Received: 10 November 2020 | Revised: 9 January 2021 | Accepted: 19 February 2021

DOI: 10.1002/ppul.25344

REVIEW

PEDIATRIC PULMONOLOGY WILEY

COVID-19 in childhood: Transmission, clinical presentation, complications and risk factors

Melissa K. Siebach RN, BSN[1,2] | Giovanni Piedimonte MD[3] | Sylvia H. Ley PhD, RD[1]

[1]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

[2]Department of Tropical Medicine, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

[3]Departments of Pediatrics, Biochemistry, and Molecular Biology, Tulane University School of Medicine, New Orleans, Louisiana, USA

Correspondence

Sylvia H. Ley, PhD, RD, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, 1440 Canal St, M.B. 8318, New Orleans, LA 70112, USA.
Email: sley@tulane.edu

Funding information

National Science Foundation, Grant/Award Number: 2031761; Dean's COVID-19 Rapid Response grant from Tulane University School of Public Health and Tropical Medicine; National Institute of General Medical Sciences of the National Institutes of Health, Grant/Award Number: P20GM109036; National Heart, Lung and Blood Institutes of Health, Grant/Award Number: RO1 HL-061007

Abstract

Children less than 18 years of age account for an estimated 2%–5% of reported severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases globally. Lower prevalence of coronavirus disease 2019 (COVID-19) among children, in addition to higher numbers of mild and asymptomatic cases, continues to provide challenges in determining appropriate prevention and treatment courses. Here, we summarize the current evidence on the transmission, clinical presentation, complications and risk factors in regard to SARS-CoV-2 in children, and highlight crucial gaps in knowledge going forward. Based on current evidence, children are rarely the primary source of secondary transmission in the household or in child care and school settings and are more likely to contract the virus from an adult household member. Higher transmission rates are observed in older children (10–19 years old) compared with younger children (<10 years old). While increasing incidence of COVID-19 in neonates raises the suspicion of vertical transmission, it is unlikely that breast milk is a vehicle for transmission from mother to infant. The vast majority of clinical cases of COVID-19 in children are mild, but there are rare cases that have developed complications such as multisystem inflammatory syndrome in children, which often presents with severe cardiac symptoms requiring intensive care. Childhood obesity is associated with a higher risk of infection and a more severe clinical presentation. Although immediate mortality rates among children are low, long-term respiratory, and developmental implications of the disease remain unknown in this young and vulnerable population.

KEYWORDS

epidemiology, pulmonology (general), social dimensions of pulmonary medicine

1 | INTRODUCTION

Children less than 18 years of age account for an estimated 1.7% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clinical infections in the United States,[1] with global estimates ranging from 2.0[2] to 4.8%.[3] The low prevalence of pediatric cases has made it difficult to draw conclusive statements about many aspects of the virus in this population, but the reported case numbers are likely an underestimation of the true pediatric case load, as many cases in children are mild or asymptomatic.[4] Initial observations report that

Abbreviations: ACE-2, angiotensin-converting enzyme 2; CDC, Center for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CXR, chest radiography; ICU, intensive care unit; KD, Kawasaki disease; MERS-CoV, Middle Eastern respiratory syndrome coronavirus; MIS-C, multisystem inflammatory syndrome in children; NP, nasopharyngeal; RNA, ribonucleic acid; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; SAR, secondary attack rate; SARS-CoV, severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSS, toxic shock syndrome; UNICEF, United Nation Children's Fund; WHO, World Health Organization.

the clinical course is generally milder and outcomes are better in children.[5] Also, as the pandemic progresses, clinicians report an increasing number of cases of multisystem inflammatory syndrome in children (MIS-C), a severe inflammatory syndrome following coronavirus disease 2019 (COVID-19) exposure or infection. Though rare, this syndrome has the potential to cause devastating outcomes in children and as the pandemic continues cases of MIS-C are likely to increase. These findings have underscored the limitations of current knowledge regarding COVID-19 in children and have raised questions about the implications for long-term respiratory and developmental prognosis. We seek to comprehensively examine what is currently known and what knowledge we still lack about transmission, clinical presentation, complications, and risk factors as they pertain to SARS-CoV-2 infection in the pediatric population. In so doing, we seek to link these four areas of concentration, providing the reader with an overview of the risk of COVID-19 to children.

2 | METHODS

A literature review was carried out to identify both published and non-peer-reviewed pre-print original studies and review papers from January to December 2020, relating to the transmission, clinical presentation, complications, and risk factors of COVID-19 in the pediatric population. Searches were conducted in PubMed, MedRxiv, and the Johns Hopkins "COVID-19, Maternal and Child Health, Nutrition" repository. Case studies and papers containing duplicate analysis of data already included in our review were not selected.

2.1 | Transmission

According to the WHO,[6] SARS-CoV-2 is transmitted directly and indirectly through the respiratory secretions of those infected. Several studies have also looked at the prevalence and implications of fecal viral shedding in the pediatric population and the implications for transmission.[7] Based on a systematic review of contact tracing programs and population studies, the susceptibility of children to COVID-19 was lower than adults, although the role that they played in transmission was not conclusive.[8]

The prominence of mild and asymptomatic illness in pediatric patients has created concern that the true prevalence of disease in this age group has been underreported.[4,5] Population-based seroprevalence studies have had conflicting results.[9–11] The seroprevalence of antibodies in children was consistent with that of adults in the same area in the UK,[9] implying that children and adults are equally susceptible to the virus, however, in Italy seroprevalence increased with age.[11] Similar to reports in the adult population, racial, and socioeconomic disparities have also been noted among pediatric populations with studies noting higher rates of transmission among racial and/or ethnic minority groups[12] with more severe health outcomes.[13]

2.1.1 | Household transmission

Table 1 presents transmission sources as reported in several pediatric studies. Available data indicate that SARS-CoV-2-positive adults living in the household are the primary source of infection for children. It should be noted that shelter-in-place orders decreased outdoor activities in most countries and likely led to the increase of viral spread within households.[14] In an investigation of 110 cases stemming from 11 infection clusters in Japan, close contact in an indoor setting contributed to all 11 clusters.[15] In South Korea, household cases were the primary source of infection until mid-March, 2020, when imported cases became the most prevalent.[4] In the UK, a population-based seroprevalence study of children reported that neither age nor gender had any association with positive results, but contact with a household member with confirmed COVID-19 was a significant predictor for seropositivity.[9]

Although children are usually infected by SARS-CoV-2-positive adults living in the household, several studies have shown that the overall risk of contagion to children is lower than that of other adults residing in the same household.[14,23] In a meta-analysis looking at secondary attack rates (SAR) in the household setting ($n = 54$ studies),[14] the overall estimated SAR for household contacts was 16.6%, while that of close contacts was just 4.8%. Spouses of infected individuals were at greater risk than other household members (37.8% vs. 17.8%), whereas the rate of secondary household transmission to children was significantly lower than adults (16.8% vs. 28.3%).[14]

A child's age may also affect the risk of transmission. In South Korea, analysis of data for 59,000 contacts of 5700 index cases found that a total of 11.8% of household contacts tested positive for COVID-19.[24] When further stratified by age, the infection rate was 18.6% for index cases aged 10–19 years, and 5.3% for ages 0–9 years.[24] Consistently, in a study of Swiss students, the seroprevalence of SARS-CoV-2 antibodies decreased with age.[10]

2.1.2 | Maternal–fetal and perinatal transmission

Vertical transmission was demonstrated with SARS-CoV-1, and the same risk theoretically exists for SARS-CoV-2, as the viral receptor (angiotensin-converting enzyme 2 [ACE-2]) is widely expressed in the placenta.[25] Although a systematic review of 18 studies ($n = 157$ mothers and 160 neonates) found no evidence of vertical transmission,[26] the growing number of confirmed neonatal cases of COVID-19 infection has reinforced the suspicion that SARS-CoV-2 is similarly capable of crossing the placenta to infect fetal lungs. A recent study identified three neonates delivered from COVID-positive mothers with pneumonia on chest radiography (CXR) obtained at birth and nasopharyngeal (NP) swabs positive for SARS-CoV-2 on Days 2 and 4 of life and negative on Day 6–7.[27] One of these patients was born at 31 weeks of gestation via cesarean delivery due to fetal distress and required resuscitation. Although vertical transmission was not found in several other neonates born to COVID-19 infected mothers, it is critical to note that most of such data have been limited by extremely small sample size

TABLE 1 SARS-CoV-2 transmission in children

Study	Participants *n*	Median Age	Positive SARS-CoV-2 *n* (%)	SARS-CoV-2 confirmed adult household contact *n* (%)	Symptomatic adult household contact *n* (%)	Sibling *n* (%)	Community/ unknown *n* (%)	International travel (imported) *n* (%)
Garazzino et al.[16] (Italy)	168	2.3	168 (100)	113 (67)	-	-	-	0 (0)
Zachariah et al.[17] (New York)	50	9	50 (100)	26 (52)	9 (18)	-	-	-
Götzinger et al.[18] (Europe)	582	5	582 (100)	324 (56)	-	24 (4)	234 (40)	-
Han et al.[4] (South Korea)	91	11	91 (100)	57 (63)[a]	-	-	15 (16)/4 (4)	15 (17)
Cura Yayla et al.[19] (Turkey)	220	10	220 (100)	217 (99)[b]	-	-	-/3 (1)	-
Lu et al.[20] (Wuhan)	171	6.7	171 (100)	131 (77)	23 (14)	-	2 (1)/15 (9)	-
Yonker et al.[21] (MA, USA)	49	12.7	49 (100)	33 (67)	-	9 (18)	9 (18)/-	-
Antunez-Montes et al.[22] (Latin America)	409	3	409 (100)	165 (40)	-	5 (1)	62 (15)/177 (43)	-

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]All household members included, author did not specify whether adult or sibling was the source.

[b]Both household and close contacts included in this data point.

(frequently $n = 1$), a lack of cord blood or amniotic fluid evidence (the gold standard to prove vertical transmission), and provide little or no information on the outcome of the infants. A more recent systematic review ($n = 205$ infants of COVID-positive mothers) found that while vertical transmission of COVID-19 is unlikely, antibodies against SARS-CoV-2 were found in 10/11 (90%) infants who were tested.[28] As pregnant women are more susceptible than the general population to respiratory pathogens including COVID-19, maternal infection and inflammation in response to the virus could affect the developing fetus and even postnatal life. With the continuing pandemic of COVID-19, there is general consensus further studies are warranted to investigate pregnant women with COVID-19, follow-up the pregnancy outcomes, and monitor postnatal development of the fetus.

2.1.3 | Breastfeeding

Based on the earliest 13 case studies/series ($n = 48$ milk samples from 32 women combined), only one sample contained virus, while SARS-CoV-2 antibodies were found in two other samples.[29] However, the sample collection and analytical methods were not provided in detail in these case reports, raising questions on methodological quality and potential for contamination. In a longitudinal study of two COVID-19 positive mothers following delivery (Day 0), the first mother's samples were all negative for SARS-CoV-2 RNA, but milk samples from days 10, 12, and 13 postdelivery were positive for the second mother.[30] The positive milk samples coincided with mild symptoms in the second mother and her infant tested positive for COVID-19 on Day 11. The first infant also tested positive for COVID-19, although viral RNA was absent in the first mother's samples.[30] In another study ($n = 64$ breastmilk samples from 18 COVID-19 positive mothers) viral RNA was isolated in one sample, but no replication-competent virus was detected.[31] Both breastmilk samples ($n = 37$ milk samples) and breast swabs ($n = 70$ swabs collected before and after cleaning the breast with soap and water before feeding) were analyzed from 18 COVID-19-positive women.[32] SARS-CoV-2 RNA was not present in the milk samples, but was present on one of the pre-cleaning swabs. Furthermore, SARS-CoV-2 antibodies were detected in all 37 milk samples.[32] In addition, a systematic review of 37 studies ($n = 77$ infants of COVID-positive mothers) found no evidence of SARS-CoV-2 transmission.[33] As SARS-CoV-2 transmission through breastmilk is unlikely, both the World Health Organization (WHO) and UNICEF currently recommend mothers with suspected or confirmed COVID-19 initiate or continue breastfeeding while following guidance on hygiene and mask use.[34,35] For situations requiring donor milk, pasteurization of human milk by the Holder method (62.5°C for 30 min) inactivates SARS-CoV-2.[36]

2.2 | Child Care

As of July 31, 52 (33 confirmed) SARS-CoV-2 cases had occurred in 29/666 (4.3%) child care facilities in Rhode Island.[37] Twenty of these facilities only reported a single case, with no evidence of secondary

transmission, while possible secondary transmission occurred in four centers, accounting for 17 cases. Contact tracing and testing data for child care facilities in Salt Lake City, Utah, in April–July, 2020, reported 31 confirmed cases of COVID-19 between three facilities, 42% (13/31) of which occurred in children.[38] Asymptomatic transmission from children to adult contacts was confirmed in two cases. Index cases for all three facilities were determined to be adult staff members.[38]

2.2.1 | School opening and transmission

Table 2 provides data from studies analyzing secondary transmission of SARS-CoV-2 in the school setting. In South Korea, children were not the primary source of transmission within schools, as secondary cases were all a result of contact with an infected staff member.[39] In England, staff had higher incidence rates than students and accounted for most cases linked to outbreaks.[40] In Ireland, no secondary transmission of COVID-19 was reported in a follow-up of 1025 exposed school contacts.[41] These exposures included activities such as music lessons and choir practice, both of which are assumed to be high-risk activities for transmission.[41] Of 18 cases of secondary transmission in Australia, five cases occurred in three schools and the other 13 occurred in a single early childhood education center where the cluster outbreak was traced to a single adult staff member.[42] The overall child-to-child SAR was 0.3% (2/649) and the child to staff SAR was 1.0% (1/103), while the staff-to-staff SAR was 4.4% (7/160) and the staff-to-child SAR was 1.5% (8/536).[42] In Switzerland, researchers randomly analyzed seroprevalence among 2585 students (6–16 years old) in 55 schools and found that at least one seropositive case was reported in 36/55 schools with no evidence of clustered outbreaks or secondary transmission.[10] In Hong Kong, only 5 of 20 cases in children (5–17 years old) were associated with two clustered school outbreaks.[43] In Germany, 137 COVID-19-positive students attended school for at least one day while infectious.[44] Only six of these cases contributed to the transmission of SARS-CoV-2 to an additional 11 students. No additional secondary transmission was reported despite extensive screening and monitoring of more than 2300 close school contacts.[44] Authors of both papers acknowledged the contribution of infection-control measures, such as social distancing and masking, to the low transmission rates.[43,44] Child-to-child transmission within the school

TABLE 2 SARS-CoV-2 secondary transmission in the school setting

Study	School types	SARS-CoV-2 index cases (age)	Contacts tested *n* (%)	Secondary infections	SAR
Yoon et al.[39] (South Korea)	5 kindergartens	5 students	670	0	0
	15 elementary schools	19 students	2453	1	0.04%
	8 middle schools	8 students	1962	0	0
	12 high schools	13 students	4747	0	0
Yung et al.[45] (Singapore)	Preschool A	1 student (5)	34	0	0
	Preschool B	1 adult staff	77 (73)	16 staff 0 students	0
	Secondary school	1 student (12)	8	0	0
Danis et al.[46] (French Alps)	3 schools	1 student (9) (visited all 3 schools while symptomatic)	55 (64)	0	0
Heavey et al.[41] (Rep. of Ireland)	1 primary school 2 seconday schools[a]	3 children 3 adult staff	-[b]	1 (staff to staff)	0
Macartney et al.[42] (Australia)	10 ECECs[c] 15 schools	12 students 15 adult staff	633 (44)	8 staff 10 students	1.2%
Ehrhardt et al.[44] (Germany)	childcare facilities primary schools secondary schools vocational schools	137 students (only 6 cases led to secondary infection)	>2300	11 students (an additional 4 students were infected from 2 staff members)	-
Stein-Zamir et al.[47] (Israel)	1 high school (grades 7–12)	2 students	1161 (99) students 151 (99) staff	153 students 25 staff	Students: 13.2% Staff: 16.6%

Abbreviations: ECEC, early childhood education and care centers; SAR, secondary attack rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Author did not specify the type of schools at which the adult staff members worked. Also, no clarification was made about whether more than one of the six cases was present in a single school.

[b]1025 contacts were monitored, symptomatic individuals were referred for testing, but exact numbers are unknown ± ECEC: early childhood education and care centers. Account for daycare, preschool and after-school care programs.

setting was uncommon and not the primary source of SARS-CoV-2 infection in children.[44]

Ten days after schools reopened in Jerusalem in May, 2020, two separate cases of COVID-19 in the same high-school led to the infection of almost 260 people.[47] Within the school community, 153 students and 25 staff members were infected. Overly crowded classrooms without appropriate social distancing and the suspension of mask-wearing for several days in response to a heat wave likely contributed to the outbreak.[47]

School infections peaked in Victoria, Australia, when community transmission was high, but transmission among children was not school driven.[48] Controlling community incidence is likely an effective means of controlling transmission within the educational setting.[40] In Sweden and Finland, the cumulative incidence rates of COVID-19 among school-age children were similar across both countries despite Sweden's decision not to close childcare facilities or primary schools. Health officials in Sweden concluded that school closures did not significantly impact the overall prevalence of COVID-19 among 1–19 year-olds.[49] Daycare, primary, or secondary school teachers were not at increased risk for SARS-CoV-2 infection.[49]

Children do not appear to be the primary drivers of SARS-CoV-2 transmission in the home or school settings and often present with mild or asymptomatic cases when infected.

3 | CLINICAL PRESENTATION IN CHILDREN

Table 3 summarizes 12 studies reporting clinical data of children with diagnosed or suspected COVID-19.[5] The heterogeneity in study participant selection criteria must be noted among these studies, which may have affected both clinical presentation and severity of the cases reported.

In a systematic review of literature regarding the clinical presentation of COVID-19 in children, the most commonly reported symptoms were fever and cough.[54] In a cohort study involving 651 pediatric cases in the UK, fever and a runny nose were more common in younger children, while vomiting, abdominal pain, headache and a sore throat showed an increasing trend with age.[50] Older children were more likely to present with respiratory distress than infants (44% vs. 7%).[17] Less common symptoms include seizures[16,50,53] and loss of taste and smell.[4,17]

A study of 2143 (731 laboratory-confirmed) pediatric cases reported to the Chinese Center for Disease Control and Prevention found that 94.1% of cases could be classified as asymptomatic, mild, or moderate.[5] The mild category (50.9%) included symptoms such as fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing.[5] In Turkey, of 220 positive pediatric cases, 145 (70.5%) were classified as asymptomatic (25.5%) or mild (45%).[19] In South Korea, 22% of COVID-19-positive study participants remained asymptomatic throughout a 3-week monitoring period.[4] A systematic review of studies (n = 4300 confirmed pediatric cases) reported that 18.9% of children were asymptomatic.[55] The majority of studies reported a mortality rate of less than 2% (Table 3).

There is a significant difference in the median age between studies, with the lowest being 2.3 years old[16] and the highest 13 years.[51] Infants (aged < 1 year) account for between 30% and 40% of participants in half of the studies (Table 3). The high proportion of infants could be influenced by a tendency for parents to seek medical attention for this age group and an increased likelihood that physicians will admit them to hospitals.[16] A multivariate analysis reported an association between neonatal period (<1 month of age) and ICU admission (odd ratio 5.06).[18,50]

Several studies noted that COVID-19 positive patients had elevated blood markers indicative of inflammation.[17,19,50,51,53] One study reported that 38.8% (47/121) of participants had high concentrations of the inflammatory marker C-reactive protein (CRP).[16] Moreover, children with more serious symptoms were found to have significantly higher CRP levels than those with a milder presentation.[17] In Turkey, lymphopenia was the most common abnormal lab value found amongst participants (13.5%; 85/220).[19]

While COVID-19 in children can present with a variety of symptoms, pediatric cases are most often mild or asymptomatic. In rare cases, children can develop severe complications following infection.

4 | COMPLICATIONS IN CHILDREN

4.1 | Multisystem inflammatory syndrome in children (MIS-C)

Starting in late April 2020, a hyperinflammatory syndrome likely related to COVID-19 has been reported in growing numbers of children.[56,57] This syndrome has been named multisystem inflammatory syndrome in children (MIS-C) and its clinical presentation has many similarities to Kawasaki Disease (KD)[58] and Toxic Shock Syndrome (TSS), particularly the elevation of multiple inflammatory markers with severe cardiac involvement.[50,56,59–62] In the UK, MIS-C is referred to as pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS).[63]

Table 4 summarizes 14 studies looking at patients with potential or diagnosed cases of MIS-C. The information is presented in table format for ease of viewing, but not necessarily for comparison among studies as they vary greatly in size and scope. Patient selection also varies among studies, with earlier studies responding to an unusual increase in KD cases in the pediatric population and selecting study cases from those with a definitive KD diagnosis. Later, as the medical and scientific community became aware of MIS-C as a distinct condition, more formal diagnostic characteristics were sought.[64] Since then, the WHO,[65] the Centers for Disease Control (CDC)[66] in the United States, and the Royal College of Paediatrics and Child Health[63] in the UK have all provided separate case definitions.

TABLE 3 Demography, clinical characteristics and outcomes of SARS-CoV-2 in children

Study	Patients *n*	Median Age	Infants (0-1 yrs) *n* (%)	Male *n* (%)	Positive SARS-CoV-2 RT-PCR *n* (%)	Underlying medical conditions *n* (%)	No symptoms *n* (%	Fever *n* (%)	Respiratory (cough/SOB) *n* (%)	Pneumonia *n* (%)	GI (vomiting/ diarrhea) *n* (%)	Hospitalized *n* (%)	ICU care/ mechanical ventilation *n* (%)	Mortality *n* (%)
Zachariah et al.[17] (New York)	50	11	14 (34)	27 (54)	50 (100)	33 (67)	0 (0)	40 (80)	23 (46)/ 17 (34)	-	7 (14)	50 (100)	-/9 (18)	1 (2)
Götzinger et al.[18] (Europe)	582	5	230 (40)[d]	311 (53)	582 (100)	145 (25)	92 (16)	379 (65)	313 (54)/-	93/198 (47)	128 (22)	363 (62)	48 (8)/25 (4)	4 (1)
Garazzino et al.[16] (Italy)	168	2.3	66 (39)	94 (56)	168 (100)	33 (20)	4 (3)	138 (32)	82 (49)/ 16 (10)	75 (45)	9 (5)/ 22 (13)	110 (65)	2 (1)/2 (1)	0 (0)
Swann et al.[50] (UK)	651	4.6	225 (35)	367 (56)	651 (100)	276 (42)	0 (0)	431/ 617 (70)	233/599 (39)/173/ 570 (30)	-	179/ 564 (32)	651 (100)	116/632 (18)/58/ 620 (9)	6/627 (1)
Dong et al.[5] (China)	2143	7	379 (18)	1213 (57)	731 (34)	-	94 (4)	-	-	-	-	-	-	-
Han et al.[4] (South Korea)	91	11	6 (7)	53 (58)	91 (100)	6 (7)	20 (22)	62 (68)	54 (60)	-	16 (18)	91 (100)[a]	0 (0)/0 (0)	0 (0)
Shekerdemian et al. [51] (USA/ Canada)	48	13	8 (17)	25 (52)	48 (100)	40 (83)	1 (2)	-	35 (73)	-	1 (2)	48 (100)	48 (100)/ 18 (38)	2 (4)
Cura Yayla et al.[19] (Turkey)	220	10	-	105 (48)	220 (100)[b]	22 (10)	55 (26)	89 (41)	79 (36)/9 (4)	74 (34)	9 (4)/17 (8)	220 (100)	3 (1)	2 (1)
Lu et al.[20] (Wuhan)	171	6.7	31 (18)	104 (61)	171 (100)	-	27 (16)	71 (42)	83 (49)/ 49 (29)	111 (65)	11 (6)/ 15 (9)	-	3 (2)/3 (2)	1 (1)
Parri et al.[52] (Italy)	100	3.3	40 (40)	57 (57)	100 (100)	27 (27)	21 (21)	28/ 54 (52)	44 (44)/ 11 (11)	20 (20)	10 (10)	67 (67)	-/1 (1)	0 (0)
Yonker et al.[21] (MA, USA)	49	12.7	2 (4)	23 (47)	49 (100)	-	0 (0)	25 (51)	23 (47)/8 (16)	-	3 (6)/3 (6)	-	-	-

(Continues)

TABLE 3 (Continued)

Study	Patients *n*	Median Age	Infants (0-1 yrs) *n* (%)	Male *n* (%)	Positive SARS-CoV-2 RT-PCR *n* (%)	Underlying medical conditions *n* (%)	No symptoms *n* (%	Fever *n* (%)	Respiratory (cough/SOB) *n* (%)	Pneumonia *n* (%)	GI (vomiting/ diarrhea) *n* (%)	Hospitalized *n* (%)	ICU care/ mechanical ventilation *n* (%)	Mortality *n* (%)
Chiara-Chilet et al.[53] (Perú)	91	6	28 (31)[d]	58 (64)	46 (51)	49 (54)	0 (0)	18 (40)	20 (18)/ 13 (14)	26 (37)[c]	11 (13)/-	91 (100)	22 (24)/-	9 (10)
Antunez-Montes et al.[22] (Latin America)	409	3	36 (9)	222 (54)	409 (100)	83 (20)	49 (12)	238 (58)	244 (60)	170 (42)	101 (25)	409 (100)	32 (10)/29 (7)	17 (4)

Note: GI symptoms include abdominal pain, vomiting, and diarrhea.

Abbreviations: Pna, pneumonia; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOB, shortness of breath.

[a]All children in study were placed in isolation, all but two of which were isolated in a hospital setting regardless of symptom status. Two children were placed in a nonhospital isolation unit (Han et al., 2020).

[b]9 (4) of total were confirmed via serum antibody testing.

[c]Abnormal chest radiography ± remaining 45 (49%) participants confirmed via Ab testing.

[d]Includes children <2 years of age.

4.2 | Clinical presentation of MIS-C

Fever, gastrointestinal complaints, rash, and conjunctivitis have been reported as the most prevalent symptoms MIS-C (Table 4), although a combination of these symptoms must be present in order for patients to meet the case definition for MIS-C or PIMS-TS.[64] Due to the overlapping clinical features of MIS-C and KD, RT-PCR and antibody testing are needed to confirm MIS-C.[58,60,67]

4.3 | MIS-C and SARS-CoV-2 testing results

Although the causality of MIS-C is currently inconclusive, several studies have noted an increase in cases 4–6 weeks following a spike in COVID-19 cases within a population.[50,62,69,72,73] In several studies, patients found to be negative for SARS-CoV-2 by RT-PCR were positive for SARS-CoV-2 antibodies.[56,59] SARS-CoV-2 RT-PCR was positive in 52% of cases, while SARS-CoV-2 antibodies were found in almost 71% of cases across all available studies (Table 4). Riphagen et al.[67] reported that all eight cases in their study tested negative for SARS-CoV-2 by RT-PCR, but no mention of antibody testing was noted.[67] Serum samples from 29 pediatric patients, showed that cases classified as MIS-C had higher IgG antibody titers than their non-MIS-C counterparts,[74] which is consistent with the delayed onset of MIS-C cases following COVID-19 exposure and/or infection.[74] UK patients with MIS-C who were antibody-positive were younger (median age 10.0 years vs. 12.4 years) and more likely to be of non-White ethnicity than those who were positive by RT-PCR,[50] suggesting that more testing is needed in younger and minority children. Conjunctivitis (71% vs. 16%) and abdominal pain (95% vs. 44%) were more common in patients positive for SARS-CoV-2 antibodies, whereas those who were diagnosed by RT-PCR testing were more likely to present with shortness of breath (52% vs. 14%).[50]

4.4 | MIS-C and patient characteristics

Due to the severity of the clinical presentation, children with MIS-C often require ICU-level care, especially to manage cardiac complications. In one study, children with MIS-C were five times more likely to be admitted to the ICU,[50] while another study reported that 14 of 15 MIS-C patients were admitted to the ICU within 24 h of hospital admission.[59] In Latin America, lower socioeconomic status was found to have a significant association with MIS-C diagnosis and the need for mechanical ventilation.[22] Different from adults, there are conflicting data regarding comorbidities that place children at higher risk for COVID-19 complications, and several studies reported that the majority of their pediatric subjects did not have any significant past medical history.[22,56,59,62,67] A possible exception to these findings was reported where five of six patients diagnosed with MIS-C had a pre-existing medical condition, four of whom were immunocompromised.[70]

TABLE 4 Demography, clinical characteristics and outcomes of multisystem inflammatory syndrome in children (MIS-C)

Study	Patients *n*	Median age *n* (%)	Male	Race/ethnicity[a] *n* (%)	Positive SARS-CoV-2 RT-PCR *n* (%)	Positive SARS-CoV-2 Ab *n* (%)	Underlying medical conditions *n* (%)	Primary (3) symptoms *n* (%)	Cardiac symptoms *n* (%)	Diagnosis of shock *n* (%)	ICU care/ mechanical ventilation *n* (%)	Mortality *n* (%)
Riollano - Cruz et al.[59] (New York)	15	12	11 (73)	10 (66) Hispanic/ Latino	9 (60)	15 (100)	4 (27%)	Fever: 15 (100); GI: 13 (87); Resp: 3 (20)	13 (87)	13 (87)	14 (93)/3 (20)	1 (7)
Riphagen et al.[67] (UK)	8	8	5 (63)	6 (75) Afro - Caribbean	2 (25)	-	2 (25)	Fever: 8 (100); GI: 8 (100); Conjunctivitis: 5 (63)	7 (88)	8 (100)	8 (100)/7 (88)	1 (13)
Whittaker et al.[64] (England)	58	9	38 (66)	22 (38) Black/ 18 (31) Asian	15 (26)	40/46 (87)	7 (12)	Fever: 58 (100) GI: 31 (58); Rash: 30 (52)	8 (14)	29 (50)	23 (40)/25 (43)	1 (2)
Feldstein et al.[56] (USA)	186	8.3	115 (62)	29 (40) Hispanic/ Latino	131 (70)[c]	-	51 (27)	Fever: 186 (100); GI: 171 (92); Rash: 110 (59)	149 (80)	90 (48)	148 (80)/37(20)	4 (2)
Verdoni et al.[60] (Italy)	10	7.5	7 (70)	8 (80) White	2 (20)	8 (80)	-	Diarrhea: 6 (60); Pna: 5 (50)	6 (60)	5 (50)	-	0 (0)
Toubiana et al.[62] (France)	21	7.9	9 (43)	12 (57) African Ancestry	8 (38)	19 (90)	0 (0)	GI: 21 (100); Conjunctivitis: 17 (81); Rash: 16 (76)	16 (76)	17 (81)	17 (81)/11 (52)	0 (0)
Grimaud et al.[57] (France)	20	10	10 (50)	-	10 (50)	15 (75)	-	Fever: 20 (100); GI: 20 (100); Rash: 20 (100)	20 (100)	20 (100)	20 (100)/8 (40)	0 (0)
Sadiq et al.[68] (Pakistan)	8	9.5	7 (88)	-	3 (38)	8 (100)	0 (0)	Fever: 8 (100); Conjunctivitis: 7 (88); GI: 6 (75)	5 (63)	2 (25)	2 (25)/1 (13)	1 (13)
Godfred-Cato et al.[69] (USA)	570	8	316 (55)	187 (41) Hispanic/ 153 (33) Black, non-Hispanic	302 (53)	418 (73)	194 (34)	GI: 518 (91); Resp: 359 (63); Conjunctivitis: 276 (48)	493 (87)	202 (35)	364 (64)/69 (13)	10 (2)
Pereira et al.[70] (Brazil)	6	8	5 (83)	-	4 (67)	-	5 (83)	Fever: 6 (100); Resp: 5 (83); GI: 4 (67)	6 (100)	5 (83)	5 (83)/5 (83)	4 (67)

(Continues)

TABLE 4 (Continued)

Study	Patients *n*	Median age *n* (%)	Male	Race/ethnicity[a] *n* (%)	Positive SARS-CoV-2 RT-PCR *n* (%)	Positive SARS-CoV-2 Ab *n* (%)	Underlying medical conditions *n* (%)	Primary (3) symptoms *n* (%)	Cardiac symptoms *n* (%)	Diagnosis of shock *n* (%)	ICU care/ mechanical ventilation *n* (%)	Mortality *n* (%)
Jain et al.[71] (India)	23	7.2	11 (48)	-	9 (39)	7 (30)	-	Fever: 23 (100); GI: 15 (70); Rash: 14 (65)	15 (65)	15 (65)	-/9 (40)	1 (4)
Torres et al.[72] (Chile)	27	6	14 (52)	(85)[b]	14 (52)	10 (37)	7 (26)	Fever: 27 (100); GI: 17 (63); Rash: 14 (52)	12 (46)	12 (44)	16 (59)/12 (44)	0 (0)
Swann et al.[50] (UK)	52	10.7	31 (60)	330 (51) White	28/50 (56)	22/50 (44)	15 (29)	Fever; Rash; Conjunctivitis	21/37 (57)	25 (48)	38 (73)/14 (27)	0 (0)
Mamishi et al.[61] (Iran)	45	7	24 (53)	-	10 (22)	35 (78)	6 (13)	Fever: (91); GI: (58); rash: (53)	25 (56)	5 (11)	-	5 (11)
Yonker et al.[21] (MA, USA)	18	7.7	14 (78)	9 (50) White	18 (100)	-	2 (11)	Fever: 18 (100); Rash: 5 (28); Vomiting: 5 (28)	-	-	-	-
Antunez-Montes et al.[22] (Latin America)	95	7	52 (55)	-	23 (24)	72/88 (82)	11 (12)	URI: 47 (50); GI: 43 (45); LRI: 23 (24)	11 (12)	14 (15)	20 (21)/9 (10)	2 (2)

Note: Cardiac symptoms ex. abnormal EKG, elevated serum troponin and/or BNP, coronary artery abnormalities, arrythmias, ventricular dysfunction, myocarditis; features of Kawasaki Disease: includes symptoms such as erythema and cracking of lips, strawberry tongue, rash, conjunctivitis, swollen hands and feet, myocarditis, lymphadenopathy (McCrindle et al.[58]); and features of shock: hypotension, tachycardia.

Abbreviations: Ab, antibodies; GI, gastrointestinal complaints ex. diarrhea, vomiting, abdominal pain; KD, Kawasaki Disease; LRI, lower respiratory tract infection ex. pneumonia, bronchitis; Pna, pneumonia; Resp, respiratory complaints ex. cough, shortness of breath; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; URI, upper respiratory tract infection ex. rhinitis, pharyngitis, tonsillitis, otitis.

[a]Largest racial or ethnic group(s) reported in each study. Language used is that of the authors. Swann et al.[50] reported that children of black ethnicity were over represented in their study population compared to the general population (10% vs. 4.7%). No other authors offered context for racial/ethnic data. It is also assumed that neither race nor ethnicity are mutually exclusive.

[b]85% of participant's parents reported being of Chilean descent.

[c]Value includes participants who tested positive for SARS-CoV-2 antibodies.

Though pediatric mortality rates are low, even among those diagnosed with MIS-C, there continues to be significant concern regarding which, if any, comorbidities place children at increased risk for COVID-19 infection.

5 | COMORBIDITIES AND SEVERITY

Obesity, chronic respiratory diseases (particularly asthma), and a compromised or suppressed immune system are the most common underlying medical conditions that have been cited. Table 5 summarizes 12 studies that have included comorbidity data.

5.1 | Obesity

Obesity was the most common comorbidity among hospitalized COVID-positive children, with a significant association between obesity and severe cases requiring mechanical ventilation in children 2 years and older.[17] A retrospective study from Wuhan, China reported that an elevated body mass index (BMI) was correlated with an increased mortality risk in COVID-19 patients aged 14–45 years.[79] In another study, 30% (14/46) of admitted pediatric patients testing positive for COVID-19 were obese, but no correlation was noted between obesity and ICU admissions.[75] Finally, an analysis of nationwide data from pediatric cases in Mexico reported that obese children were 39% more likely to have a SARS-CoV-2 infection.[77]

The effect of the COVID-19 lockdown policies on weight gain in children is also of concern. A cross-sectional survey of 584 households in the United States reported that families are buying more nonperishable and highly processed foods, and a third of families also reported an increase in their consumption of snack foods and desserts.[80] In a longitudinal study of 41 obese youth in Italy, the intake of food items linked to obesity, such as potato chips, red meat, and sugary drinks had increased significantly while time spent in sports activities had decreased during the first 3 weeks of the national lockdown.[81] The wide disruption in the diet and activities of children due to lockdown policies has the potential to worsen the ongoing obesity epidemic, which in turn places children at greater risk for COVID-19 infection.[82]

5.2 | Chronic respiratory disease

As COVID-19 is primarily a respiratory illness, asthma and other respiratory conditions were initially thought to place children at higher risk for more severe symptoms. However, there are conflicting data about the risk of COVID-19 in children with chronic respiratory illnesses. A study looking exclusively at COVID-19 patients receiving ICU care[51] did not show a significantly higher proportion of asthmatics than studies looking at all hospitalized children.[69] Underlying respiratory conditions were present in only 4.3% (21/491) of those requiring general care, while 10.4% (12/115) of those requiring ICU care reported the same.[50] Not one of 67 studies included in a systemic review reported asthma as a comorbidity or risk factor for children and COVID-19.[83] In a study of COVID-19 pediatric cases in Mexico, asthma was reported in 3.8% (806) of all cases, but was not associated with increased severity of infection; those reporting asthma were not more likely to develop pneumonia, nor were they at higher risk for hospitalization.[77]

Surprisingly, an Italian study reported a much lower prevalence of asthma in their pediatric COVID-19 cohort than in the general population (2% vs. 11%).[78] Researchers postulated the potential for asthma to act as a protectant due to adaptation in the immune response of pediatric asthmatics.[78] Behavioral factors may also have contributed to the lower prevalence of pediatric asthmatics among COVID cohorts. Several studies reporting a significant decrease in pediatric asthma-related visits to emergency departments and an increased utilization of telehealth raise the possibility that parents with vulnerable children are being proactive in protecting them against unnecessary exposure to COVID-19.[84,85]

5.3 | Immune system compromise

Comorbidities involving immunocompromise include organ transplants, malignancies, and aplastic anemia (Table 5). Notably, some studies used immunocompromised and immunodeficient interchangeably.[18] Individuals using immunosuppressants and those receiving chemotherapy and/or radiation are considered to be immunosuppressed.

Available data concerning the risk of COVID-19 in patients with immunodeficiencies and/or immunosuppression are contradictory. In a study of 91 pediatric cases in South Korea, none reported an existing immunodeficiency.[4] These 91 cases account for 76.5% of all pediatric cases in the country, excluding a cluster outbreak within a religious community.[4] In Spain, 8/51 (15%) of the total pediatric COVID-19 cases for a single month were immunocompromised.[86] Only 8.1% (53/599) of pediatric cases in the UK reported use of immunosuppressants before being hospitalized for COVID-19.[50] There was no association between immunosuppressant use and critical care admission.[50] In Mexico, immunodeficiencies were reported in 3.8% (808) of all cases and were associated with a four-fold increase of COVID-19 pneumonia and eight-fold increase in the risk of hospital admission.[77]

5.4 | Viral co-infections

In a retrospective study from China, researchers reported that 47.1% (16/34) of COVID-19-positive pediatric patients were infected with additional respiratory pathogens, including *Mycoplasma pneumoniae*, influenza type A and B, and respiratory syncytial virus (RSV).[87] In another study from China, 10 pediatric patients were extensively evaluated and all were negative for both common viruses (RSV, influenza, etc.), SARS-CoV, and MERS-CoV.[7] In Italy, 5.9% (10/168) of

TABLE 5 Demography and comorbidities of SARS-CoV-2 positive children

Study	Participants *n*	Median Age	Male *n* (%)	Comorbidities *n* (%)	Obesity[a] + *n* (%)	Chronic Respiratory Illness *n* (%)	Asthma *n* (%)	Immuno-compromised/ suppressed[b] *n* (%)
Zachariah et al.[17] (New York)	50	11	27 (54)	33 (67)	11 (22)	2 (4)	6 (12)	8 (16)
Shekerdemianet al.[51] (USA/Canada)	48	13	25 (52)	40 (83)	7 (15)	2 (4)	-	11 (23)
Chao et al.[75] (New York)	46	13	31 (67)	-	14 (30)	-	11 (24)	3 (7)
Godfred-Cato et al.[69] (U.S.)	570	8	316 (55)	-	146 (26)	48 (8)	-	-
Kim et al.[76] (USA)	576	8	292 (51)	94/222 (42)	42/111 (38)	40/222 (18)	30/222 (14)	12/222 (5)
Leon-Abarco[77](Mexico)	21,161	-	-	-	655 (3)	-	806 (4)	808 (4)
Ciprandi et al.[78] (Italy)	52	6.2	24 (46)	-	-	-	1 (2)	-
Garazzino et al.[16] (Italy)	168	2.3	94 (56)	33 (20)	-	7 (4)	-	3 (2)/4 (2)
Götzinger et al.[18] (Europe)	582	5	311 (53)	145 (25)	-	29 (5)[c]	16 (3)	3 (1)/29 (5)
Han et al.[4] (South Korea)	91	11	53 (58)	6 (7)	-	0 (0)	3 (3)	0 (0)
Swann et al.[50] (UK)	651	4.6	367 (56)	276 (42)	-	-	45/615 (7)	48/615 (8)/53/599 (9)
Yonker et al.[21] (MA, USA)	49	12.7	23 (47)	-	13 (27)	-	6 (12)	0 (0)
Antunez-Montes et al.[22] (Latin America)	409	3	222 (54)	83 (20)	-	-	-	18 (4)/12 (3)

Abbreviations: BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Obesity is defined as BMI (or sex and weight for length percentiles for patients younger than 2) at or above the 95th percentile for age.

[b]Solid organ transplant, hematologic malignancies, solid tumors, hematopoietic stem cell transplant recipient, aplastic anemia.

[c]Study explicitly states or demonstrates the inclusion of asthma in data point for chronic respiratory illness.

study participants had co-infections,[16] while in Perú, *M. pneumoniae* was found in 10% (9/91) of participants.[53] In Latin America, 3.4% (14/409) of participants tested positive for a viral co-infection, although no significant association was found between co-infections and ICU admission or mechanical respiratory support.[22] In contrast, in Europe, 5% (29/582) of participants tested positive for a viral co-infection and patients with one or more viral co-infections were more likely to have signs or symptoms of upper or lower respiratory tract infection at presentation.[18] Individuals with viral co-infection were also significantly more likely to require ICU admission, respiratory support, and vasoactive medications.[18]

Overall, there is limited data regarding the presence of viral coinfections within the COVID-19-positive pediatric population. There is also limited evidence regarding the influence of these co-infections in either increasing a patient's susceptibility to COVID-19 or in contributing to a more severe course of disease. With expected peaks of additional respiratory pathogens like influenza and respiratory syncytial virus during the winter season, we will likely experience the true impact of multiviral respiratory infections in terms of both incidence and clinical severity.

6 | SUMMARY

Preliminary findings are generally optimistic respecting incidence and severity of SARS-CoV-2 infection in the pediatric population. Children do not appear to be the primary source of transmission within either the household or school environments, and are most likely to contract the virus from an adult household member. As SARS-CoV-2 transmission through breastmilk is unlikely, the current recommendation for mothers with suspected or confirmed COVID-19 is to initiate or continue breastfeeding while following guidance on hygiene and mask use. Findings on perinatal transmission are inconclusive, and further studies of pregnancy outcomes and post-natal fetal development of infants of COVID-positive women are warranted.

The large proportion of cases studied thus far have shown that children often have a mild or asymptomatic presentation. While rare, there are hundreds of children in the United States that have met case definition for MIS-C.[69] Despite the potential for catastrophic outcomes, the WHO, the CDC, and the Royal College of Paediatrics and Child Health have all provided formal diagnostic criteria for MIS-C,[63,65,66] allowing for faster treatment and an overall positive prognosis for those children who are diagnosed.[69] In addition, mortality rates remain low.[50,56,64,69] Findings on chronic respiratory illnesses, compromised immunity, and viral co-infections as risk factors for COVID-19 in children are inconclusive, but comorbidities such as obesity are associated with a higher risk of infection and a more severe clinical course of disease.[17,75,77,79]

The lower incidence and severity of SARS-CoV-2 infections in children should not allow our focus to shift away from a highly vulnerable population with potential developmental implications. The novelty of COVID-19 has presented many challenges, but there are also unique opportunities to study longitudinally children that have been affected from infancy through childhood and into adulthood. Continued testing and longer-term investigations are warranted to provide data on risk factors for infection and MIS-C, long-term respiratory and developmental outcomes, as well as behavioral and lifestyle influences. Indeed, such knowledge may assist in framing public policy responses that would protect children and mitigate future epidemics.

ACKNOWLEDGMENTS

This study was supported by the National Science Foundation grant (2031761) and Dean's COVID-19 Rapid Response grant from Tulane University School of Public Health and Tropical Medicine; GP was supported by grant RO1 HL-061007 from the National Heart, Lung and Blood Institutes of Health; SHL was supported by grant P20GM109036 from the National Institute of General Medical Sciences of the National Institutes of Health. The funder/sponsor did not participate in the work.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Melissa K Siebach: conceptualization (supporting); methodology (equal); writing original draft (lead); writing review & editing (equal). **Giovanni Piedimonte**: writing original draft (supporting); writing review & editing (equal). **Sylvia H Ley**: conceptualization (lead); funding acquisition (lead); methodology (equal); supervision (lead); writing original draft (supporting); writing review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

ORCID

Giovanni Piedimonte https://orcid.org/0000-0003-1640-1928
Sylvia H. Ley https://orcid.org/0000-0003-0084-2630

REFERENCES

1. COVID-19 CDC. Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):422-426.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242.
3. Korean Society of Infectious Diseases, Korean Society of Pediatric Infectious Diseases, Korean Society of Epidemiology, Korean Society for Antimicrobial Therapy, Korean Society for Healthcare-associated Infection Control and Prevention, Korea Centers for Disease Control and Prevention. Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci*. 2020;35(10):e112.
4. Han MS, Choi EH, Chang SH, et al. Clinical characteristics and viral RNA detection in children With coronavirus disease 2019 in the

Republic of Korea [published online ahead of print August 28, 2020]. *JAMA Pediatr*. 2021;175:73. https://doi.org/10.1001/jamapediatrics.2020.3988
5. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702. https://doi.org/10.1542/peds.2020-0702
6. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020. Available at https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions. Accessed September 28, 2020.
7. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med*. 2020;26(4):502-505.
8. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis [published online ahead of print September 25, 2020]. JAMA Pediatr https://doi.org/10.1101/2020.05.20.20108126
9. Waterfield T, Watson C, Moore R, et al. Seroprevalence of SARS-CoV-2 antibodies in children: a prospective multicentre cohort study [published online ahead of print November 10, 2020]. *Arch Dis Child*. 2020. https://doi.org/10.1136/archdischild-2020-320558
10. Ulyte A, Radtke T, Abela IA, et al. Variation in SARS-CoV-2 seroprevalence in school-children across districts, schools and classes. *medRxiv*. 2020. https://doi.org/10.1101/2020.09.18.20191254
11. Pagani G, Conti F, Giacomelli A, et al. Seroprevalence of SARS-CoV-2 significantly varies with age: preliminary results from a mass population screening [published online ahead of print September 23, 2020]. *J Infect*. 2020;81:e10-e12. https://doi.org/10.1016/j.jinf.2020.09.021
12. Goyal MK, Simpson JN, Boyle MD, et al. Racial and/or ethnic and socioeconomic disparities of SARS-CoV-2 infection among children. *Pediatrics*. 2020;146(4):e2020009951. https://doi.org/10.1542/peds.2020-009951
13. Freeman MC, Gaietto K, DiCicco LA, et al. A comprehensive clinical description of pediatric SARS-CoV-2 infection in Western Pennsylvania. *medRxiv*. 2020. https://doi.org/10.1101/2020.12.14.20248192
14. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis of secondary attack rate. *JAMA Netw Open*. 2020;3(12):e2031756. https://doi.org/10.1001/jamanetworkopen.2020.31756
15. Nishiura H, Oshitani H, Kobayashi T. Closed environments facilitate secondary transmission of coronavirus disease 2019 (COVID-19). *medRxiv*. 2020. https://doi.org/10.1101/2020.02.28.20029272
16. Garazzino S, Montagnani C, Donà D, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. *Euro Surveill*. 2020;25(18):2000600.
17. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients With coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr*. 2020;174(10):e202430. https://doi.org/10.1001/jamapediatrics.2020.2430
18. Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661.
19. Cura Yayla BC, Ozsurekci Y, Aykac K, et al. Characteristics and management of children with COVID-19 in Turkey. *Balkan Med J*. 2020;37(6):341-347.
20. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *New Engl J Med*. 2020;382(17):1663-1665.
21. Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses [published online ahead of print August 20, 2020]. *J Pediatr*. 2020;227:45-52. https://doi.org/10.1016/j.jpeds.2020.08.037
22. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, et al. COVID-19 and multisystem inflammatory syndrome in Latin American children: a multinational study [published online ahead of print October 12, 2020]. *Pediatr Infect Dis J*. 2020;40:e1-e6. https://doi.org/10.1097/INF.0000000000002949
23. Schmidt E, Steinhagen K, Rupp J. Heavy exposure of children aged 9 to 12 years with SARS-CoV-2 did not lead to infection [printed online ahead of time September 12, 2020]. *J Pediatric Infect Dis Soc*. 2020;9:620-621. https://doi.org/10.1093/jpids/piaa116
24. Park YJ, Choe YJ, Park O, et al. Contact tracing during coronavirus disease outbreak, South Korea, 2020. *Emerg Infect Dis*. 2020;26(10):2465-2468.
25. Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, Yagil C. ACE2 expression and activity are enhanced during pregnancy. *Am J Physiol Regul Integr Comp Physiol*. 2008;296:1953-1961.
26. Thomas P, Alexander PE, Ahmed U, et al. Vertical transmission risk of SARS-CoV-2 infection in the third trimester: a systematic scoping review [published online ahead of print July 1, 2020]. *J Matern Fetal Neonatal Med*, 1-8. https://doi.org/10.1080/14767058.2020.1786055
27. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020;174(7):722-725. https://doi.org/10.1001/jamapediatrics.2020.0878
28. Bwire GM, Njiro BJ, Mwakawanga DL, Sabas D, Sunguya BF. Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: a living systematic review [published online ahead of print October 22, 2020]. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.26622
29. Lackey KA, Pace RM, Williams JE, et al. SARS-CoV-2 and human milk: what is the evidence? *Matern Child Nutr*. 2020;16:e13032. https://doi.org/10.1111/mcn.13032
30. Groß R, Conzelmann C, Müller JA, et al. Detection of SARS-CoV-2 in human breastmilk. *Lancet*. 2020;395(10239):1757-1758.
31. Chambers C, Krogstad P, Bertrand K, et al. Evaluation for SARS-CoV-2 in breast milk from 18 infected women. *JAMA*. 2020;324(13):1347-1348.
32. Pace RM, Williams JE, Järvinen KM, et al. COVID-19 and human milk: SARS-CoV-2, antibodies, and neutralizing capacity. *medRxiv*. 2020. https://doi.org/10.1101/2020.09.16.20196071
33. Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review [published online ahead of print August 28. *Ann N Y Acad Sci*. 2020;1484:32-54. https://doi.org/10.1111/nyas.14477
34. UNICEF. *Adoption of Breastfeeding Recommendations in the Context of COVID-19*. 2020. Available at https://mcusercontent.com/fb1d9aabd6c823bef179830e9/files/3a61b1ba-9a63-4500-a672-ed743fcfd904/Breastfeeding_survey_COVID19_Brief_final.pdf. Accessed October 3, 2020.
35. World Health Organization. Breastfeeding and COVID-19. 2020. Available at https://www.who.int/news-room/commentaries/detail/breastfeeding-and-covid-19. Accessed October 8, 2020.
36. Unger S, Christie-Holmes N, Guvenc F, et al. Holder pasteurization of donated human milk is effective in inactivating SARS-CoV-2. *CMAJ*. 2020;192(31):E871-E874.
37. Link-Gelles R, DellaGrotta AL, Molina C, et al. Limited secondary transmission of SARS-CoV-2 in child care programs - Rhode Island, June 1-July 31, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(34):1170-1172.
38. Centers for Disease Control and Prevention. Transmission dynamics of COVID-19 outbreaks associated with child care facilities — Salt Lake City, Utah, April–July 2020 | MMWR. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1319-1323.

39. Yoon Y, Kim K-R, Park H, Kim S, Kim Y-J. Stepwise school opening online and off-line and an impact on the epidemiology of COVID-19 in the pediatric population. *J Korean Med Sci*. 2020;35(46):e414. https://doi.org/10.3346/jkms.2020.35.e414
40. Ismail SA, Saliba V, Lopez Bernal J, Ramsay ME, Ladhani SN. SARS-CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England [published online ahead of print December 8, 2020]. *Lancet Infect Dis*. 2020;21:344-353. https://doi.org/10.1016/s1473-3099(20)30882-3
41. Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. *Euro Surveill*. 2020;25(21):2000903. https://doi.org/10.2807/1560-7917.ES.2020.25.21.2000903
42. Macartney K, Quinn HE, Pillsbury AJ, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. *Lancet Child Adolesc Health*. 2020;4(11):807-816.
43. Fong MW, Cowling BJ, Leung GM, Wu P. Letter to the editor: COVID-19 cases among school-aged children and school-based measures in Hong Kong, July 2020. *Euro Surveill*. 2020;25(37):2001671. https://doi.org/10.2807/1560-7917.ES.2020.25.37.2001671
44. Ehrhardt J, Ekinci A, Krehl H, et al. Transmission of SARS-CoV-2 in children aged 0 to 19 years in childcare facilities and schools after their reopening in May 2020, Baden-Württemberg, Germany. *Euro Surveill*. 2020;25(36):2001587. https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001587
45. Yung CF, Kam K, Nadua KD, et al. Novel coronavirus 2019 transmission risk in educational settings [published online ahead of print June25. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa794
46. Danis K, Epaulard O, Bénet T, et al. Cluster of Coronavirus Disease 2019 (COVID-19) in the French Alps, February 2020. *Clin Infect Dis*. 2020;71(15):825-832.
47. Stein-Zamir C, Abramson N, Shoob H, et al. A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. *Euro Surveill*. 2020;25(29):2001352.
48. Russell FM, Ryan K, Snow K, Danchin M, Mulholland K, Goldfeld S *COVID-19 in Victorian schools: an analysis of child-care and school outbreak data and evidence-based recommendations for opening schools & keeping them open*. 2020. Available at: https://www.mcri.edu.au/sites/default/files/media/covid_in_schools_report_final_10112020_exec_summary.pdf. Accessed October 1, 2020.
49. Public Health Agency of Sweden. COVID-19 in schoolchildren – A comparison between Finland and Sweden. 2020. Available at: http://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/c/covid-19-in-schoolchildren/. Accessed October 1, 2020.
50. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249. https://doi.org/10.1136/bmj.m3249
51. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children With coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020;174(9):1-6.
52. Parri N, Lenge M, Buonsenso D. Group CIiPEDCR. Children with Covid-19 in pediatric emergency departments in Italy. *N Engl J Med*. 2020;383(2):187-190. https://doi.org/10.1056/NEJMc2007617
53. Chilet CC, Vilchez ML, Afaray JM, et al. Clinical-epidemiological and treatment characteristics of children with COVID-19 in a tertiary referral center in Perú. *medRxiv*. 2020. https://doi.org/10.1101/2020.09.18.20186866
54. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review [published online ahead of print July 29, 2020]. *Pediatr Pulmonol*. 2020;55:2565-2575. https://doi.org/10.1002/ppul.24991
55. Liu C, He Y, Liu L, Li F, Shi Y. Children with COVID-19 behaving milder may challenge the public policies: a systematic review and meta-analysis. *BMC Pediatr*. 2020;20(1):410.
56. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *New Engl J Med*. 2020;383(4):334-346.
57. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care*. 2020;10(1):69.
58. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. https://doi.org/10.1161/cir.0000000000000484
59. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. Multisystem inflammatory syndrome in children related to COVID-19: a New York City experience [published online ahead of print June 25, 2020]. *J Med Virol*. 2020;93:424-433. https://doi.org/10.1002/jmv.26224
60. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778.
61. Mamishi S, Movahedi Z, Mohammadi M, et al. Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in 45 children: a first report from Iran. *Epidemiol Infect*. 2020;148:e196. https://doi.org/10.1017/S095026882000196X
62. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. https://doi.org/10.1136/bmj.m2094
63. Royal College of Paediatrics and Child Health. Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). 2020. Available at: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims. Accessed September 25, 2020.
64. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269.
65. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. 2020. Available at: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed September 25, 2020.
66. Centers for Disease Control and Prevention. HAN Archive - 00432 | Health Alert Network (HAN). 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed September 25, 2020.
67. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608.
68. Sadiq M, Aziz OA, Kazmi U, et al. Multisystem inflammatory syndrome associated with COVID-19 in children in Pakistan. *Lancet Child Adolesc Health*. 2020;4(10):e36-e37.
69. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080.
70. Pereira MFB, Litvinov N, Farhat SCL, et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. *Clinics (Sao Paulo)*. 2020;75:e2209.
71. Jain S, Sen S, Lakshmivenkateshiah S, et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India [published online ahead of print August 11. *Indian Pediatr*. 2020;57:1015-1019. https://doi.org/10.1007/s13312-020-2026-0

72. Torres JP, Izquierdo G, Acuña M, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic [published online ahead of print August 31, 2020]. *Int J Infect Dis*. 2020;100:75-81. https://doi.org/10.1016/j.ijid.2020.08.062
73. Belot A, Antona D, Renolleau S, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. 2020;25(22):2001010. https://doi.org/10.2807/1560-7917.ES.2020.25.22.2001010
74. Anderson EM, Diorio C, Goodwin EC, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19 [published online ahead of print December 2, 2020]. *J Pediatric Infect Dis Soc*. 2020. https://doi.org/10.1093/jpids/piaa161
75. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. *J Pediatr*. 2020;223:14-19. https://doi.org/10.1016/j.jpeds.2020.05.006
76. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged < 18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1081-1088.
77. Leon-Abarca JA. Obesity and immunodeficiencies are the main pre-existing conditions associated with mild to moderate COVID-19 in children [published online ahead of print August 12, 2020]. *Pediatr Obes*. 2020;15. https://doi.org/10.1111/ijpo.12713
78. Ciprandi G, Licari A, Filippelli G, Tosca MA, Marseglia GL. Children and adolescents with allergy and/or asthma seem to be protected from coronavirus disease 2019. *Ann Allergy Asthma Immunol*. 2020;125(3):361-362.
79. Zhang F, Xiong Y, Wei Y, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients [published online ahead of print May 21, 2020]. *J Med Virol*. 2020;92:2536-2542. https://doi.org/10.1002/jmv.26039
80. Adams EL, Caccavale LJ, Smith D, Bean MK. Food insecurity, the home food environment, and parent feeding practices in the era of COVID-19 [published online ahead of print August 6, 2020]. *Obesity (Silver Spring)*, 2020. https://doi.org/10.1002/oby.22996
81. Pietrobelli A, Pecoraro L, Ferruzzi A, et al. Effects of COVID-19 lockdown on lifestyle behaviors in children with obesity living in Verona, Italy: a longitudinal study. *Obesity (Silver Spring)*. 28(8), 2020:1382-1385.
82. Nogueira-de-Almeida CA, Del Ciampo LA, Ferraz IS, Del Ciampo IRL, Contini AA, Ued FDV. COVID-19 and obesity in childhood and adolescence: a clinical review. *J Pediatr (Rio J)*. 2020;96(5):546-558.
83. Castro-Rodriguez JA, Forno E. Asthma and COVID-19 in children: a systematic review and call for data. *Pediatr Pulmonol*. 2020;55(9):2412-2418. https://doi.org/10.1002/ppul.24909
84. Simoneau T, Greco KF, Hammond A, Nelson K, Gaffin JM. Impact of the COVID-19 pandemic on pediatric emergency department utilization for asthma [published online ahead of print December 4, 2020]. *Ann Am Thorac Soc*. 2020:AnnalsATS.202007-765RL. https://doi.org/10.1513/AnnalsATS.202007-765RL
85. Taquechel K, Diwadkar AR, Sayed S, et al. Pediatric asthma health care utilization, viral testing, and air pollution changes during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*. 2020;8(10):3378-3387. https://doi.org/10.1016/j.jaip.2020.07.057
86. Pérez-Martinez A, Guerra-García P, Melgosa M, et al. Clinical outcome of SARS-CoV-2 infection in immunosuppressed children in Spain [published online ahead of print August 30, 2020]. *Eur J Pediatr*. 2020;180:967-971. https://doi.org/10.1007/s00431-020-03793-3
87. Zhang C, Gu J, Chen Q, et al. Clinical characteristics of 34 children with coronavirus disease-2019 in the west of China: a multiple-center case series. *PLoS Med*. 2020;17:e1003130. https://doi.org/10.1371/journal.pmed.1003130

How to cite this article: Siebach MK, Piedimonte G, Ley SH. COVID-19 in childhood: Transmission, clinical presentation, complications and risk factors. *Pediatric Pulmonology*. 2021; 56:1342–1356. https://doi.org/10.1002/ppul.25344