ARDS) or respiratory failure (requiring mechanical ventilation), shock or other organ failure.

Asymptomatic infections in children were relatively common in the reviews examined, where the pooled prevalence ranged from 7.6% to 27.7% (when n greater than 1,000). The review with the most patients (n=7,780) reported 19.3% of patients were asymptomatic. Most systematic reviews reported asymptomatic patients in 10%–19% of all children, including infants (less than one year) (Figure 4). Authors did not always indicate if all asymptomatic patients had normal chest radiography or CTs, which

may explain some of the variability in asymptomatic prevalence. In addition, the proportion of asymptomatic patients could be the result of children not expressing verbally that they had mild symptoms.

**Figure 4. Disease severity of COVID-19 in children, by prevalence of disease severity reported in systematic reviews (n=16–36, left axis)**




Mild to moderate pediatric infections were the most common disease severity classification, ranging widely from 33.0% to 100.0% (when n greater than 1,000). The study with the most patients (n=5,684) reported 84% of patients had mild to moderate infections. Most systematic reviews reported mild to moderate infections in 80% to 89% of all patients.

Severe COVID-19 infection in children was rare, with less than 0.1% to 7.0% (n greater than 1,000) of all cases being considered severe (e.g., requiring hospitalization, breathing support). The study with the most patients (n=5,684) reported 7.0% of patients had severe infections. Most of the systematic reviews reported severe infections in less than 10% of children.

Like severe infections, critical COVID-19 illness in children was rare, with less than 0.1% to 14.9% (when n greater than 1,000) of all cases being considered critical (e.g., requiring ICU). The study with 14.9% critical cases focused on comorbidities in severe cases and those that died. The review with the most patients (n=7,780) reported 3.3% of patients had critical infections. Most of the systematic review reported critical infections in less than 10% of children.

Deaths in pediatric patients were exceedingly rare, with reviews reporting pediatric mortality rates from 0.0% to 0.3%. The review with the most patients (n=7,780) reported a mortality rate of 0.09%.

In Canada, children 0–19 years old comprised 1.4% of hospitalized patients (n=12,118); 1.3% of ICU patients (n=2,468); and 0.03% of patients who died (n=9,285).[11] In Ontario, as of October 1, 2020, there has been a single death reported in a child, representing 0.035% of all deaths (n=2,851) in the province.[79] In a USA study of hospitalized children (n=208), the mortality rate was 0.5%.[41]

Dong et al. reported infants less than one year old had more severe and critical infections; however, only 34.1% of children had laboratory-confirmed COVID-19.[78] Hospitalization rates in the USA were considerably lower in those less than 19 years old (8.0 per 100,000 population; 24.8/100,000 in those less than 2 years old), compared to adults (164.5/100,000).[41] These results need to be interpreted with caution, as physicians are more likely to admit an infant with COVID-19 than an older teenager, irrespective of severity.

In a study of deaths among those younger than 21 years old (n=121) in the USA, Bixler et al. reported deaths were highest in Hispanic children (44.6%), followed by Black (28.9%) and Caucasian (14.0%) children.[80] In this study, 41.3% of pediatric deaths occurred in those 18–20 years old.

## Complications

While out of scope for this umbrella review, a number of complications have been associated with COVID-19 in children. Multisystem inflammatory syndrome in children (MIS-C) and new onset Type 1 diabetes mellitus have been reported in the pediatric population during the pandemic.[81-85] Guillain-Barré syndrome (GBS) has also been reported in children, although uncommon (n=4, out of 73 cases of GBS reported in patients with COVID-19).[86] The long-term sequelae in children are not well-understood; however, as research accumulates, we expect to learn more about additional long-term impacts.

De Bernardo et al. reported on complications in neonates less than three months old (n=25), with pneumonia (12%) being the most common, followed by respiratory distress (8%), and sepsis or pneumothorax (4%).[67]

In a systematic review, Hoang et al. noted that complications were reported in 21 primary studies, in which mechanical ventilation (n=42 patients) was the most common complication, followed by shock (n=19), MIS-C (n=11), kidney failure (n=9), disseminated intravascular coagulation (DIC) (n=9) and cardiac injury (n=8).[61] Mustafa and Salem reported on four patients with complications that encompassed coagulopathy, DIC, hydronephrosis, hypoglobulinemia, intussusception, kidney stones, multi-organ system failure, septic shock and status epilepticus.[39] Panda et al. reported on 42 children with neurological complications (encephalopathy, n=25; meningeal signs, n=17; seizure, n=12); rare (undefined) complications were cranial nerve palsy, GBS, intracranial hemorrhage and vision impairment.[43]

To date, most of the evidence indicates children experience mild to moderate disease severity, with a low mortality rate. Researchers have suggested numerous hypotheses to explain why the COVID-19 experience is milder in children. One leading hypothesis is that a child's immune response is less robust, resulting in a lower likelihood of severe disease from cytokine storm.[87-89] In addition, children may have partial immunity to COVID-19 due to exposure to other respiratory pathogens (e.g., seasonal coronaviruses, respiratory syncytial virus, *Mycoplasma pneumoniae*).[87,89] Additional explanations for mild disease in children include a lower viral load in children, less comorbidities in children and a more active innate immune response.[87,89] Differences in distribution and functioning of renin angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE-2) receptors in children and adults have also been proposed as a reason for milder disease in children.[89] Further research is needed to fully understand the variable pathology of COVID-19 in children and adults.

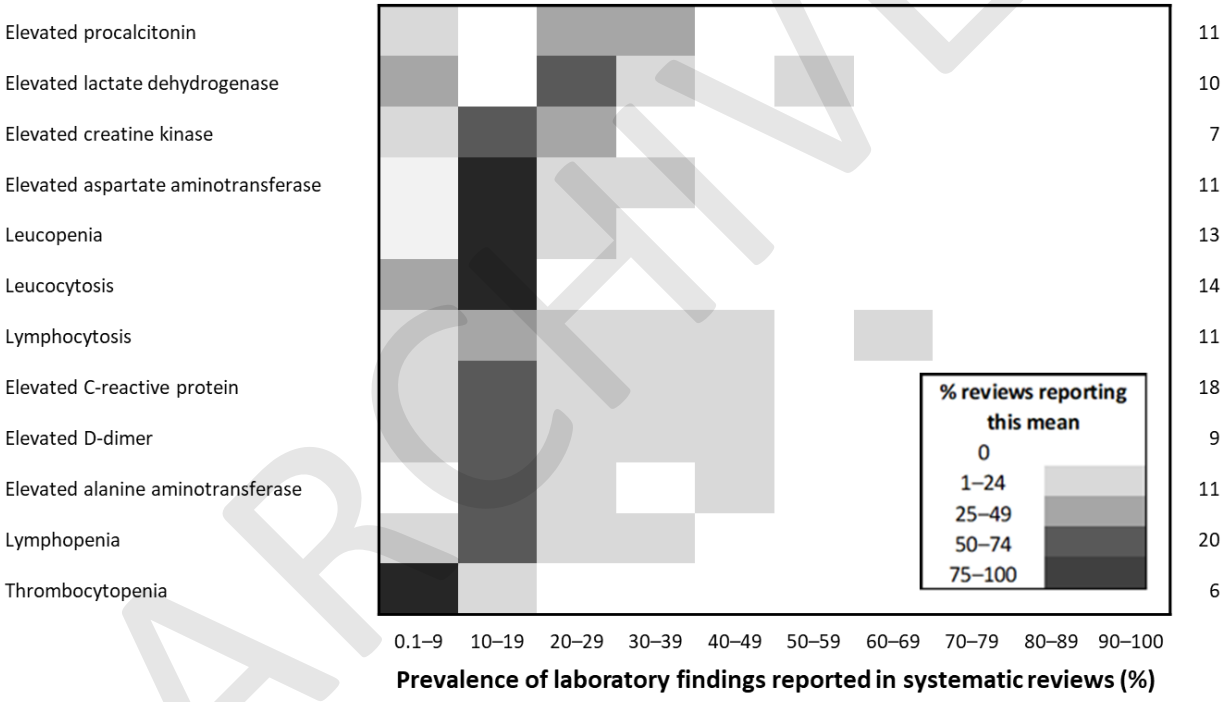
# Laboratory Findings in Children with COVID-19

Twenty-one systematic reviews reported on laboratory findings in children (includes patients during acute and convalescent phase of disease) (Table 6).[30,31,33-37,39,44,46-48,50,54,59-61,68,71,72,90] The laboratory abnormalities with the highest prevalence were elevated procalcitonin (PCT, 20%–39%) and elevated lactate dehydrogenase (LDH, 20%–30%) (Figure 5). Most studies reported 10% to 19% of pediatric patients had elevated creatine kinase (CK), elevated aspartate aminotransferase (AST), leucopenia, leucocytosis, lymphocytosis, elevated C-reactive protein (CRP), elevated D-dimer, elevated alanine aminotransferase (ALT), lymphopenia and thrombocytopenia.

Other laboratory findings reported in fewer than four systematic reviews included elevated creatinine, elevated erythrocyte sedimentation rate, elevated urea, high or low hemoglobin, and elevated interleukin-6 (IL-6). The high variability in results was likely due to varying reference ranges used in primary studies of pediatric patients. In addition, laboratory findings varied widely by disease severity; therefore, abnormal findings are likely from patients with severe disease and those that required hospitalization.

In a systematic review, Yasuhara et al. reported laboratory findings by age group (less than one year, n=29; 1–10 years, n=61; over 10 years, n=24) with older children experiencing higher prevalence of elevated PCT, D-dimer, creatinine and AST; however, no statistical analysis was performed.[36] Yoon et al., in a systematic review, examined whether there were differences among laboratory findings by age (less than 10 years; 10 year and older) for both symptomatic and asymptomatic cases. No significant differences were found between age groups.[37]

**Figure 5. Laboratory findings in children with COVID-19, by prevalence of findings reported in systematic reviews (n=6–20, left axis)**




# Imaging Findings in Children with COVID-19

Twenty-six systematic reviews reported on imaging findings in children (Table 7).[30-37,44,46-48,50,52,53,56,60,61,67,71,73,91-95] The variable terminology used to describe imaging results from chest radiography (X-rays) and CTs made summarizing the findings difficult and we did not prepare a consensus figure for this research question; however, there was general agreement among systematic reviews in terms of the predominant findings. Ground-glass opacities were the most common imaging finding in children (30%–39%). Normal CTs were reported in 30% to 49% of patients; however, it is not clear whether these patients were mostly asymptomatic or symptomatic. Most other findings (e.g.,

consolidation/pneumonia) were found in 10% to 29% of patients. Pleural effusion was relatively uncommon, in less than 10% of patients.

In a systematic review, Yasuhara et al. reported imaging findings (CT and X-ray) by age group (less than one year, n=29; 1–10 year, n=61; over 10 years, n=24) and found the prevalence of ground-glass opacities increased with age; however, no statistical analysis was performed.[36] Yoon examined whether there were differences among imaging findings by age (less than 10 years vs. 10 years and older) for both symptomatic and asymptomatic cases.[37] In asymptomatic cases, ground-glass opacities were more common in children 10 and older (83.3% vs. 20.85%; p=0.009); there were no differences by age in symptomatic cases.

In systematic reviews comparing imaging findings in children and adults, children were more likely to show normal findings. Nino et al. reported children more commonly showed normal imaging results, but were less likely to report bilateral consolidation and ground-glass opacities.[94] Azadbakht et al. reported lower prevalence of findings such as ground-glass opacities, bilateral patchy shadows and pneumonia in children, compared to adults.[91]

# Co-infections Associated with COVID-19 in Children

Nine systematic reviews investigated co-infections in children, with high variability between studies due to the relatively low numbers of patients included (Table 8).[30,31,40,46,53,61,71,74,96] Where reported, the prevalence of co-infections in children ranged from 5.6% to 10.0% (when n greater than 100 patients) (Table 8). The most common co-infections were *Mycoplasma pneumoniae*, influenza virus (A or B) and respiratory syncytial virus.

It was not clear whether patients with co-infections are more prone to severe disease or had worse outcomes. Most of the primary studies comprising the systematic reviews included children from the northern hemisphere when influenza was not active; therefore, co-infections with seasonal respiratory viruses may change as knowledge evolves during the winter of 2020 and 2021 in the northern hemisphere.

# Comorbidities Associated with COVID-19 in Children

Fourteen systematic reviews reported on comorbidities in children with COVID-19, with high variability between systematic reviews (Table 9).[30-33,35,39,46,47,53,56,61,68,71,76] The prevalence of comorbidities, regardless of disease severity, ranged from 2.0% to 35.6% of cases (when n greater than 500). Congenital heart disease, asthma and immune system compromise were the most commonly reported underlying conditions in children with COVID-19 (mostly hospitalized patients). It is possible that a large number of the children with comorbidities were already being cared for in a hospital setting and COVID-19 was a secondary finding detected during care.

In a study of 556 hospitalized children in the USA, the most common underlying conditions were obesity (37.8%), chronic lung disease (18.0%), prematurity (15.4%), neurological disorder (14.0%) and asthma (13.5%).[41] Hispanic and Black children had higher prevalence of underlying conditions (45.7% and 29.8%, respectively) compared to Caucasian children (14.9%).

In a study of deaths among those less than 21 years old (n=121) in the USA, 75.2% of patients had an underlying condition.[80] The most common underlying condition was chronic lung disease (28.1%), followed by obesity (27.3%), neurologic and developmental disease/disorder (21.5%), cardiovascular

disease (18.2%), cancer or immune system compromise (14.0%), diabetes mellitus (9.1%), chronic kidney disease (4.1%), chronic liver disease (2.5%) and "other" conditions (30.6%).

Among school-aged children (n=7,738) 5–17 years old in the USA with COVID-19, 2.8% had at least one underlying condition (5–11 years, 2.4%; 12–17 years, 3.0%). The most commonly-reported underlying condition was chronic lung disease (asthma, emphysema and chronic obstructive pulmonary disease [COPD]; 54.5%), neurologic and neurodevelopmental disorders (9.2%), immunosuppression (6.8%), diabetes mellitus (6.2%), psychological/psychiatric illness (5.8%), cardiovascular disease (4.7%), current/former smoker (4.3%), severe obesity (body mass index [BMI] ≥40 kg/m$^2$; 4.1%), chronic kidney disease (1.5%), hypertension (1.2%), autoimmune disease/condition (1.1%), chronic liver disease (0.8%), substance use (0.4%) and "other" conditions (17.1%).[42]

In a retrospective cohort study in the USA, Song et al. compared children hospitalized with seasonal influenza to those with COVID-19 and found children with COVID-19 were more likely to have an underlying condition (65% vs. 42%; OR: 2.6; 95% CI: 1.4–4.7); the most common underlying conditions in patients were developmental delay and seizures.[65]

# Viral Shedding of COVID-19 in Children

Five systematic reviews reported on viral shedding in children and were generally in agreement with one another (Table 10).[33,45,51,67,97] Detection of virus in respiratory samples (primarily nasopharyngeal swabs, but also oropharyngeal, pharyngeal, nasal, sputum, tracheal aspirate, nasal/throat oro/naso-pharyngeal and saliva samples) lasted an average of 9 to 11 days from symptom-onset; however, virus detection in fecal samples (also rectal and anal swabs) lasted an average of 16 to 24 days. No systematic reviews examined the period of infectiousness in various samples from children.

In a rapid scoping review, Byrne et al. inferred the infective period in children using a random effects meta-regression model (infectiousness inferred from virus isolation and PCR detection studies).[98] In asymptomatic patients, the estimated median period of infectiousness was 6.5 to 9.5 days from symptom-onset. In post-symptomatic patients, the period from symptom-onset to clearance of virus was estimated at 13.4 days (95% CI: 10.9–15.8); clearance in children was estimated at 5.8 days shorter in duration compared to adults (95% CI: 1.7–10.0). The median period of infectiousness, prior to symptom onset, was less than 1 to 4 days. The authors estimated the maximum period of infectiousness at 18.1 days (95% CI: 15.1–21.0).

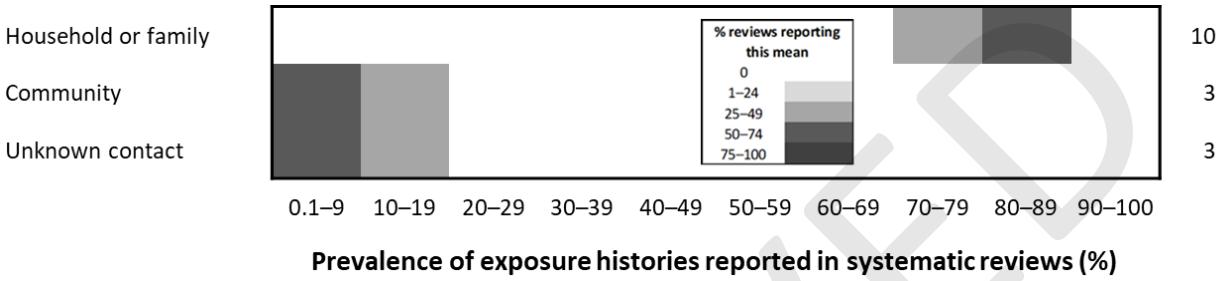
In a recent systematic review of COVID-19 patients of all ages, Walsh et al. did not identify any studies investigating the length of infectivity in pediatric patients, with studies only reporting on viral loads and viral detection.[99] Viral loads (upper respiratory tract) were highest at symptom onset and remained relatively high during the first week. In general, viral loads in fecal samples peaked two to three weeks later than viral loads in upper respiratory tract samples, which can have implications for potential fecal-oral transmission and wastewater surveillance for COVID-19.

# COVID-19 Exposure History for Children

Thirteen systematic reviews reported on exposure history of pediatric COVID-19 patients, with agreement among the systematic reviews (Table 11).[30-33,35,40,47,53,57,59-61,71] The most commonly-reported exposure was household/contact with family members (80%–89%) (Figure 6).

Since most of these systematic reviews include primary research conducted during periods of school and childcare center closures and lock-down measures, exposure to infected family members within the household was expected. Further research, during periods of less restrictive public health measures and with settings such as schools reopened, is needed to assess the full spectrum of potential exposure routes for pediatric patients.

**Figure 6. Exposure histories of children with COVID-19, by prevalence of exposure type reported in systematic reviews (n=3–10, left axis)**




In a systematic review and meta-analysis by Viner et al., there was decreased risk of children becoming infected in the household compared to adults (OR: 0.56; 95% CI: 0.37–0.85) compared to when household and non-household contacts are considered (OR: 0.91; 95% CI: 0.69–1.21).[38]

In a rapid scoping review, Rajmil et al. reported children were exposed to COVID-19 from positive family members in about 75% to 100% of cases.[100] In a systematic review and meta-analysis, secondary attack rates in households ranged from 15.7% to 47.6% in adults and from 5.2% to 26.9% in children.[101] The risk of household transmission in adults was three times higher than the risk in children (OR: 3.67; 95% CI: 2.76–4.87; p<0.001). Without addressing age, the risk of household transmission was ten times higher than other non-household contacts (OR: 10.72; 95% CI: 5.70–20.17; p<0.001).

# Limitations

We acknowledge that the populations and population subsets for reporting outcomes in systematic reviews may have varied and may not be comparable between reviews. Therefore, population-specific detail was not included in the umbrella review and readers are encouraged to interpret the data provided cautiously.

Due to time constraints, we did not perform data extraction or quality assessments in duplicate. However, data extracted by the lead author was fact-checked by one of three additional authors. In addition, we performed quality assessments in duplicate for at least 28% of systematic reviews. We did not assess each systematic review for bias; however, the AMSTAR tool specifically addresses whether or not authors assessed bias in their work. Given that 85% of the systematic reviews included in the umbrella review were scored as critically low or low methodological quality, caution is needed when interpreting results.

Researchers performed most of the systematic reviews early in the pandemic (79.2% [38/48], March through May); therefore, the body of evidence on each research question may have changed since then and is expected to evolve. We did not detect any major differences over the study period for most of the research questions. However, prevalence of COVID-19 in children increased and aspects of co-infections

and exposure location are expected to change as schools reopen and children are involved in more activities outside of the household.

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