

The Evolving Epidemiologic and Clinical Picture of SARS-CoV-2 and COVID-19 Disease in Children and Young People

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UNICEF Office of Research | Innocenti Working Paper

WP-2020-07 | August 2020

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August 2020

This Innocenti Working Paper has been published without undergoing layout, copy-editing or proofreading. It is being released to rapidly share results of our work with the wider research and practitioner communities, and to encourage discussion of methods and findings.

Abstract: The initial impression that paediatric SARS-CoV-2 infection is uncommon and generally mild has been replaced by a more nuanced understanding of infectious manifestations in children and adolescents across low-, middle-, and high-income countries, with recognition of a widening disease spectrum. Critical knowledge gaps, especially in low- and middle-income countries, remain that have significant public policy and programme implications. Insufficient data disaggregated by age, geography and race/ethnicity are hindering efforts to fully assess prevalence of infection and disease manifestations in children and adolescents and their role in transmission. Potential biologic differences in susceptibility to infection and transmissibility between children, adolescents and adults need to be assessed. Determination of mother-to-child SARS-CoV-2 transmission during pregnancy, the peripartum period, or through breastfeeding requires appropriate samples obtained with proper timing, lacking in most studies. Finally, predictors of disease progression, morbidity and mortality in children need to be determined and whether these predictors vary by geographic location and in settings where poor nutritional and health conditions and other vulnerabilities are more frequent. Countries, UN agencies, public health communities, donors and academia need to coordinate the efforts and work collectively to close the data and knowledge gaps in all countries (high-, middle- and low-income) for better evidence to guide policy and programme decision-making for children and COVID-19 disease.

Keywords: COVID-19, SARS-CoV2, Children, Adolescents, Young people, disease, infection, MIS-C, co-morbidities, transmission, income-level, demographics, testing, data, disaggregated.

Acknowledgements

This paper was commissioned by UNICEF Office of Research – Innocenti to examine the state of the science on epidemiology of SARS-CoV-2/COVID-19 in children and adolescents. Its purpose is to synthesize the best and latest data and research on COVID-19, and draw conclusions based on the facts that can inform practitioners, policy, and programming. The paper will be updated monthly up to November 2020 as more and new evidence emerges.

We also acknowledge the constructive inputs and comments received from Kate Strong, Regina Guthold, Theresa Diaz, David Ross and Nigel Rollins of the World Health Organization, and Gunilla Olson, UNICEF Office of Research and Luwei Pearson, UNICEF Health Section.

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KEY FINDINGS AND RECOMMENDATIONS

- The risks of SARS-CoV-2 infection in children and young people appear to differ geographically, with reported COVID-19 disease cases in children and adolescents varying widely between countries; however, this may reflect differences in testing practices between countries. A higher proportion of cases among the under-20s have been reported in low- and middle-income countries, but there has been a shift in age over time in COVID-19 cases in many pandemic settings to younger individuals, including adolescents.
- Some studies have found the susceptibility to SARS-CoV-2 infection in children and young people under 20 was approximately half that of adults. However, selective testing for the virus may mean that many cases among children and young people are going undiagnosed, and differentiation of the proportion of cases by age group among children and adolescents is often not provided.
- Predictors of disease progression and severe morbidity and mortality in children must be determined. As with adults, the existence of non-infectious and infectious co-morbidities and vulnerabilities—including obesity and other forms of malnutrition—may increase the severity of COVID-19 disease and mortality in children, especially in those residing in regions with significant poverty, high population density and crowding, and elevated levels of other underlying health conditions.
- Alarming, in some countries like the United States of America and the United Kingdom of Great Britain, risks of increased infection and disease severity correspond with equity lines, with certain ethnicities and income groups at greater risk of severe illness and death from COVID-19 disease.
- The role of children and adolescents in transmission of SARS-CoV-2 infection requires rapid evaluation. Available evidence suggests transmission risk may be lower from younger children to other children and adults than from adults to children or adults, but further evaluation is needed determine whether children will play a more substantive role in community spread once mitigation measures are eased. Additionally, transmission risk from adolescents appears similar to adults, and there may be a growing role of younger adults and adolescents in community transmission over time.
- Modelling scenarios have found a high risk of indirect health and social impacts of the pandemic on child, adolescent and maternal health. For example, with disruption in essential health care, including HIV, malaria and tuberculosis treatment and prevention services, it is anticipated there may be an increase in under-five and maternal deaths, mother-to-child HIV transmission, and HIV, tuberculosis and malaria deaths due to reduced timely diagnosis and treatment and prevention activities.

- The newly emerging multisystem inflammatory syndrome (MIS-C) further underscores the need for better reporting, monitoring and analysis to understand the COVID-19 disease health risks for children and young people. There may be a widening spectrum of COVID-19-related disease in children, ranging from asymptomatic to post-infection conditions including MIS-C.
- But critical knowledge gaps persist, especially in low- and middle-income countries. This research report is an urgent call for disaggregated data, especially as the pandemic evolves and expands in low resource settings, where children are at greater risk of poor nutritional and health conditions as well as other vulnerabilities.
- Effective, context-specific policies and programmes must be informed by an understanding of the patterns of vulnerability across age, sex, race/ethnicity, income, geography and intersections with co-morbidities and underlying vulnerabilities.
- The authors call on governments, UN agencies, public health communities, donors and academia to coordinate their efforts and work collectively to close the data and knowledge gaps on SARS-CoV-2 infection/COVID-19 disease, and make data publicly available for better evidence to guide policy and programme decision-making for children and adolescents.

1. Introduction

In December 2019, a novel coronavirus - Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in Wuhan City, China, causing a cluster of cases of severe pneumonia (Huang C). The coronavirus virus rapidly spread, resulting in an epidemic throughout China and evolving into a global pandemic with increasing number of cases worldwide. In February 2020, the World Health Organization designated the disease caused by SARS-CoV-2 virus as COVID-19 disease (shorthand for Coronavirus Disease 2019). Individuals of all ages are susceptible to SARS-CoV-2 infection, but older age and underlying co-morbidities are known to be associated with increased risk of disease severity and mortality. However, despite the rapidly increasing amount of evidence on SARS-CoV-2 infection and COVID-19 disease, data and

evidence on how it affects children (age <10 years) and adolescents (age 10-19 years) remain limited and conflicting, with an increased spectrum of disease manifestations emerging (e.g., multisystem inflammatory syndrome). There is a wide knowledge gap between high- and low-/middle-income countries (LMICs), both because the pandemic has emerged later among LMICs and the resources to conduct the needed epidemiologic and clinical studies are more limited in such settings. Critical data and research needs have emerged with important public policy and programme implications.

Given the rapid growth and evolving nature of evidence on paediatric SARS-CoV-2 and COVID-19 disease, a scoping review of the scientific literature and data was conducted related to

SARS-CoV-2/COVID-19 disease in children and adolescents. The paper reviews the evidence on the epidemiology of SARS-CoV-2 infection in children and adolescents accumulated over the past eight months since the COVID-19 pandemic has started, susceptibility and transmissibility of infection in children and adolescents, potential for mother to child transmission during pregnancy and breastfeeding, and clinical manifestations of disease (morbidity and mortality) in children and adolescents, including in relation to pre-existing co-morbidities and vulnerabilities. The paper uses data from published scientific literature and online data from 42 countries with such data publicly available online (Annex 1). The paper acknowledges the critical data and evidence gaps for children and adolescents due to lack of age disaggregation and limited public availability of comparable data, especially from low- and middle-income countries.

The review focuses on the following:

- The burden of COVID-19 disease in children and adolescents by country and income group and as a percentage of all cases for the 42 countries (or 22 per cent of 188) that have age disaggregated data publicly available online.
- Clinical features of the SARS-CoV-2 and COVID-19 disease in children and how they compare with adults, including co-morbidities and severity of disease (from published scientific research articles mainly in high-income countries).
- Transmissibility between children and adolescents to other children/adolescents and to adults, including mother to child transmission (from published scientific research articles mainly in high-income countries).
- Evolving severity of disease in children and adolescents in the form of the multi inflammatory syndrome (MIS-C) (from published scientific research articles mainly in high-income countries).
- The final section has the conclusions and policy, programme and data and research implications.

2. Literature and Data Scoping and Search Criteria

A scoping review of the literature from PubMed, supplemented by periodic review of pre-print papers from Science Direct and MedRxiv, was conducted for reports published between January 2, 2020 through June 27, 2020 using terms “newborns or neonates or children or adolescents” and “SARS-CoV2”, “COVID-19” and “novel coronavirus”. An update to the review was conducted through August 10, 2020 for new publications of relevance. This review was focused on papers reporting on the epidemiology, factors associated with transmission, and the clinical features and disease manifestations of SARS-CoV-2/COVID-19 disease in infants, children, and adolescents. As of February 2020, two groups were conducting ongoing systematic reviews of journal articles on COVID-19 and maternal and child health: the American Academy of Pediatrics (Boast) and The Johns Hopkins Center for Humanitarian Health (Johns Hopkins). These ongoing systematic review sites are reviewed for additional papers that would address the focus noted above. Annex 1 provides links to the online data on COVID 19 prevalence from 42 countries with such data publicly available online.

Given we are just eight months into the pandemic and the urgent need for information, studies to date have been produced rapidly with

varying quality, with most from high-income countries (HICs). Some studies are small case series, and some reports have included suspected, as well as, confirmed cases. The scoping review tried to focus on studies with larger sample size (as opposed to case reports or small case series) that included individuals with laboratory-proven infection. However, for some topics, such as neonatal infection with SARS-CoV-2, case reports were included. A total of 1,232 papers were reviewed, of which 224 met the criterion and were included in the scoping review.

There is no public global database with age disaggregated data, hence the COVID-19 disease caseload data for children and adolescents were accessed from 42 country-specific online databases, dashboards and published reports, where publicly available (Annex 1).

The following provides a summary of the current epidemiology of SARS-CoV-2 and COVID-19 disease in children across countries and the evolving manifestations of infection and disease in the paediatric and adolescent population, identifying gaps in the current data and knowledge base and provide policy, programme and evidence implications.

3. The Current Situation of SARS-CoV-2/COVID-19 and Children and Adolescents

Eight months after COVID-19 first appeared, a clear understanding of how it affects children and adolescents is still lacking; the dominant narrative is that incidence and severity of SARS-CoV-2 infection /COVID-19 disease remains low among children

It should be noted that there is a general possibility of underreporting of COVID-19 cases—as patients with mild symptoms,

especially children and adolescents, may not be counted and reported, as they might not have been tested in some countries. Initial epidemiologic data on COVID-19 disease from China suggested that children and adolescents had significantly lower rates of and less severe COVID-19 disease than adults, with 2 per cent of confirmed cases aged 0–19 years, despite 24 per cent of the population being in this age group, and 0.9 per cent aged <10 years (12 per cent of the population), and no deaths in children age <10 years (Pan, Zhang Y). Subsequent data from additional countries, mainly high-income, continue to report low numbers of children diagnosed with COVID-19. Children continue to constitute a low proportion of those diagnosed with COVID-19 in reports from Europe and United States. However, the exact incidence of COVID-19 in children is difficult to ascertain. Global data are not readily available disaggregated by age, and country data likewise lack age breakdown or may only provide aggregate data for those <20 years. Data on the proportional age breakdown between birth to 19 years is limited, and existing reports or databases often use different and overlapping age categories.

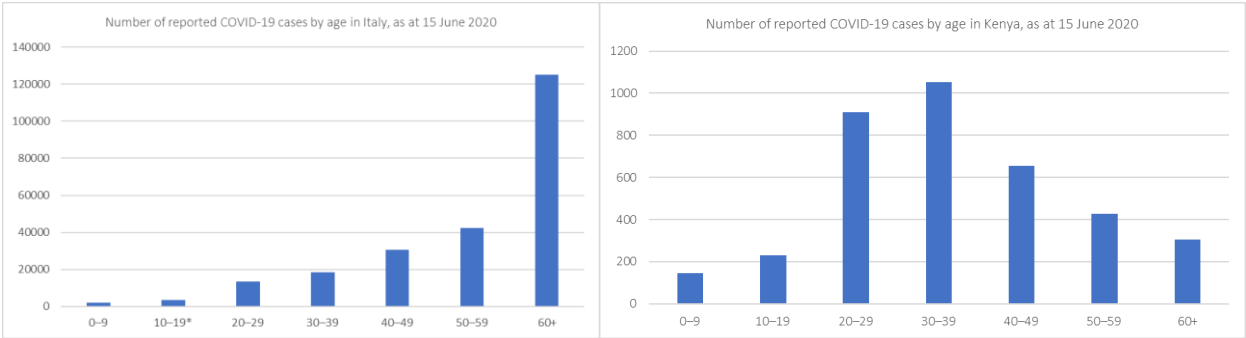
...although there appears to be wide variation among countries

The common narrative, at least for now, is that children and adolescents (0–19 years) have been largely spared the adverse direct effects of SARS-CoV-2 and COVID-19 disease on their own health and survival. This narrative is based predominantly on early data from the first affected countries of the virus, notably from China (Wuhan Province) and Italy in early 2020, and other high-income countries including the United States and European nations. But demographic profiles differ widely among countries, and assumptions and narratives made on evidence taken from ageing societies and mainly from high-income countries may not hold

for more youthful and growing populations in low- and middle-income countries (LMICs). The vast majority of the world’s children and adolescents live in LMICs, and with the observed upward trend in reported COVID-19 caseloads in these and in high-income settings, it is imperative to evaluate the direct effects of the disease on children and adolescents. The data below, despite the limitations, illustrate the

contrast between the age cohort profiles of COVID-19 caseloads for Kenya and Italy (*Figure 1*), and suggests that children worldwide may be more affected by COVID-19 disease as the pandemic continues than the dominant narrative so far suggests. This contrasting pattern is observed for other countries as well, with available data.

Figure 1: Number of reported COVID-19 cases by age in Italy and Kenya, as of June 2020



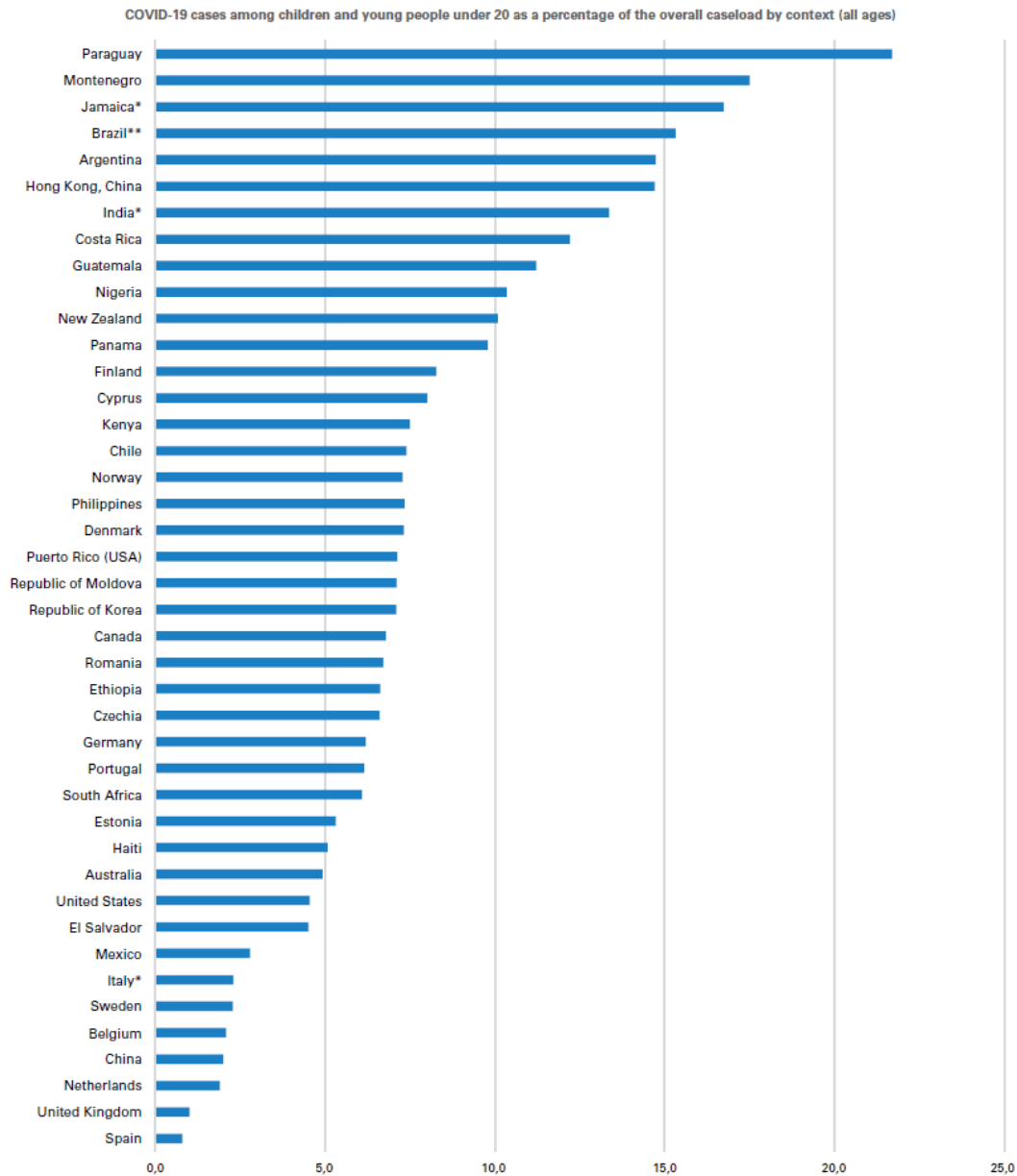
Note: *Age range is 10-18 years
Source: Statista, 'Distribution of Coronavirus Cases in Italy as of June 22, 2020, by Age Group. Available at: <www.statista.com/statistics/1103023/coronavirus-cases-distribution-by-age-group-italy>, accessed 15 June 2020

Source: Kenya, Ministry of Health, 'COVID-19 Outbreak in Kenya: Daily situation report – 90', 15 June 2020. Available at: <www.health.go.ke/wp-content/uploads/2020/06/Kenya-SITREP-090-15-Jun-2020.pdf>, accessed 15 June 2020.

Data from 42 country-specific publicly available online surveillance databases, dashboards and reports indicate that there is a broad spectrum of COVID-19 burden among those <20 years as a share of national caseloads, ranging from 23 per cent in Paraguay to just 1 per cent in Spain as of 15 June 2020 (*Figure 2*). This may be indicative of differences in demographic structures of high- and low-income countries or

differing policies related to SARS-CoV-2 diagnostic testing; if testing is confined to individuals with severe disease, children may be less likely to be tested as they appear to have milder disease with infection. Accurate, age-disaggregated data are critical to better understand the geographic variations and age distribution in paediatric cases and for design of context specific policies and programmes.

Figure 2: COVID-19 infections among children and adolescents (<20 years) as a share of total national caseloads varies widely among countries, June 2020



Note: * Uses different age definitions, intervals or overlapping categories: Italy age range is 0–18 years; India age ranges overlap (0–10 years and 10–20 years); Jamaica and Nigeria age range is 0–20 years.

** Brazil includes cases reported on admission to hospital only.

Source: Authors analysis based on reported COVID-19 cases from various country specific online databases, dashboards and reports (see *Annex 1* for list of countries and web links of sources of data)

Additionally, there has been a shift in age over time in COVID-19 cases in some pandemic settings. In the United States, there has been a steady increase in the number and rate of COVID-19 cases in children, particularly those over age 5 years. As of August 17 2020, 7.3 per cent of cases in the United States were in children under age 18 years (1.7 per cent in children 0–4 years and 6.1 per cent in those 5–17 years); this contrasts with 1.7 per cent of cases being in children in April 2020 (CDC COVID-19 April 2020; COVID-Data Tracker www.cdc.gov/covid-data-tracker/index.html#demographics). Using national data on COVID-19 cases in Germany comparing the relative risk of a COVID-19 case being in a given age group in the early vs later period of the pandemic, there was a relative increase over time in the prevalence of infection in persons age 15–34 years (particularly those 20–24 years) relative to other age groups (Goldstein). Similar findings were reported in Spain and in Washington State in the US (Malmgren MedRxiv, de Salazar MedRxiv). Thus, while children, adolescents and young adults may be more likely to have asymptomatic or mild infection, there may be a growing role of younger adults and adolescents in transmission in the community over time.

Population-based surveillance and studies of SARS-CoV-2 infection, which could better determine the risk faced by children and adolescents to the virus and disease, has been relatively limited and have inconsistent results

With screening for SARS-CoV-2 predominantly based on symptoms of COVID-19 disease, the true extent of SARS-CoV-2 infections among children and the wider community is unknown. Information regarding SARS-CoV-2 infection requires population-based surveillance, which has been relatively limited. The Viner meta-analysis evaluated eight published/pre-print population prevalence studies (VinerMedRxiv).

Because of significant differences in the populations studied (demography, exposure history, time-point in the epidemic) and differences in defining infection (virologic testing to evaluate incidence of current infection versus serologic testing to evaluate prevalence of past infection), a meta-analysis was not able to be done.

Four studies (two viral prevalence studies in Iceland and Italy and two seroprevalence studies from the Netherlands and Spain) suggested a lower SARS-CoV-2 seroprevalence in children than adults while four studies (two viral prevalence studies in Stockholm and United Kingdom and two serosurveys from Geneva and Gangelt, Germany) showed no difference in SARS-Cov-2 seroprevalence between children and adults.

The Geneva serosurvey data were published on June 11 including a larger number of individuals (2,766 participants from 1,339 households), and now report a lower seroprevalence, 0.8 per cent among 123 children aged 5–9 years tested compared with 9.6 per cent in 332 adolescents age 10–19 years, which was similar to 1,942 individuals age 20–64 years, 8.8 per cent (Stringhini). In contrast, updated data from the United Kingdom pilot national serosurvey of 9,912 households conducted between April 26 and June 18 2020 continues to report no difference in seroprevalence between children age 2–11 years (0.38 per cent, 95 per cent CI 0.16-0.75) seropositive), 12–19 years (0.30 per cent, 95 per cent CI 0.11-0.66), and those >20 years (ranging from 0.33-0.57 per cent) (UK Office for National Statistics).

In a recent cross-sectional seroprevalence study using residual clinical specimens from 2 commercial laboratories from 16,025 persons (1,205, or 7.5 per cent, were age <18 years) from 10 geographically diverse cities in the United States, seroprevalence ranged from 1.0 to 6.9 per cent, with no clear association with

age; seroprevalence in those <18 years ranged from 0.7 to 5.8 per cent (Havers JAMA Int Med)

Thus, findings from the the contact tracing and the population-based studies are inconsistent, and most had small numbers of children and adolescents included. There are currently insufficient data to draw definitive conclusions regarding SARS-CoV-2 infection susceptibility, incidence and prevalence in children and adolescents. Most studies do not provide an age breakdown that differentiates younger children from older children/adolescents, and this may mask differences in susceptibility between younger children and older children/adolescents. For example, recent data from a review of 22,333 SARS-CoV-2 rtPCR tests conducted at a tertiary care hospital in New Zealand showed a significantly lower proportion of positive tests in children age <10 years (0.08 per cent) compared to those 10-14 years (2.6 per cent), while those in children 10-14 years was slightly higher than in adults age 20+ (1.5 per cent) (Chhibber).

The narrative is also based on limited age-disaggregated data in terms of quantity and consistency

It is difficult to determine proportional age breakdown of COVID-19 cases within the 0 to 19-year age range for children and adolescents. Data are limited, and the existing databases and reports often use different age categories (e.g., 1–5 years and 6–10 years versus 1–4 years and 5-9 years). National granular age disaggregated data on laboratory-confirmed COVID-19 pediatric cases have been published from the United States and China (CDC COVID19, Dong Y) (*Table 1*). COVID-19 disease has been diagnosed across the full breadth of age categories—from the neonatal period through adolescence—with over 50 per cent occurring in the adolescent age group in these reports. National age-disaggregated data are, therefore, crucial to enable countries to determine the age-appropriate health resources needed for prevention and care for infected children and adolescents.

Table 1: COVID-19 Cases in Children by Age Category

Country	Total Number of Paediatric Cases	Age Breakdown of Cases (Years)				
USA ¹	2,572	<1 398 (15%)	1-4 291 (11%)	5-9 388 (15%)	10-14 682 (27%)	15-17 813 (32%)
China ²	731	<1 86 (12%)	1-5 137 (19%)	6-10 171 (23%)	11-15 180 (25%)	16-18 157(21%)
<i>Total</i>	<i>3,303</i>	<i>484 (15%)</i>	<i>428 (13%)</i>	<i>559 (17%)</i>	<i>862 (26%)</i>	<i>970 (29%)</i>

¹ CDC COVID-19 Response Team. MMWR 2020 Apr 6

² Dong Y et al. Pediatrics. 2020 Mar 16

Low case rates of COVID-19 among children and adolescents to date may reflect selective testing of only the most symptomatic individuals for SARS-CoV-2 infection—or decreased susceptibility to infection.

Because surveillance data predominantly reflect individuals diagnosed with COVID-19 disease, there is concern that low case rates among children may reflect selective testing of only the most severely symptomatic individuals

for SARS-CoV-2 infection. There is debate as to whether the low incidence of COVID-19 disease/SARS-CoV-2 infection is related to children being more likely asymptomatic or having atypical/mild symptoms compared with adults—reducing the likelihood of them being tested for SARS-CoV-2—or whether they are less likely to be exposed to infected individuals outside of the household given mitigation measures such as school closure, or whether it reflects a true lower susceptibility to infection (Davies, Zhang).

The definition of what constitutes a “case” has varied between studies and also in national surveillance and monitoring systems: individuals with symptomatic COVID-19 disease; individuals with a positive SARS-CoV-2 real-time polymerase chain reaction (rtPCR) test in respiratory or other samples, indicating current infection; or individuals positive for SARS-CoV-2 IgM and/or IgG antibody, indicating past infection. Additionally, there are multiple SARS-CoV-2 rtPCR and antibody tests, with varying sensitivity (Whitman, Lieberman), and the sensitivity, specificity and predictive value of rtPCR tests may not have been assessed in respiratory samples from children or adolescents.

The issue of children’s susceptibility to SARS-CoV-2 has been explored in studies reporting on contact investigations following an index COVID-19 case. Small studies involving virologic testing of contacts in family clusters demonstrate infection can be acquired by children living in a family with an infected adult, although pediatric infections were generally mild, often with atypical (e.g., gastrointestinal symptoms) or no symptoms (Wolf GK, Qian G, Mao, Posfay-Barbe, Chan J). Larger studies of contact evaluations have had mixed findings, with some reporting similar rates of secondary infection in children and adults while others

report lower rates of secondary infection in children.

Table 2 provides a brief summary of 22 of the larger contact tracing studies (including 30 or more children/adolescent contacts) that have been published or are in pre-print, including details on type of study, pediatric age breakdown and numbers included in the study and key findings. It is important to note that comparability between the studies is problematic. Some studies focused on household contacts only, while others included other types of close contacts; age breakdown categories vary between studies; the number of child contacts in most studies is small compared to number of adult contacts; and symptom status of the index case was rarely reported. Additionally, household density and the extent of isolation of contacts from the index case following the initial diagnosis may be important in terms of risk of acquisition of infection but was generally not reported (Madewell).

Twelve of the studies suggest lower rates of acquisition of secondary infection among children compared to adults, while ten suggest similar rates of acquisition among children compared to adults (one of these studies found similar rates as adults in children >10 years, but lower rates in those <10 years). Of seven studies reporting lower rates of acquisition in children that included further breakdown of child age, six reported the lowest rates of acquisition were in the youngest children (age 0–5 years) (Li W, Park, Korea, Somekh, Yung, Rosenberg). Four studies noted that children were more likely to have asymptomatic infection than adults (Yousaf, Maltezou, Hua, Dattner).

Table 2. Contact Tracing Studies with Pediatric Age Data

Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Yousaf, <i>Clin Infect Dis</i> US (Wisconsin, Utah)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–17 years (N=69) 	<ul style="list-style-type: none"> Similar secondary infection rates in children (20.3 per cent for age <18 years) and adults 18–49 years (N=89, 22.5 per cent) Children <18 years were more likely to be asymptomatic than those >18 years; upper respiratory tract symptoms most common in those with symptoms
Fateh-Moghadam, <i>MedRxiv</i> Italy	<ul style="list-style-type: none"> Community and household contacts Pediatric age breakdown: 0–14 years (N=1,024) 	<ul style="list-style-type: none"> While children had <u>lower</u> risk of acquiring infection (8.4 per cent) than 4,730 adults (13.4 per cent), they had a <u>higher</u> risk of <u>transmitting</u> infection to others than other age groups Workplace contacts at higher risk of infection; no difference by gender
Liu T, <i>Emerg Microb Infect</i> Guangdong Province China (included Madewell paper)	<ul style="list-style-type: none"> Community and household contacts Pediatric age breakdown: 0–9 years (N=1,048) and 10–19 years (N=819) 	<ul style="list-style-type: none"> Compared to young adults 20–29 years (N=2,420, infection rate 2.3 per cent), risk of acquiring infection <u>higher</u> in children age 0–9 years (5.7 per cent) and 10–19 years (4.0 per cent) and adults aged 60–69 years (N=831, 11.1 per cent). Higher secondary infection if symptomatic index case; higher in females
Yung CF, <i>J Pediatr</i> Singapore	<ul style="list-style-type: none"> Pediatric household contacts of confirmed cases Pediatric age breakdown: 0–4 (N=78), 5–9 (N=74), and 10–16 years (N=61) 	<ul style="list-style-type: none"> Young children <5 years were at <u>lowest</u> risk of infection (1.3 per cent) compared to 5–9 years (8.1 per cent) and 10–16 years (9.8 per cent) Most likely to be infected if household index case mother
Somekh E, <i>Pediatr Infect Dis J</i> Israel	<ul style="list-style-type: none"> Household contacts in 13 families Pediatric age breakdown: 0–4 years (N=18) and 5–17 years (N=40) 	<ul style="list-style-type: none"> Young children <5 years at <u>lowest</u> risk (11.8 per cent) compared to those 5–17 years (32.5 per cent) and adults (N=36, 58.3 per cent)
Korea CDC, <i>Osong Pub Health Res Perspect</i> Korea	<ul style="list-style-type: none"> “Close contacts” Pediatric age breakdown: 0–9 years (N=88) and 10–19 years (N=67) 	<ul style="list-style-type: none"> <u>No secondary infections in children 0–9 years, no significant difference in infection rate in children 10–19 years (1.5 per cent) and older individuals (range 0.62 per cent in 486 adults age 20–29 and 1.1 per cent in 91 adults age 70–79 years)</u> Male sex and household contact associated with infection
Park YJ, <i>Emerg Infect Dis</i> South Korea	<ul style="list-style-type: none"> Contact tracing Pediatric age breakdown: 29 index age 0–9 years (57 household contacts) and 124 index 10–19 years (N=231 household contacts) 	<ul style="list-style-type: none"> Evaluated infectivity of index patients by age; highest rates secondary infection with household contacts. Household contacts exposed to index children <u>10–19 years had highest infection rate</u> (18.6 per cent) Household contacts exposed to index children age <u>0–9 years had lowest infection rate</u> (5.3 per cent) but this <u>was similar</u> to exposure to index adults <u>20–29 years</u>, 7.0 per cent; infection rates were 11.7 per cent with exposure to index cases age 30 to 49 years and 18.0 per cent for exposure to index cases >50 years. Non-household contacts had <u>similar infection rates</u> with exposure to index cases that were children (1.1 and 0.9 per cent for 0–9 and 10–19 years, respectively) and index cases that were adults 20–69 years (range 1.1 to 1.8 per cent)
Zhang W, <i>Emerg Infect Dis</i> Guangzhou, China	<ul style="list-style-type: none"> Contact of persons with pre-symptomatic infection Pediatric age breakdown: 0–17 years (N=46) 	<ul style="list-style-type: none"> <u>No significant difference</u> in secondary infection rate by age (4.3 per cent in children 0–17 years, 2.9 per cent for adults 18–30 years (N=104), 1.4 per cent for adults 31–50 years, and 6.3 per cent for those >50 years.

Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Wang Y, <i>BMJ Global Health</i> Beijing, China (included Madewell paper)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–17 years (N=36) 	<ul style="list-style-type: none"> Secondary attack rate <u>lower</u> in children <18 years (36.1 per cent) compared with adults (N=92, 69.6 per cent) There were no secondary infections from exposure to index case age <18 years.
Luo L, <i>MedRxiv</i> Guangzhou China (included Madewell paper)	<ul style="list-style-type: none"> “Close contacts” Pediatric age breakdown: 0–17 years (N=783) 	<ul style="list-style-type: none"> <u>No significant difference</u> in secondary infection by age between children <17 years (1.8 per cent) and adults age 18–44 years (N=2,338, 2.2 per cent) Age >60 years (N=824, 4.2 per cent), household contact and symptomatic index case associated with risk infection
Li W, <i>Clin Infect Dis</i> 2 hospitals Wuhan China (included in Viner, Madewell papers)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–5 years (N=44) and 6–17 years (N=56) 	<ul style="list-style-type: none"> Secondary attack rate in children <18 years (4 per cent: 2.3 per cent age 0–5 years and 5.4 per cent age 6–17 years) was <u>lower</u> than adults (N=292, 20.5 per cent) Secondary attack rate lower when index patient quarantined after symptoms; highest among spouses; no difference by gender
Maltezou H, <i>J Med Virol</i> National registry Greece	<ul style="list-style-type: none"> Household contacts, 23 families with at least one child and COVID-19 case Pediatric age breakdown: 0–18 years (N=43) 	<ul style="list-style-type: none"> <u>Similar</u> secondary attack rate children (30/43, 69.8 per cent children vs 38/66, 57.6 per cent adults); adult to child in 19 clusters and adult to adult in 12 clusters. However, <u>no cases of transmission from an infected child</u> (N=43) to another child or adult. Children more likely asymptomatic than adults (40 vs 11 per cent adults); viral load was high, moderate and low in 40.7, 18.6 and 40.7 per cent, respectively infected children (vs 34.5, 51.7, and 13.8 per cent, respectively, in adults).
Hua C-Z, <i>J Med Virol</i> Zhejiang Province China (included Madewell paper)	<ul style="list-style-type: none"> Household contacts, 314 families with COVID-19 case and children Pediatric age breakdown: ≤14 years (N=325) 	<ul style="list-style-type: none"> <u>Lower</u> secondary attack rate children (43/325, 13.2 per cent children vs 108/510, 21.2 per cent adults) Children more likely to have asymptomatic infection, 23.3 per cent vs 7.4 per cent adults.
Rosenberg ES, <i>Clin Infect Dis</i> US (NY) (included Madewell paper)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–<5 (N=25); 5–<18 years (N=131) 	<ul style="list-style-type: none"> <u>Lower</u> secondary attack rate children (5/25, 20.0 per cent, 0–<5 years; 37/131, 38.2 per cent, 5–<18 years, vs 182 adults >18 years (range 41.7 to 53.4 per cent).
Dattner I, <i>MedRxiv</i> , Bnei Brak Israel (included Madewell paper)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–19 years (N=1,544) 	<ul style="list-style-type: none"> <u>Lower</u> SARS-CoV-2 detection in children (512/1,544, 33 per cent, 0–19 years, vs 998/1,809 adults, 55 per cent) Children more likely to have asymptomatic infection, 28 per cent, vs 12 per cent adults
Jing Q-L, <i>Lancet Infect Dis</i> Guangzhou Municipal CDC, China (included in Viner, Madwell paper)	<ul style="list-style-type: none"> “Close contacts” Pediatric age breakdown: <20 years (N=244) 	<ul style="list-style-type: none"> In households, attack rate <u>lower</u> in children <20 years (4.1 per cent) compared to those 20–59 years (N=1,432, 6.4 per cent) and >60 years (N=499, 7.0 per cent) Higher rate infection in household contacts; cases as contagious during incubation as during symptoms; no difference by gender
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Cheng H-Y, <i>JAMA Intern Med</i> Taiwan (included in Viner paper)	<ul style="list-style-type: none"> All contacts Pediatric age breakdown: 0–19 years (N=281) 	<ul style="list-style-type: none"> <u>Similar</u> infection rates in children (0.4%) and adults age 20–39 years (N=1,161, 0.5 per cent) and slightly higher among older adults 40–59 years (N=794, 1.1 per cent) and ≥ 60 years (N=331, 0.9 per cent). Higher risk of transmission around the time of symptom onset in index case; household and non-household family contacts more likely infected than health care or other settings

Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Wu J, <i>Clin Infect Dis</i> Zhuhai, China (included in Viner, Madewell papers)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–3 years (N=10), 4–18 years (N=21) 	<ul style="list-style-type: none"> Secondary infection rate <u>lower</u> in children 4–18 years (4.8 per cent) compared to adults 19–60 years (N=81, 37.0 per cent); in children 0–4 years, infection rate 40 per cent. Underlying medical conditions and history direct exposure to Wuhan higher risk for secondary infection; greater closeness of exposure and duration exposure, lack of quarantine of index case, and greater household size associated with infection
Bi Q, <i>Lancet Infect Dis</i> Shenzhen, China (included in Viner paper)	<ul style="list-style-type: none"> Close contact Pediatric age breakdown: 0–9 years (N=148) and 10–19 years (N=85) 	<ul style="list-style-type: none"> <u>No significant difference</u> in secondary infection rates by age; infection rate in children <10 years (7.4 per cent) and 10–19 years (7.1 per cent) similar to the population average of 6.6 per cent. Individual >60 years, household contact and those traveling with an index case associated with infection
Zhang J, <i>Science</i> Wuhan and Shanghai (included in Viner paper)	<ul style="list-style-type: none"> Close contact Pediatric age breakdown: 0–14 years (N=709) 	<ul style="list-style-type: none"> Secondary infection rates <u>lower</u> in children age <14 years (6.2 per cent) compared to adults 15–64 years (N=5,242, 8.6 per cent), with highest infection rates in those ≥65 years (N=589, 16.3 per cent) Household contact, travel history to Wuhan/Hubei, exposure prior to strict social distancing measures, female sex associated with infection
Mizumoto K, <i>MedRxiv</i> Japan (included in Viner paper)	<ul style="list-style-type: none"> Household contacts Pediatric age breakdown: 0–19 years (N=175) 	<ul style="list-style-type: none"> Secondary infection rate <u>lower</u> in children 0–19 years (5.7 per cent) compared to adults >19 years (N=2,312, 12.3 per cent)
Luo L, <i>Ann Int Med</i> Guangzhou China	<ul style="list-style-type: none"> Close contacts 391 index cases Pediatric age breakdown: 0–17 years (N=357) 	<ul style="list-style-type: none"> Secondary infection rate <u>similar</u> in children 0–17 years (3.9 per cent) compared to adults 18–44 years (N=1,784, 2.8 per cent), adjusted odds ratio 0.78, 95 per cent confidence interval 0.41–1.50.

A preprint systematic review and meta-analysis of contact tracing and population-screening studies by Viner and colleagues explored the issue of child susceptibility to infection (eight studies are included in *Table 2*) (VinerMedRxiv). Their meta-analysis of the contact tracing studies found children and adolescents <20 years had 56 per cent lower likelihood of a positive virologic test for SARS-CoV-2 after index exposure than adults >20 years (pooled odds ratio 0.44, 95 per cent confidence interval [CI] 0.29–0.69), with substantial between study heterogeneity (63 per cent). The authors noted there were insufficient data to do sensitivity analyses separating younger children from adolescents because few studies reported sufficient age disaggregation.

A more recent pre-print from Madewell and colleagues reported on a systematic review and meta-analysis of 10 household contact tracing studies, including two studies overlapping with Viner (nine studies are included in *Table 2*) (Madewell). They also found that the household secondary attack rate was significantly lower in children <18 years (15.7 per cent) than in adults (31.0 per cent), with significant heterogeneity.

In an age-structured mathematical model using epidemic data from China, Italy, Japan, Singapore, Canada and South Korea, and including heterogeneous contact rates between age groups, Davies and colleagues from the London School of Hygiene and Tropical Medicine estimated that susceptibility to SARS-CoV-2 infection in children and adolescents <20 years was approximately half that of adults aged over 20 years—findings similar to the meta-analyses (Davies, Viner, Madewell). The estimated probability of clinical symptoms increased with age, with 29 per cent of children age <10, 21 per cent of adolescents 10–19, and 27 per cent of young adults 20–29 years

developing symptoms of disease compared to 63 per cent in those age 60–69 years.

Potential biologic differences in susceptibility to SARS-CoV-2 infection in children may exist

Susceptibility to SARS-CoV-2 may be related to host-cell expression of the viral receptor, angiotensin-converting enzyme-2 (ACE-2), and protease-cleaving enzymes on the cell membrane such as transmembrane serine protease 2 (TMPRSS2), which facilitates viral-cell membrane fusion. A study evaluated ACE-2 gene expression in nasal epithelial specimens that were collected in 2015–2018 in 305 individuals from age four to 60 years as part of a study involving patients with asthma (Bunyavanich). Children age 4–9 years had significantly lower expression of ACE-2 in the nasal epithelium compared to older children 10–17 years, young adults 18–24 years, and adults ≥ 25 years. ACE2 expression was higher with each increasing age group even after adjusting for sex and prevalence of asthma.

Several other studies have found similar correlations of ACE2 expression and age. A study evaluating several public gene-expression datasets found that gene expression for ACE-2 and TMPRSS2 in nasal tissue as well as bronchial tissue was lower in children compared to adults (Sharif-Askari). An evaluation of ACE2/TMPRSS2 expression and other COVID-19-related genes across various tissues from healthy subjects and individuals with various comorbidities suspected to predispose to COVID-19 found mRNA profiles that varied by tissue type and comorbidity, with differential patterns of expression by age (Radzikowska). In an analysis of soluble ACE2 (sACE2) protein expression in serum collected from older children and adolescents in a pediatric osteoporosis prevention study, low sACE levels were found through age 12 years, increasing through adolescence with a larger

increase in male than female adolescents (Sward). A similar study including younger children as well as adults found significantly greater ACE2 protein expression in serum of healthy adults compared to healthy infants and toddlers, with higher expression in adult males versus females but no significant male-female differences in young children (Pavel).

Lower ACE2 expression in the nasal epithelium of the upper respiratory tract—the first point of contact for the SARS-CoV-2 virus—and the lower respiratory tract could result in decreased susceptibility to acquisition of SARS-CoV-2 infection and/or lower levels of viral replication in children than adults (Patel). If confirmed, these findings could account for potential decreased susceptibility to SARS-CoV-2 acquisition and/or replication in children, and may also provide a basis for susceptibility differences between young children and older children/adolescents.

However, if infected, young children may be as infectious as adolescents and adults

A number of studies from multiple countries have documented that children infected with SARS-CoV-2 have similar SARS-CoV-2 viral load (as measured by rtPCR) in their respiratory tract as adults.

In an evaluation of SARS-CoV-2 viral load in nasopharynx in the U.S., children age 5–17 years had had similar SARS-CoV-2 upper respiratory tract viral load compared to adults age ≥ 18 years, as measured by median PCR cycle threshold (a lower cycle threshold means higher levels of virus), while children younger than age 5 years had higher levels than older children and adults (Heald-Sargent). These results are consistent with a German study of 47 SARS-CoV-2-infected children between ages 1–11 years; 15 had an underlying condition or were hospitalized but the majority were free of

symptoms. The children who did not have symptoms had viral loads as high or higher than symptomatic children or adults (Jones MedRxiv). Similarly, a study of pediatric hospital-based screening in France found that among 22 infected children, the median SARS-CoV-2 rtPCR cycle threshold was similar in children with ($n=11$) or without ($n=10$) clinical symptoms (Poline). Finally a study from the Swiss National Reference Center for Emerging Viral Diseases compared nasopharyngeal viral load in 53 children compared to 352 adults who were tested in the first 5 days after symptom onset; no significant differences in SARS-CoV-2 RNA were seen between children and adults (Baggio).

While these studies do not directly measure infectious virus, in a study using cell culture to assess cultivable SARS-CoV-2 in the upper respiratory tract of 23 children with COVID-19, replicating virus was isolated from 52 per cent of children of all ages, ranging from age 7 days to 15.9 years (L’Huillier).

Data on transmission from children to adults and from children to children is conflicting

Data are conflicting regarding the risk of SARS-CoV-2 transmission from children to adults. While data have indicated that children are more likely to have mild or asymptomatic disease, transmission has been demonstrated to occur from asymptomatic infected individuals within family clusters (Bai, Wei W). Additionally, studies of quantitative viral load in upper respiratory specimens have found similar viral load in asymptomatic and symptomatic patients, suggesting similar transmission potential regardless of symptoms (Zou L, Kam K, Huff). For example, an asymptomatic six-month old infant with SARS-CoV-2 infection had high viral load detected on nasopharyngeal testing, similar to that in his symptomatic

mother, with the infant remaining positive for 17 days (Kam K).

Most SARS-CoV-2 infections in children have been associated with transmission from an adult household member to the child; for example, in a study of familial clusters among 40 children age <16 years with documented SARS-CoV-2 infection in Geneva, in 79 per cent of households, an adult family member had suspected or confirmed SARS-CoV-2 prior to diagnosis in the child, and only 8 per cent of households reported the child developed symptoms before other household members (Posfay-Barbe).

Child-to-adult transmission has been documented in a few case reports including a small number of individuals. In a study of 10 paediatric cases of COVID-19 in China, a three month-old infant residing in an endemic area transmitted infection to both parents, who developed symptomatic COVID-19 a week after they cared for the sick infant without protection measures (Cai J). In a survey of 144 household contacts of 32 symptomatic children infected with SARS-CoV-2, although most cases originated in an adult household member, 7 cases of presumed child to adult transmission were identified (Therani). However, in a preprint review of 31 household transmission cluster studies, only three clusters (10 per cent) identified a child <18 years as the index case (Zhu Y). In a sensitivity analysis in which child with asymptomatic infection in any household with an adult index case was presumed to be the asymptomatic index case, then potentially six of 28 (21 per cent) clusters could be due to a child index case. The authors conclude that data to date suggest children have not played a substantial role in household transmission of SARS-CoV-2. Four of the household contact tracing studies in *Table 2* reported on transmission from children to adults; two reported no cases of transmission from children

to adults, while two studies reported similar or higher risk of transmission from children than adults to adults (Wang, Maltezou, Fateh-Moghadam, Park).

Because children may have been sequestered more than adults during the outbreak, including out of a school environment, it may be more difficult for children to initiate disease chains as they may be less likely to be exposed to the virus and therefore to become infected in the first place. As mitigation measures are eased, this may change. In an investigation of SARS-CoV-2 attack rates among 594 attendees at an overnight camp in Georgia following an index case of infection in an adolescent staff member, virologic testing was positive in 260 individuals (attack rate 44 per cent), with the highest attack rate, 51 per cent, in the youngest age group 6–10 years, compared to 44, 33 and 29 per cent in those aged 11–17 years, 18–21 years, and 22–59 years, respectively (Szablewski MMWR). Thus, SARS-CoV-2 spread efficiently in a youth-centric setting resulting in high attack rates among persons in all age groups. Asymptomatic infection occurred in 26 per cent of those infected with available symptom data.

Transmission in school settings

Several studies have reported on school-related contact tracing. In a contact investigation of 12 COVID-19 cases linked to a single case in the French Alps, one nine-year old child, who was coinfecting with other respiratory viruses (picornavirus and influenza A), attended three schools while mildly symptomatic but did not transmit the SARS-CoV-2, although there was a high proportion of picornavirus and influenza infection among school contacts (Danis K). In an evaluation of contact tracing records from children and adults in Ireland diagnosed with COVID-19 who attended a school setting prior to national school closures on March 12 2020 ,

three paediatric (one primary and two secondary school attendance) and three adult cases of confirmed COVID-19 with a history of school attendance were identified; of 924 child and 101 adult contacts in schools that were evaluated, no confirmed cases of COVID-19 were identified, although only symptomatic contacts received virologic testing (Heavey).

In Australia, virologic and serologic screening of 663 of 1448 school-related contacts of 27 COVID-19 cases (12 students, 15 staff) from 25 schools and early childhood education and care (ECEC) settings in New South Wales identified secondary infection in only 18 individuals from four settings (three schools and one ECEC; attack rate 18/663, 2.8 per cent) (Macartney). Finally, a study of contact tracing of three pre-school or secondary school settings in Singapore following a documented case of SARS-CoV-2 in a student or adult in the setting found no evidence of further disease transmission to children in these settings (Yung CF). Of note, while schools in Singapore had not closed, public health measures were implemented including terminal cleaning; measures to reduce student mixing, including suspension of extracurricular/sports activities and staggered recess breaks; and quarantine and monitoring for symptoms of all students from the same class following detection of an index case.

South Korea analyzed national data from pediatric patients with confirmed COVID-19 and association of infections with school reopening policies (Yoon). They reported no sudden increase in pediatric cases after school reopening; 45 children from 40 schools and kindergartens were diagnosed with COVID-19 after in-person classes started. Among the 32 children with source case identification available, 55.6 per cent were infected by family members, but this varied by age, with 79.1 per cent of children age <10 years infected by

family members compared to only 28.6 per cent of adolescents. More than 11,000 students and staff were tested in contact investigations and only one additional student was found infected in the same classroom.

These data suggest that children have not played a significant role in school transmission of SARS-CoV-2. However, as mitigation measures have eased and schools have been reopened, clusters of school infections have been reported in multiple countries, prompting re-closure of affected schools in some cases (NPR, Independent.co.uk, CNN, CNN, MSN). In Israel, 10 days following school reopening, a major outbreak of COVID-19 occurred at a high school following diagnosis of SARS-CoV-2 in two students with mild symptoms; diagnostic rtPCR testing of the complete school community documented infection in 153 students (attack rate 13.2 per cent) and 25 staff members (attack rate 16.6 per cent) (Stein-Zamir). Additionally, 87 confirmed SARS-CoV-2 infections occurred among non-school close contacts of these cases. Most cases among students were mild or asymptomatic. The outbreak coincided with an extreme heat wave where schoolchildren were exempted from wearing face-masks for 3 days and continuous air conditioning was operating, and classrooms were crowded. In Santiago Chile, following diagnosis of SARS-CoV-2 infection in a staff member in a private school community, 52 members of the school community were confirmed positive for SARS-CoV-2 (seven students, 18 staff and 27 parents). SARS-CoV-2 antibody testing was performed 8–10 weeks later among 1,009 students and 235 staff; overall antibody prevalence was 9.9 per cent in students, with higher positivity in younger students, and 16.6 per cent prevalence in staff (Torres CID). Similar reports are now emerging in the United States as schools begin to reopen (CNN, MSN).

Further evaluation is needed to determine whether children (and schools) will play a more substantive role in community spread once mitigation measures are eased, and whether children are less infectious than adults or less susceptible to infection. Similar to evaluation of work place environments, it will be important to assess if mask wearing and other measures can reduce the risk of infection in the school setting.

Mother to Child Transmission of SARS-CoV-2: possible but not proven

With the initial coronavirus SARS-CoV-1 and MERS epidemics, there were no confirmed cases of maternal-fetal vertical transmission (Schwartz D). For *in utero* transmission, the pathogen must be present in blood and be able to cross the placenta and infect the fetus. Although SARS-CoV-1 and the MERS virus are detected relatively frequently in blood samples (33–78 per cent) (Ng, Kim SY), viremia secondary to SARS-CoV-2 appears much less frequent. In eight studies that have evaluated SARS-CoV-2 viremia in patients with COVID-19, viremia was detected in 21 of 587 samples, for a prevalence of 3.6 per cent, significantly lower than the other serious coronaviruses. (Ling Y, Xie C, Wang W, Wu J, Young B, Chen W, Huang C, Chang JF) SARS-CoV-2 viremia is more frequent in individuals with severe COVID-19 disease and correlates with highly elevated levels of IL-6 (Xu D, Chen X). Thus, it would be anticipated that viremia would be limited primarily to pregnant women who are critically ill with COVID-19.

The SARS-CoV-2 ACE2 receptor and TMPRSS2, the protease that cleaves both the viral spike protein and the ACE2 receptor to facilitate infection, have been identified in both placental and fetal tissues as early as the first trimester, but co-expression of both mediators in the placenta appears to be limited, suggesting the

placenta could be resistant to SARS-CoV-2 infection (Li M, Weatherbee, Pique-Regi). However, alternative host cell proteases may be able to cleave the spike protein, including furin and cathepsin B, which are expressed in a variety of tissues, including the placenta (Wang Q, Jaimes). It is therefore possible for SARS-CoV-2, should it reach the placenta through viremia, to potentially cross the placenta to reach and infect the fetus.

Another mechanism for SARS-CoV-2 to reach the fetus would be through disruption of the placental barrier through ischemic injury, allowing virus to directly reach fetal tissues without requiring placental infection (Mahyuddin). Abnormal placental pathology has been described in COVID-19 positive women, with the most common finding being vascular malperfusion (Komine-Aizawa). In a study of placentas from 20 women with SARS-CoV-2 infection who delivered at Weill Cornell Medical Center in New York City, 18 of whom were asymptomatic, 50 per cent of the placentas showed some evidence of vascular malperfusion or fetal vascular thrombosis; however, placental disruption may not be accompanied by transmission, as all infants tested negative for the virus and were asymptomatic (Baergen).

The University of Birmingham is conducting a “living systematic review” of publications related to SARS-CoV-2/COVID-19 in pregnancy and effect on pregnancy and infant outcomes (U Birmingham). While SARS-CoV-2 infection has been reported to be detected in a small number of infants born to pregnant women with COVID-19, determination of *in utero* infection is complex, and requires sampling of appropriate tissues or fluids near the time of birth (Shah, Blumberg). As of June 16, 2020, there were reports of 869 infants born to 1,483 women with COVID-19 with data on infant testing. Of these, 52 (6 per cent) infants were

suspected or confirmed to have SARS-CoV-2 detected following exposure to the virus *in utero*, intrapartum or postnatally.

Thirteen of the 52 (25 per cent) of infants were born to mothers who were not diagnosed with COVID-19 until after delivery, and hence transmission was likely horizontal. Of the remaining 39 infants born to mothers with antepartum COVID-19 diagnosis, most studies that reported detection of SARS-CoV-2 in infant nasopharyngeal specimens were from samples taken from infants aged one day or older, and horizontal transmission cannot be ruled out in such cases. Only eight infants had a positive nasopharyngeal swab for the virus within 12 hours after birth; however, none of these infants had virus detected in cord blood, neonatal blood, amniotic fluid or the placenta (Li M-Xu, Knight, Carosso).

There have been a small number of reports of SARS-CoV-2 detection in cord blood, placenta, or amniotic fluid, or SARS-CoV-2 IgM antibody detection in neonatal blood; in all but one case, the infants had negative nasopharyngeal tests, no symptoms, and/or IgM turned negative by 12–28 days (Buonsenso, Penfield, Algarroba, Baud, Dong L, Zeng, Wu, Fenizia). In one case, SARS-CoV-2 was detected in maternal blood, vaginal fluids, and placenta, with preterm vaginal delivery; the infant had a positive cord blood and positive nasopharyngeal rtPCR test at delivery but negative at 1 week, and was asymptomatic and had normal laboratory findings (Ferizia).

There is only one relatively convincing recent case of intrauterine infection reported to date (Vivanti). This was a pregnant woman with severe COVID-19 who required emergency preterm cesarean delivery for fetal distress. SARS-CoV-2 was detected in maternal blood, amniotic fluid collected during cesarean delivery, placental tissues, neonatal blood,

bronchoalveolar lavage fluid (the infant required short-term intubation for prematurity), and infant nasopharyngeal and rectal swabs collected at 1 hour, 3 and 18 days of life; placental examination had fibrin deposition with infarction and acute/chronic intervillitis. The infant developed neurologic signs at age 3 days with abnormal magnetic resonance imaging (MRI); evaluations for alternative infective etiologies were negative, and the infant improved gradually and was discharged at 18 days, with subsequent improvement in MRI imaging.

SARS-CoV-2 has rarely been detected in human breast milk (WHO, Lackey, Kimberlin). There have been five case reports of detection of SARS-CoV-2 in breast milk to date (Fenizia, Wu Y, Tam, Bastug, Grob). Breast milk was only transiently positive in one woman (positive day 1, negative day 3) and only tested at one time point in another; both infants tested negative despite breastfeeding (Fenizia, Wu Y). In the other three cases (two of whom were women infected postnatally), more than one breast milk sample was positive and their infants tested positive by nasopharyngeal rtPCR, but all were exposed to their infected mothers (without masks in two) and the broader environment in which the mothers acquired their infection, and thus it is not possible to determine if breast milk was the source of their infection (Tam, Bastug, Grob). It is important to note that the presence of SARS-CoV-2 RNA by rtPCR in human milk does not necessarily confirm the presence of infectious virus capable of replicating in host cells (Lackey, Widders). SARS-CoV-2-specific antibody IgG, IgM and IgA antibody has been detected in breast milk of infected women, but it is unclear if this would be protective to the breastfeeding infant (Fox). Both the World Health Organization and the American Academy of Pediatrics has concluded that the benefits of breastfeeding outweigh the risk of potential

infection, particularly with appropriate adherence to infection prevention and control measures by the mother (WHO, AAP).

In summary, while mother-to-child transmission of SARS-CoV-2 is possible during pregnancy and delivery, it has only been confirmed in one case report. Determination of mother-to-child SARS-CoV-2 transmission requires appropriate samples obtained with proper timing, including amniotic fluid, placenta, neonatal blood, and nasopharyngeal and other samples from the infant at birth; unfortunately, collection of the needed tissues and fluids and/or data on timing of infant testing is not provided in many studies to date.

Determination of SARS-CoV-2 transmission through breastfeeding will be difficult to distinguish from horizontal transmission from the mother/environment, as an infant with sole exposure to SARS-CoV-2 through breast milk without the mother and outside of the household environment will be extremely unusual. Studies to evaluate the replication competence of SARS-CoV-2 in breast milk—including in the presence of SARS-CoV-2 antibody—are needed to determine the possibility of breast milk transmission.

Emerging studies from the US and the UK suggest that race/ethnicity may influence risk of SARS-CoV-2 infection and severity of COVID-19 disease, including in children

In the United States, higher rates of severe COVID-19 disease and mortality in adults have been observed among African Americans (Price-Haywood, Moore JT). Similarly, in the United Kingdom COVID-19 is more common among black and ethnic minority individuals (de Lusignan, Khunti). This may reflect social determinants that make these populations more vulnerable to infection, such as economic insecurity, poor neighborhood and housing

conditions, employment in occupations at higher risk of viral exposure, and availability of healthcare, as well as higher prevalence of chronic co-morbidities such as hypertension, diabetes and obesity among minority populations, or an undefined biologic factor (Bhala, Tal, Yaya, Hooper).

There have been limited data on COVID-19 and race/ethnicity in children, and most paediatric studies have not reported race/ethnicity data. In the United States, the Centers for Disease Control reported on 576 children hospitalized with laboratory confirmed COVID-19 March 1–July 25 2020; Hispanic and non-Hispanic black children had higher cumulative rates of COVID-19-associated hospitalizations (16.4 and 10.5 per 100,000, respectively) than did non-Hispanic white children (2.1 per 100,000) (Kim). Studies from four hospitals in New York City, Chicago and United Kingdom have also noted a predominance of minority race/ethnicity in children hospitalized with COVID-19, although this may reflect the catchment populations of the hospitals (Bandi, Zachariah, Chao, Harman). In the largest study to date, a cross-sectional analysis of 1,000 children tested for SARS-CoV-2 at a pediatric urban testing site with free testing upon physician referral of children with mild symptoms in Washington DC found that 207 (20.7 per cent) children tested positive for SARS-CoV-2, with significant differences by race/ethnicity. In comparison to non-hispanic white children, non-hispanic black and hispanic children had significantly higher rates of SARS-CoV-2 infection, 7.3 per cent, 30.0 per cent, and 46.4 per cent, respectively, remaining significant after adjustment for age, sex and median family income (Goyal). Positivity rates also differed by median family income, with children residing in households with lower median family income having higher rates of infection (infection rate of 8.7 per cent in those in households in highest fourth quartile of family income compared to 23.7 per cent, 27.1

per cent and 37.7 per cent in children in quartiles 3, 2 and 1). Higher rates of reported exposure to SARS-CoV-2 were reported in minority children and in less socioeconomically advantaged households.

While these data may reflect socio-economic, demographic and contact patterns (e.g., household size and composition) in minority communities, they are concerning given the extension of the pandemic from high-income to low- and middle-income countries where health and other vulnerabilities are more prevalent. At a minimum, studies of SARS-CoV-2 in children should also report on race/ethnicity as well as other modifiers such as gender, economic status, and co-morbidities.

4. Features of SARS-CoV-2 in Children and Adolescents

Experience with other severe coronavirus infections, Serious Acute Respiratory Virus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome coronavirus (MERS), suggested SARS-CoV-1 and MERS infections occurred less commonly and less severely in children than adults (Zimmerman).

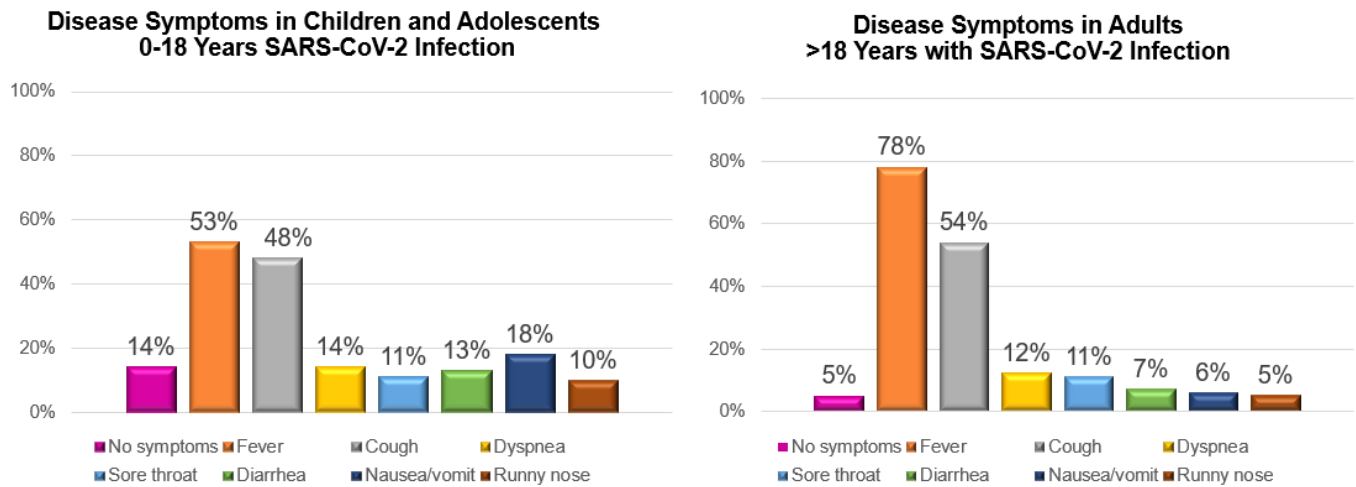
In a review of SARS-CoV-2/COVID-19 in children and adolescents from 49 studies including 1,780 children and adolescents, primarily from Italy, United States and China, 57 per cent had asymptomatic or mild disease (15 and 42 per cent, respectively) and 39 per cent had moderate disease; severe or critical disease was observed in only 2.7 per cent of children (2.0 and 0.7 per cent, respectively) (Liguoro). This contrasts with data from adults with COVID-19;

severe/critical disease was observed in 16 per cent of 1,099 adults with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces in an initial report from China (Guan). Similarly, hospitalization rates in children are lower than in adults; in the United States, an evaluation of hospitalization data from 14 states found hospitalization rates increased with age, from 0.3 per cent in persons aged 0–4 years, 0.1 per cent in those age 5–17 years compared to 2.5 per cent in those 18–49 years and 7.4 to 13.8 in those aged 50 to ≥ 65 years (Garg).

Clinical findings

A recent systematic review and meta-analysis of 148 studies published between December 1 2019 and March 28 2020 including 12,149 patients with confirmed SARS-CoV-2/COVID-19 provided a comparison of signs and symptoms among 11,058 adults and 1,056 children and adolescents from 15 countries (the majority, 87 per cent, from China) (Jutzeler). More children than adults had asymptomatic infection, 14 per cent vs 5 per cent, respectively (*Figure 3*). Signs and symptoms in children and adolescents were similar to those in adults, but were lower in frequency in children; fever was present in 53 per cent of children compared to 78 per cent of adults, and cough in 48 per cent versus 54 per cent, respectively. Gastrointestinal symptoms were somewhat more common in children than adults, with diarrhea in 13 per cent of children versus 7 per cent of adults and nausea/vomiting in 18 per cent of children versus 6 per cent of adults; similarly upper respiratory tract findings such as rhinorrhea were more common in children, 10 per cent, versus 5 per cent of adults.

Figure 3: Symptoms of SARS-CoV-2 in children and adolescents compared with adults
(Jutzeler et al. *Travel Med Infect Dis* 2020;37:101825)

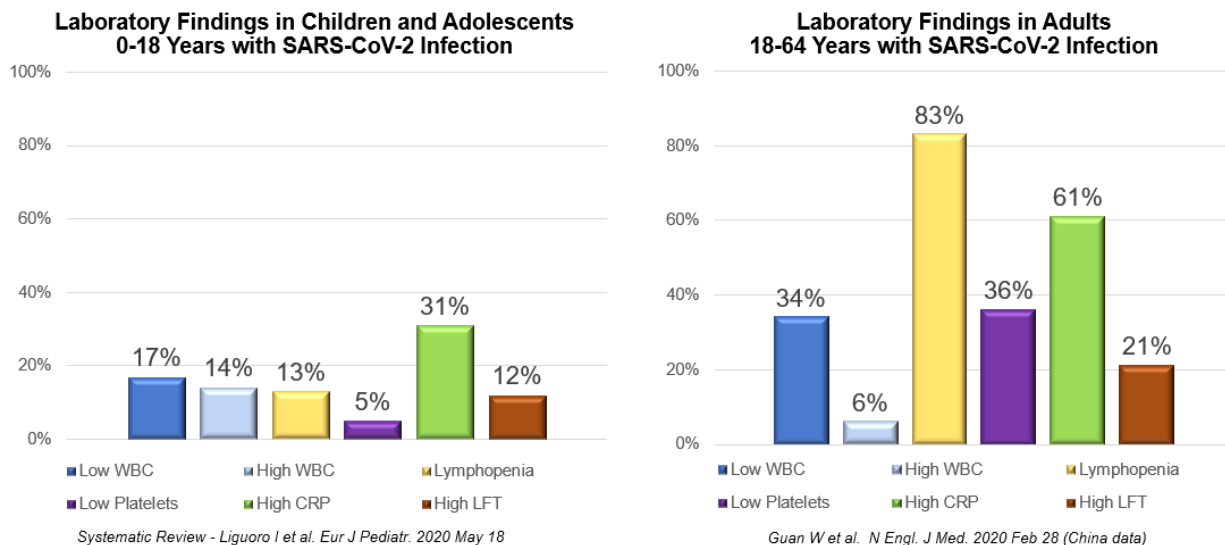


Laboratory findings

Laboratory findings in children were reported in the systematic review from Liguoro et al, with data from 655 children from 38 studies (Liguoro). White blood count was normal in most, with only 17 per cent demonstrating low white cell count and 5 per cent lymphopenia; in contrast, 34 per cent of adults in a large study

of infected adults in China had low white cell count and 83 per cent lymphopenia (Figure 4) (Guan). Markers of inflammation were lower in children, with elevated c-reactive protein (CRP) observed in 31 per cent of children compared to 61 per cent of adults. Lymphopenia and elevated CRP are both associated with poorer prognosis among adults.

Figure 4: Laboratory Findings of SARS-CoV-2 in children and adolescents compared with adults



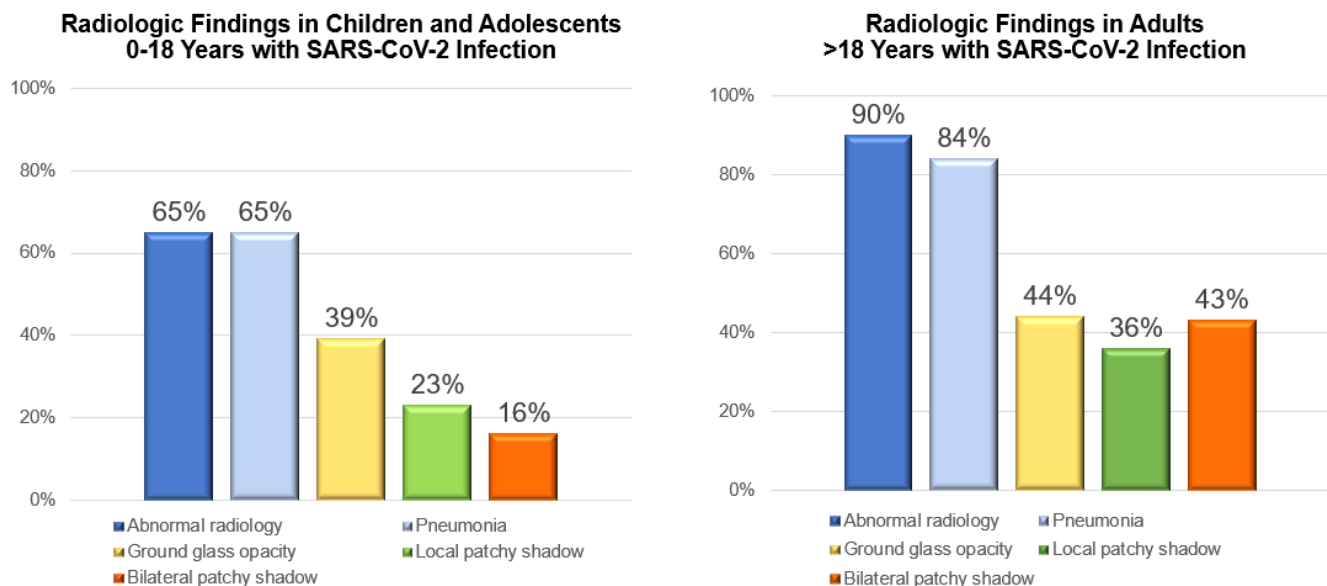
Radiologic findings

Comparison of radiologic findings between children/adolescents and adults was available from the Jutzeler systematic review, including 313 children/adolescents and 7,780 adults (Jutzeler).

Radiologic abnormalities in children and adolescents were similar to those in adults, but

were lower in frequency in children (*Figure 5*). Overall, 65 per cent of children/adolescent had abnormal chest radiography compared to 90 per cent of adults; pneumonia was observed in 65 per cent of children and 84 per cent of adults. Ground glass opacity was similar in children and adults (39 per cent and 44 per cent, respectively). Local or bilateral patchy density was seen in a smaller proportion of children than adults.

Figure 5: Radiologic Findings of SARS-CoV-2 in children and adolescents compared with adults (Jutzler et al. *Travel Med Infect Dis* 2020;37:101825)



Treatment

While hospitalization rates in children/adolescents are lower than adults, once admitted to the hospital, children have similar rates of ICU admission as adults; in the US, 33 per cent of hospitalized children/adolescents and 32 per cent of adults required ICU admission (Garg, Kim MMWR, Kim CID).

However, need for invasive interventions is higher in hospitalized adults: invasive mechanical ventilation was required in 6 per

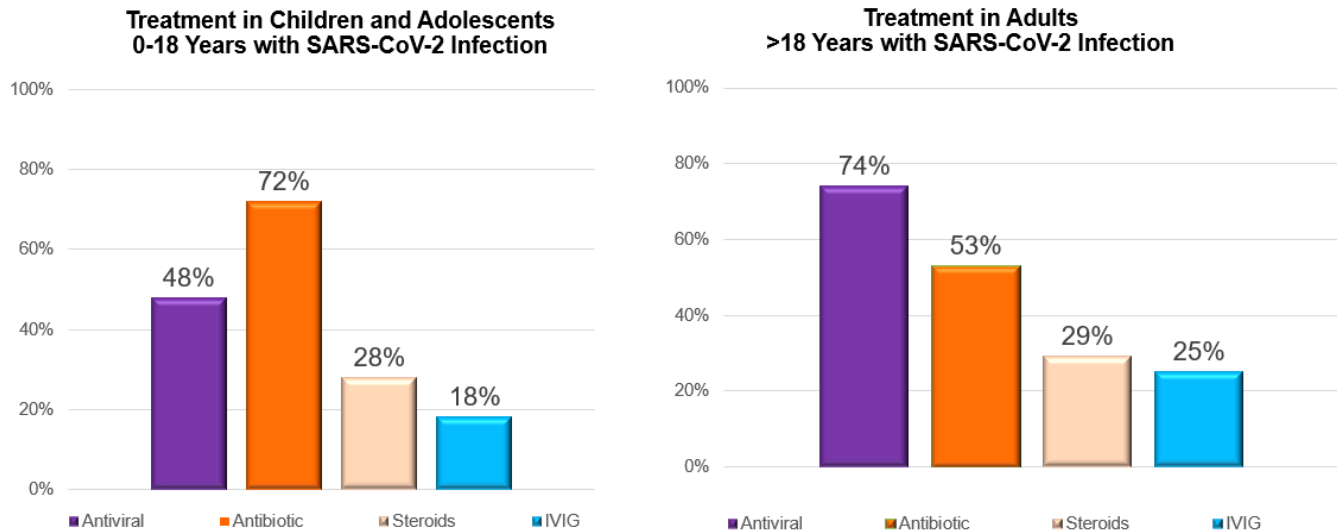
cent of children compared to 19 per cent of adults (Kim MMWR, Kim CID).

Comparison of COVID-19 treatments between children/adolescents and adults was available from the Jutzeler systematic review, including 83 children/adolescents and 6,068 adults (Jutzeler) (*Figure 6*). Children/adolescents were somewhat less likely to receive antivirals (48 per cent) and more likely to receive antibiotics (72 per cent) than were adults (74 per cent and 53 per cent, respectively) (Jutzeler). Use of

corticosteroids and intravenous immunoglobulin was relatively similar.

Mortality is significantly lower in hospitalized children/adolescents, 0.5 per cent, compared to hospitalized adults, 17 per cent (Kim MMWR, Kim CID).

Figure 6: Treatment of SARS-CoV-2 in children and adolescents compared with adults
(Jutzler et al. *Travel Med Infect Dis* 2020;37:101825)



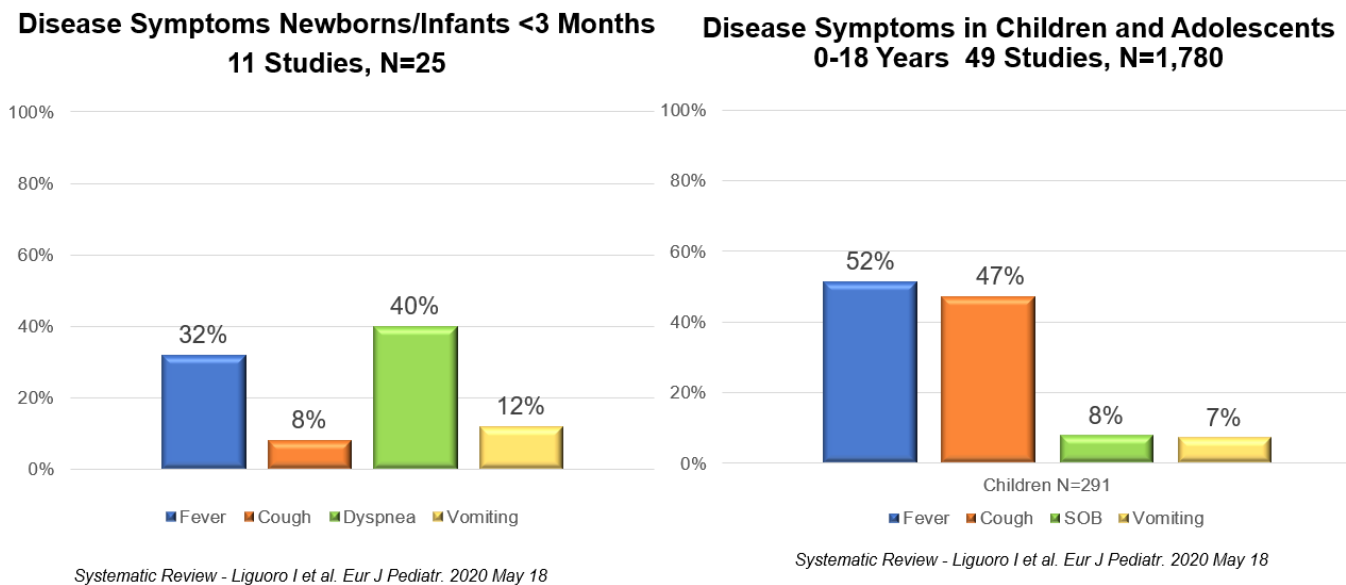
Newborns/infants age <3 months compared with all children and adolescents

Data to compare SARS-CoV-2/COVID-19 presentation in infants under age 3 months to children/ adolescents was available in the Liguoro meta-analysis, with data from 12 papers on 25 newborns and infants <3 months of age (Liguoro). Neonates (84 per cent) primarily underwent SARS-CoV-2 screening because of maternal COVID-19 disease. Given the small number of newborns/infants, caution is needed in interpreting comparisons with older children. Similar to older children, 88 per cent of newborns/infants had asymptomatic,

mild, or moderate symptoms (20 per cent, 48 per cent and 20 per cent, respectively). However, a higher proportion of newborns/infants had severe illness (12 per cent) versus all children (2.7 per cent).

In contrast to the overall group of children, more newborns/infants had reported dyspnea (shortness of breath) and few had a cough (*Figure 7*). Fever was observed in only 32 per cent of infants versus 52 per cent of all children. Gastrointestinal symptoms were somewhat more likely in newborns/infants. Again, given the small number of newborns/infants, caution is needed in interpreting comparisons with older children.

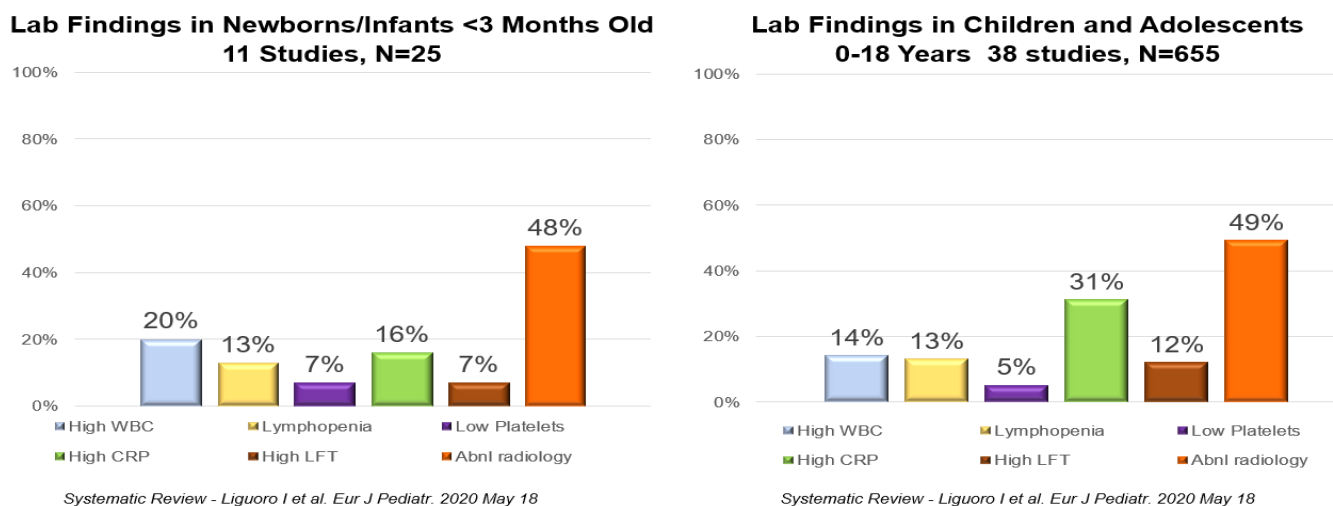
Figure 7: Symptoms of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents



Laboratory findings demonstrated more leukocytosis (elevated white cell count) in newborns/infants than overall children and they had elevated CRP levels; 64 per cent of neonates had a chest radiograph, and abnormal

findings were observed in 48 per cent, similar to overall children (Figure 8). Given the small number of newborns/infants, caution is needed in interpreting comparisons with older children.

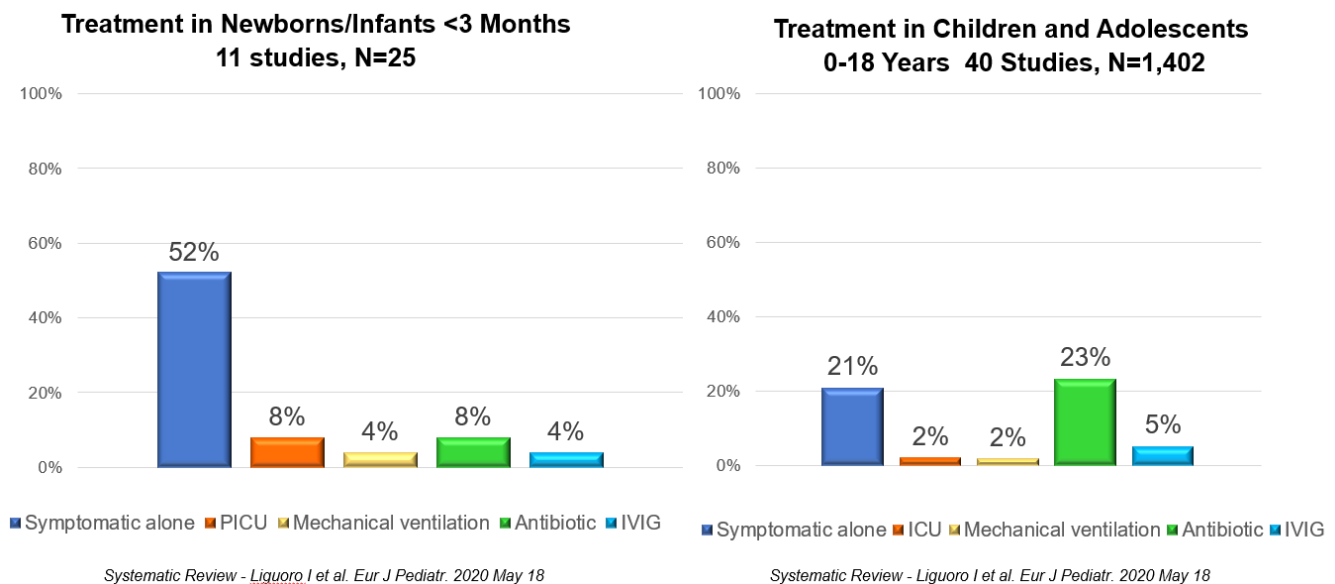
Figure 8: Laboratory and radiologic findings of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents



More newborns/infants received only symptomatic treatment, 52 per cent, compared with 21 per cent for children overall. However, 8 per cent were admitted to the neonatal intensive care unit compared to 2 per cent pediatric intensive care for children overall (Figure 9). This may have been because infants

born to mothers with COVID-19 disease are more likely to be born preterm or that they were admitted for observation because of COVID-19 disease in their mother (Trad). Again because of the small sample size for newborns/infants, caution should be exercised in interpreting results.

Figure 9: Treatment of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents



Since the meta-analysis has been published, data on an additional 102 infants <3 months with laboratory-confirmed horizontally-acquired SARS-CoV-2 infection have been published in 16 case reports and 9 small case series. Table 3 contains data on individual papers including numbers, age, exposures, symptoms, laboratory findings and outcomes.

Only ten infants (10 per cent) were asymptomatic. Fever was the most common presenting symptom (and the only symptom a few single case reports), followed by cough, upper respiratory symptoms, feeding difficulty or vomiting; 11 infants (11 per cent) had some neurologic symptoms, including lethargy,

hyporeactivity, irritability, high-pitched crying/hyperexcitability and in one case, possible seizure. Over 90 per cent of infants had no comorbidities; of those with comorbidities, these were primarily prematurity or congenital defects. Coinfections were observed in eight children, primarily urinary tract infection in six and one case each of human metapneumovirus and rhinovirus. Only a few children showed signs of hyperinflammation or lymphopenia. Radiologic exam was primarily confined to infants with respiratory symptoms, with 33 of 52 with an exam with reporting abnormal radiographs, most with mild abnormalities.

Most infants (90 per cent) were admitted to the hospital. While the majority of infants received antibiotics and a work-up to rule out sepsis, most care was supportive only; intensive care was required by only 20 infants, oxygen support in 13, and mechanical ventilation in eight. There were no deaths.

Thus, SARS-CoV-2 infection in young infants, as in older children, was primarily mild, requiring supportive treatment only, although serious, life-threatening illness was seen in a small minority of children, with no mortality.

Table 3: SARS-CoV-2/COVID-19 in Infants Age <3 Months – Case Reports and Series

Author, Journal, Country	Number Infants, Age, Exposure	Symptoms, Laboratory, Outcomes
De Bernardo G <i>J Perinatol</i> multi-country	N=25 Age 1–25 days Exposure: parents/household	<ul style="list-style-type: none"> Fever 10 (40%); vomiting 4 (16%), cough/shortness breath 3 (12%); 4 (20%) asymptomatic CXR (N=15) abnormal (mild) 13, normal 2 Hospitalization: ICU 8 (32%), mechanical ventilation 5 (20%); complications: pneumothorax and sepsis 1, pneumonia 3; discharge day 5–40; <i>no deaths</i>
McLaren SH <i>Pediatrics</i> US	N=7 Age 11–58 days Exposure: 1 household, 6 unknown	<ul style="list-style-type: none"> Fever 100% (only symptom in 3, 43%); cough 2 (29%), URI 1, vomiting 1, feeding difficulty 1 (14% each); no comorbidity CXR normal 4/4, lab normal, negative blood/CSF cultures; <i>coinfection</i> 2, 29% (E Coli UTI) Hospitalized: 6 (86%), no oxygen/ventilation; discharge day 1–2; <i>no deaths</i>
Wei M <i>JAMA</i> China	N=2 Age 2–3 months Exposure: household	<ul style="list-style-type: none"> <u>No</u> fever; runny nose, cough; no comorbidity Hospitalized: supportive care, no complications; <i>no deaths</i>
Cui Y <i>J Infect Dis</i> China	N=1 Age 55 d Exposure: parents	<ul style="list-style-type: none"> <u>No</u> fever; rhinorrhea, dry cough CXR abnormal (mild); elevated LFT and elevated cardiac enzymes, other lab normal including CRP, d-dimer; negative viral panel Hospitalized: antibiotics, supplemental oxygen; improved over 13 days
Robbins E <i>Ped Infect Dis J</i> US	N=1 Age 58 days Exposure: not provided	<ul style="list-style-type: none"> Fever, periorbital edema; no comorbidity CXR normal, lab normal, negative cultures and respiratory panel Hospitalized: antibiotics; discharge day 2
Mirahmadizadeh A <i>Arch Ped Infect Dis</i> Iran	N=1 Age: 11 days Exposure: mother	<ul style="list-style-type: none"> <u>No</u> fever; diarrhea, no respiratory distress; no comorbidity CXR mild abnormal, lab normal including CRP; negative cultures Hospitalized: NICU, antibiotics, supportive care; discharge day 6
Mahdavi <i>ID Cases</i> Iran	N=1 Age 18 days Exposure: household (symptoms)	<ul style="list-style-type: none"> Fever, respiratory distress, nasal congestion, cough, wheezing; no comorbidity CXR and CT abnormal; lab including CRP normal, negative cultures Hospitalized: NICU, antibiotics, oxygen; discharge day 7
Cao W <i>Medicine</i> China	N=1 Age 35 days Exposure: household	<ul style="list-style-type: none"> <u>No</u> fever; asymptomatic (tested due to contacts); in hospital, cough, vomit x 1 day; no comorbidity Chest CT normal; lab including CRP normal, negative respiratory panel Hospitalized: supportive therapy, recombinant interferon alfa-2b; discharge day 17
Eghbalian F <i>Clin Pediatr</i> Iran	N=1 Age 6 days Exposure: mother (symptoms)	<ul style="list-style-type: none"> <u>No</u> fever, asymptomatic (admitted due to maternal symptoms); no comorbidity CXR, ECHO normal; lab normal including CRP, negative cultures Hospitalized: NICU for isolation, monitoring only, discharge day 6

Author, Journal, Country	Number Infants, Age, Exposure	Symptoms, Laboratory, Outcomes
Lorenz N <i>Ped Infect Dis J</i> Germany	N=1 Age 1 day Exposure: mother	<ul style="list-style-type: none"> Fever at 24 hours, lethargic; "encephalitic symptoms (high pitched crying, hyperexcitable) at 54 hours; developed cough, respiratory distress 80 hr CXR abnormal; negative head sonogram and cultures Hospitalized: NICU, oxygen CPAP to day 6; discharge day 14
Meslin P <i>Ped Infect Dis J</i> France	N=6 Age 11 days to 2 months Exposure: household	<ul style="list-style-type: none"> Fever 100% (only symptom in 3); rhinitis 2, cough, vomiting in 1; comorbidity 1 (PDA) CXR abnormal 1/1; lab normal including CRP Hospitalized: no ICU, 1 required oxygen for 2 days, rest supportive; discharged day 4–12, <i>no deaths</i>
Ng KF <i>Ped Infect Dis J</i> UK	N=3 Age 5 day–2 months Exposure: 1 known, 2 unknown	<ul style="list-style-type: none"> Fever 2 (67%); cough, coryza 1, decreased feeding 2, apnea 1; comorbidity: 1 (preterm 34 wk, small atrial-septal defect) CXR abnormal 1/1 (preterm); <i>coinfection</i> seasonal CoV in preterm infant Hospitalization: 1 (33%) (preterm) requiring PICU, oxygen CPAP; discharge day 8; <i>no deaths</i>
Wardell H <i>J Ped Infect Dis Soc</i> US	N=4 Age 19–24 days Exposure: household	<ul style="list-style-type: none"> Fever 100%; cough/congestion 1, lethargy 1, decreased oral intake 1; no comorbidity CXR abnormal in 2/2; ECHO abnormal 1/2; normal CRP, ferritin, troponin 2/2; elevated NT-proBNP 1/1; mild increase D-dimer 2/2; negative blood/CSF culture; <i>coinfection</i> 2 (50%) (E Coli UTI, human metapneumovirus) Hospitalized: antibiotics 100%; 1 remdesivir and acyclovir; 2 (50%) ICU with oxygen by nasal cannula; discharge day 2–9; <i>no deaths</i>
Tchidjou <i>J Trop Ped</i> France	N=1 Age 6 weeks Exposure: Parents	<ul style="list-style-type: none"> Fever only Lab normal including CRP, negative respiratory screen; <i>coinfection</i> UTI <i>Citrobacter koseri</i> Hospitalized: antibiotics; discharge day 5
Nyholm S <i>Acta Paediatr</i> Sweden	N=1 Age 9 weeks Exposure: parents	<ul style="list-style-type: none"> <u>No</u> fever; apnea, irritability, tachycardia; comorbidity: preterm 30-week twin CXR abnormal; lab mild increase in procalcitonin, IL-6, D-dimer, ferritin, lymphopenia; negative cultures and respiratory panel Hospitalized: PICU, antibiotics, mechanical ventilation x 6 days; discharge day 9
Del Barba P <i>Pediatr Pulmonol</i> Italy	N=1 Age 38 days Exposure: parents	<ul style="list-style-type: none"> Fever, rhinitis, mild hyporeactive CXR increased markings; lab normal including CRP except increased procalcitonin, troponin T, D-dimer but ECHO normal except small pericardial effusion; negative cultures Hospitalized: Supportive, no oxygen or antiviral therapy, discharge day 14
Mithal LB <i>J Pediatr</i> US	N=18 Age 10–88 days Exposure: contacts in 14, unknown 4	<ul style="list-style-type: none"> Fever 14 (78%); cough 8 (44%), GI 4 (22%), poor feeding 5 (28%), 1 asymptomatic (screened due to parents); no comorbidity CXR normal 5/5; WBC low 2/12, negative cultures (except urine) and respiratory panel; <i>coinfection</i>: 1 UTI (<i>Strep agalactiae</i> and <i>Klebsiella oxytoca</i>) Hospitalized: 9 (50%), antibiotics, supportive care only, discharged day 1–3; <i>no deaths</i>

Author, Journal, Country	Number Infants, Age, Exposure	Symptoms, Laboratory, Outcomes
Cook J <i>Lancet Child Adoles Health</i> UK	N=1 Age 8 weeks Exposure: unknown	<ul style="list-style-type: none"> • <u>No</u> fever; poor feeding, sneezing, dyspnea – presented in respiratory failure and shock; comorbidity: preterm 27 wks • CXR abnormal; ECHO normal; lab: renal, liver dysfunction 1st week; lymphopenia, elevated IL6, ferritin, CRP; negative cultures and respiratory panel • Hospitalized: ICU with mechanical ventilation x16 days; antibiotics, acyclovir, remdesivir; still inpatient off respiratory support day 24
Precit MR <i>J Ped Infect Dis Soc</i> US	N=1 Age 10 days Exposure: household	<ul style="list-style-type: none"> • <u>No</u> fever; increased nasal secretions and laboured breathing/respiratory failure, hypoxia; no comorbidity • CXR abnormal; lab normal; negative cultures and viral panel; 2nd admission human metapneumovirus positive • Hospitalized: PICU, oxygen by cannula, no antiviral; discharge day 4 (return 5 days later, admit 1 day)
Dumpa V <i>Cureus</i> US	N=1 Age 22 days Exposure: community	<ul style="list-style-type: none"> • Fever, poor feeding; no comorbidity • CXR normal, lab normal; negative cultures and respiratory panel • Hospitalized: supportive care; discharge day 2
Feld L <i>Pediatrics</i> US	N=3 Age 28–43 days Exposure: household	<ul style="list-style-type: none"> • Fever 3, 100%, feeding difficulty 3 (100%), lethargy/irritability 2 (66%); comorbidity (single left kidney) • Lab: lymphopenia; negative cultures and respiratory panel • Hospitalized 2/3 (66%): no oxygen support needed; discharged at day 2–3; <i>no deaths</i>
Sinelli MT <i>Pediatrics</i> Italy	N=1 Age 3 days Exposure: mother (postpartum)	<ul style="list-style-type: none"> • At age 3 days: Perioral cyanosis, poor sucking, no respiratory distress but moderate hypoxia; no comorbidity • CXR mildly abnormal, CT normal; ECHO normal; negative cultures and respiratory screen • Hospitalized: NICU, antibiotics, oxygen by cannula; discharge day 18
Chacon-Aguilar R <i>An Pediatr</i> Spain	N=1 Age 26 days Exposure: household	<ul style="list-style-type: none"> • Fever, nasal discharge, vomiting, paroxysmal episodes (?seizures); no comorbidity • Cranial ultrasound and EEG normal; except elevated DPK and LDH lab normal including CRP; negative cultures and respiratory screen • Hospitalized: supportive care; discharge day 6
Nathan N <i>Lancet</i> France	N=5 Age <3 months Exposure: community	<ul style="list-style-type: none"> • Fever 100%; runny nose, cough 4 (80%), neurologic symptoms (hypotonia, drowsiness or moaning) 4 (80%); no comorbidity • CXR normal; lab normal including CRP; negative cultures (including CSF 4/4) • Hospitalized: supportive care; discharge day 1–3; <i>no deaths</i>
Munoz <i>N Engl J Med</i> US	N=1 Age 3 weeks Exposure: household	<ul style="list-style-type: none"> • <u>No</u> fever - hypothermia; nasal congestion, tachypnea, hypoxia, hypotension • CXR abnormal, ECHO normal; lab elevated procalcitonin and CRP; negative cultures; <i>coinfection</i>: rhinovirus • Hospitalized: PICU, antibiotics, hydroxychloroquine/azithromycin, mechanical ventilation x 5 days with pneumothorax complication; discharge day 9

Author, Journal, Country	Number Infants, Age, Exposure	Symptoms, Laboratory, Outcomes
Kan MJ <i>J Ped Infect Dis Soc</i> US	N=1 Age 5 weeks Exposure: household	<ul style="list-style-type: none"> Fever only; comorbidity hydronephrosis and duplex kidney Lab: leukopenia, lymphopenia with normal CRP; negative cultures and respiratory panel Hospitalized: antibiotics, supportive care, discharge day 3
Aghdam MK <i>Infect Dis</i> Iran	N=1 Age 15 days Exposure: parents (symptoms)	<ul style="list-style-type: none"> Fever, lethargy; no comorbidity CXR normal, ECHO patent foramen ovale; lab normal including CRP; negative cultures and influenza Hospitalized: NICU, antibiotics, oxygen; discharge day 6
Mogharab V <i>J Formosan Med As</i> Iran	N=1 Age 75 days Exposure: not provided	<ul style="list-style-type: none"> Fever, cough, dyspnea; no comorbidity Chest CT abnormal, lab normal Hospitalized: oxygen, improved
Paret M <i>Clin Infect Dis</i> US	N=2 Age 25 and 56 days Exposure: 1 parents (symptoms), 1 unknown	<ul style="list-style-type: none"> Fever only; comorbidity in one 35-week preterm infant Lab normal including CRP; Negative cultures and respiratory panel Hospitalized: antibiotics; discharge day 3
Canarutto D <i>Ped Pulmonol</i> Italy	N=1 Age 32 days Exposure: father (symptoms)	<ul style="list-style-type: none"> Fever, rhinitis, cough; no comorbidity CXR normal, lab including CRP normal, negative cultures Hospitalized: antibiotics, supportive only, discharge day 5
Le HT <i>Lancet Child Adoles Health</i> Vietnam	N=1 Age 3 months Exposure: household	<ul style="list-style-type: none"> Fever, rhinorrhoea, nasal congestion; no comorbidity CXR and ECHO normal, lab normal including CRP and procalcitonin; negative respiratory panel Hospitalized: supportive only, discharge 9 days
White A <i>Neonatology</i> US	N=3 Age 18–33 days Exposure: household 2, unknown 1	<ul style="list-style-type: none"> Fever 3 (100%); rhinorrhoea, mild hypoxia; youngest infant bilateral conjunctivitis, hypotension CXR very mild changes 3/3; one had lymphopenia and mild elevation CRP, rest lab normal including CRP and procalcitonin; negative cultures and respiratory panel Hospitalized: NICU, antibiotics, supplemental oxygen; discharge day 3–4; <i>no deaths</i>
Gregorio-Hernandez R <i>Eur J Ped</i> Spain	N=3 Age 2–78 days Exposure: mother in 1, contact with infected infant 2	<ul style="list-style-type: none"> All asymptomatic: one infant diagnosed due to postpartum maternal fever, others tested due to contact investigation in NICU after this diagnosis; comorbidities 100%: preterm/bronchopulmonary dysplasia; meconium aspiration syndrome/severe hypoxic-ischemic encephalopathy; Hirschsprung's Lung ultrasound abnormal all; 2/3 (66%) elevated inflammatory markers: laboratory elevated CRP 1, ferritin 2, D-dimer 2. Hospitalization: one infant: mechanical ventilation birth–6 days and oxygen cannula 16 days; one infant: oxygen dependent due to BPD/preterm, still in hospital; one infant admitted for Hirschsprung's disease no respiratory support needed; <i>no deaths</i>

Severe SARS-CoV-2 infection in children and adolescents

In the United States between March 1–July 25, 2020, 576 children and adolescents were reported to the COVID-19-Associated Hospitalization Surveillance System (COVID-NET), a population-based surveillance system in 14 states (Kim). Comorbidities were reported in 42.3 per cent. Younger children were at higher risk of hospitalization; the cumulative COVID-19-associated hospitalization rate was highest among children aged <2 years, 24.8/100,000, compared to those aged 2–4 years (4.2/100,000) and 5–17 years (6.4/100,000). Among 208 children with a medical chart review completed, 69, 33.2 per cent, required intensive care unit admission and invasive mechanical ventilation was required by 12, 5.8 per cent. However, only one child, with multiple underlying conditions, 0.5 per cent, died during hospitalization.

While children have lower rates of mechanical ventilation and death than adults, 1 in 3 children hospitalized with COVID-19 in the United States were admitted to the intensive care unit, which is the same as observed for hospitalized adults (Kim). Children admitted to pediatric intensive care units with significant COVID-19 disease have a high rate of co-morbidities as well as mortality. In a study of 48 children admitted to 46 pediatric intensive care units (PICU) in Canada and the United States between March 14 and April 3, 2020, 31 (83 per cent) had significant pre-existing co-morbidities. Co-morbidities in these 31 children included medically complex conditions (children with a long-term dependence on technology support including tracheostomy associated with developmental delay or genetic abnormalities) in 19, immune suppression/malignancy in 11, obesity in 7, diabetes in 4, seizures in 3, congenital heart in 3, sickle cell disease in 2,

chronic lung disease in 2, and other congenital abnormalities in 2 (Shekerdemian). Seventy-three per cent of children presented with respiratory symptoms, 38 per cent required mechanical ventilation, and their mortality rate was 4 per cent, both with both deaths occurring in adolescents.

In a report on 177 children diagnosed with COVID-19 at Children's National Medical Center in Washington DC, 25 per cent required hospitalization, with 5 per cent needing critical care and 2.3 per cent mechanical ventilation (DeBiasi). Co-morbidities were more common in children who were hospitalized than those not hospitalized (63 per cent vs 32 per cent, respectively, $p < 0.001$), with neurological disorders more common in the hospitalized cohort (19 per cent vs 2 per cent, $p < 0.001$) and cardiac, hematologic, and oncologic diagnoses also significantly more common in hospitalized children. Children aged <1 year and adolescents/young adults aged >15 years accounted for 64 per cent of those hospitalized; adolescents/young adults >15 years represented 66 per cent of critical care admissions, with the median age of critically ill patients significantly higher than those not critically ill (17.3 vs 3.6 years, $p = 0.04$).

A third report from a single center in Paris, France, reported on 27 children admitted to the PICU; comorbidities were present in 70 per cent (primarily neurologic, respiratory or sickle cell disease) (Oualha). Mechanical ventilation was required by nine, 33.3 per cent, of children, and extracorporeal membrane oxygenation by one. There were five deaths (18.5 per cent), three in older adolescents and two in children ≤ 6 years; three had no underlying conditions.

A final report from 10 PICUs in Chile, Columbia, Italy, Spain and the United States described on 17 children with COVID-19 admitted to the

PICU; as in the above reports, children with co-morbidities were common, 71 per cent (Gonzalez-Dambrauskas). Invasive mechanical ventilation was required by eight, 47 per cent, and there was one death, 5.9 per cent, in a three-year-old child.

In summary, although children generally appear to have milder COVID-19 disease than adults, they can be extremely ill and if admitted to paediatric ICU have elevated mortality. As in adults with COVID-19, the existence of co-morbidities may increase the severity of disease as well as mortality in children.

Underlying medical conditions and outcomes in children and adolescents

The current published studies on the interaction of COVID-19 disease and underlying co-morbidities and vulnerabilities are mainly from HICs and among adults. The main causes of death for young children that are more common in LMICs—e.g. pneumonia, malaria, diarrhea—are not yet covered here. More data and research are needed to understand the role of pre-existing health conditions and COVID-19 disease among children and adolescents in LMICs.

Pre-existing underlying health conditions are common in adults hospitalized for COVID-19. In the United States, 92 per cent of hospitalized adults had at least one underlying medical condition, most commonly hypertension, obesity, chronic metabolic disease and cardiovascular disease (CDC COVID19). Pre-existing health conditions, while less frequent in children, were observed in 61 per cent of hospitalized children in the same report, most commonly obesity, asthma and neurologic disease (CDC COVID19).

A review of 20 studies from 26 countries (primarily from China and the United States) including 655 infected children with data on co-morbidity, reported that 233, 35.6 per cent, had an underlying condition (Hoang). The most common co-morbidity was immunosuppressive conditions, 30.5 per cent, followed by respiratory conditions, 21.0 per cent, cardiovascular conditions 13.7 per cent, and medically complex/congenital malformation disorders in 10.7 per cent. Hematologic and neurologic conditions, obesity and prematurity were reported in under 4 per cent.

In recent data from the COVID-NET population-based surveillance of hospitalized children in the United States, 222 children had data on underlying conditions; 94 of 222, 42.3 per cent, had an underlying condition, most commonly obesity, chronic lung disease, or neurologic disorder (*Table 4*) (Kim).

Table 4. Underlying Medical Conditions in Children and Adolescents Hospitalized with COVID-19 in the United States March 1–July 25 2020

Condition	Number with condition/total (%)
<i>Any underlying condition</i>	94/222 (42.3%)
Obesity	42/111 (37.8%)
Chronic lung disease	40/222 (18.0%)
Asthma	30/222 (13.5%)
Prematurity (gestational age <37 weeks)	10/65 (15.4%)
Neurologic disorder	31/222 (14.0%)
Immunocompromised condition	12/222 (5.4%)
Feeding tube dependent	12/222 (5.4%)
Chronic metabolic disease	10/222 (4.5%)
Diabetes mellitus	6/222 (2.7%)
Blood disorder	8/222 (3.6%)
Sickle cell disease	5/222 (2.3%)
Cardiovascular disease	7/222 (3.2%)
Congenital heart disease	4/222 (1.8%)

Nutrition/Obesity and SARS-CoV-2

While there are concerns that a malnourished status may be associated with immune dysfunction, there are currently no data regarding the susceptibility to or disease course of SARS-CoV-2 among children or adults with severe malnutrition (e.g., underweight, stunting) (Briguglio). The lack of data is not surprising given that SARS-CoV-2 is just beginning to increase in low-and middle-income countries where severe nutritional deficiencies in children and adults is often more prevalent.

Obesity has been identified as a co-morbidity in both adults and children requiring hospitalization with SARS-CoV-2, and has been shown to be an independent risk factor for hospital admission and adverse outcomes including need for intensive care unit admission, mechanical ventilation and mortality (de Carvalho Sales-Peres, Steinberg, Tartof,

Kass). In a report on 50 hospitalized children with COVID-19 in New York City, 22 per cent of all children and 67 per cent of children with severe disease were obese (Zachariah). Obesity is associated with chronic low-grade inflammation and a disrupted immune response, and has been shown to impair the adaptive immune response to infection through alterations in T-cell function secondary to perturbations in T-cell metabolism stemming from nutrient, hormone and adipokine dysregulation in obese individuals (Korakas, Green).

Asthma and SARS-CoV-2

In a study at Rush University Medical Center in Chicago of 474 children <18 years who had virologic testing as out-patients for SARS-CoV-2 between March 12 and April 20 2020, 25 (5.2 per cent) were positive, and the prevalence of

pre-existing asthma did not differ significantly between those who were positive for SARS-CoV-2 and those who were negative (12 per cent vs 10.2 per cent, respectively). Among those children admitted to the hospital, only one had asthma and also had sickle cell acute pain crisis (Bandi).

Similarly, in a study at Children's National Medical Center in Washington DC, although asthma was the most prevalent underlying condition in 177 children with COVID-19, it was not more common in children who were hospitalized compared to not hospitalized (16 per cent and 22 per cent, respectively) or in the more critically ill cohort (DeBiasi).

Among adult in-patients in Wuhan China, the prevalence of asthma in patients with COVID-19 was 0.9 per cent, markedly lower than that in the adult population in Wuhan and was not significantly different between severe and non-severe cases (Li X). Consistent with these data, a study of ACE2 gene expression from nasal or lower airway epithelial brush samples from three cohorts of children and adults with and without asthma found ACE2 expression was decreased in the nasal epithelium of children and adults with asthma and allergic sensitization (Jackson).

Cancer/Immune Suppression and SARS-CoV-2

There have been few reports of SARS-CoV-2 and cancer in children. A case of severe COVID-19, with concomitant influenza A, in a child undergoing myelosuppressive therapy for T-cell acute lymphocytic leukemia in China was reported (Sun). A survey on COVID-19 incidence was sent to pediatric hematology/oncology departments in Europe, with responses from 32 centers in 25 countries (Hrusk). Of >200 children tested for SARS-CoV-2, only nine cases of infection were identified; none required

intensive care and they had mild, self-limited infection.

In Italy, 14 pediatric hematology-oncology centers adopted a policy to screen all childhood cancer patients for SARS-CoV-2 before starting chemotherapy or entering the hospital for supportive measures; 10 of 247 children tested positive, all in northern Italy where the epidemic was more prevalent (Cesaro). Among these children, eight were completely asymptomatic while two presented with mild fever; chemotherapy was paused until rtPCR tests turned negative and all children did well. Similarly, in Memorial Sloan Kettering Cancer Center in New York City, 20 childhood cancer patients with SARS-CoV-2 infection were identified of 178 tested. Only 5 per cent required hospitalization for symptoms of COVID-19 (Boulad).

Similar results were reported from the Association of Pediatric Oncology and Hematology (AIEOP) in Italy which collected data from 13 AIEOP centers on SARS-CoV-2 infection diagnosed in 29 pediatric oncology patients while on chemotherapy/immunotherapy or after stem cell transplantation; median age was 7 years (Bisogno). The course of SARS-CoV-2 was mild in all cases, with 17 children being asymptomatic and 12 developing mild symptoms; 15 were hospitalized but none needed intensive care. Among 26 patients on chemotherapy or immunotherapy, treatment was suspended in 16 patients for median of 26 days while 10 continued their chemotherapy (two with minor modifications).

The European Rare Kidney Disease Reference Network has a ongoing survey of 16 pediatric nephrology centers across 11 countries to report outcomes among children with kidney disease on immunosuppressive medication who

are diagnosed with COVID-19. Through April 2020, 18 such children have been reported; all had a mild clinical course, with 7 (39 per cent) not admitted to the hospital and none admitted to the hospital requiring admission to intensive care (Marlais).

Similarly, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) conducted a survey among 102 affiliated centers in Europe on COVID-19 cases in children with inflammatory bowel disease (IBD) (Turner). Within Europe, eight children with IBD and COVID-19 have been reported; all had mild infection without the need for hospitalization despite treatment with immunosuppressive medication, steroids or biologics nor was there evidence of IBD disease worsening.

Congenital Cardiac Disease and SARS-CoV-2

A small case series of seven pediatric patients with congenital heart disease hospitalized with COVID-19 were reported from Atlanta, Georgia (Simpson). New or worsening heart failure was common, with four presenting with acute congestive heart failure, one with de novo acute heart failure and three with acutely decompensated chronic heart failure. In addition to heart failure, new cardiac arrhythmias and evidence of myocardial inflammation were noted. The majority of cases (five of seven) were under age one year.

HIV and SARS-CoV-2

A systematic review of COVID-19 in adults with HIV infection reported on 252 coinfecting patients from 25 studies, the vast majority from high or middle-income countries with one case report from Uganda (Mirzaei). In this analysis, overall outcome of COVID-19 in adults living with HIV appeared similar to the overall adult

population with HIV, with mortality associated with co-morbidity and age and not HIV infection. Most patients were male, with a mean age of 52 years; the majority (98 per cent) were receiving antiretroviral therapy, CD4 cell count <200 cells/mm³ was reported in only 13.1 per cent, and only 0.9 per cent had HIV viral load >1,000 copies/mL. Multi-morbidity was reported in nearly two-thirds of patients. Disease was mild to moderate in 66.5 per cent, with 16.8 per cent admitted to the intensive care unit. Mortality occurred in 36 (14.3 per cent), with 90 per cent of deaths occurring in individuals age >50 years, and 64.3 per cent had multi-morbidities.

However, a preliminary analysis of public sector data in adults age >20 years by the Provincial Health Data Centre in the Western Cape, South Africa found that adults with HIV infection had a modestly higher risk of mortality from COVID-19 disease than HIV-uninfected individuals (hazard ratio 2.75, 95 per cent CI 2.09–3.61), with no significant difference by HIV viral suppression status (Nordling, Bhekisisa, Davies). Other risk factors included male sex, older age, non-communicable disease co-morbidities such as diabetes and hypertension, and history of current or past tuberculosis. The majority of adults with HIV who died of COVID-19 had other co-morbidities, including diabetes and hypertension; thus mortality was not being seen in individuals with advanced HIV disease but rather individuals living with HIV who were on treatment but had significant co-morbidities associated with increased mortality risk in individuals without HIV infection. They estimated that <10 per cent of COVID-19 deaths in the Western Cape were associated with HIV. Two recent pre-print papers from the United Kingdom have also similarly suggested that adults living with HIV infection with COVID-19 co-infection may have an increased mortality risk, with older age, black ethnicity,

and co-morbidities being associated with complications and mortality (Geretti, Bhaskaran).

Importantly, there are, however, no data on children, adolescents and pregnant women with HIV infection and SARS-CoV-2/COVID-19 to date .

5. The Evolving Spectrum of SARS-CoV-2 in Children

The emergence of multi-system inflammatory syndrome in children and its relation to SARS-CoV-2 infection is a worrying development that needs close and constant monitoring and response

In mid-late April 2020, reports from Western Europe identified a new febrile paediatric entity multi-system inflammatory syndrome temporally associated with SARS-CoV-2 infection in children, with 230 suspected cases reported in the United Kingdom and European Union (European Centers for Disease Prevention and Control). The syndrome consists of systemic hyperinflammation, multi-organ involvement, abdominal pain and gastrointestinal symptoms, features similar to Kawasaki Disease (KD), and prominent cardiogenic shock and myocardial dysfunction. Most children have either a respiratory sample positive for SARS-CoV-2 by rtPCR or the

presence of IgM and/or IgG SARS-CoV-2 antibody, although they may not have had symptoms of infection; in those with a history of symptoms, the syndrome occurs two to four weeks after resolution, suggesting a post-infectious, delayed hyperinflammatory immune response to infection (Whittaker).

By early May cases were also reported in the United States, and in mid-May, the U.S. Centers for Disease Control and Prevention (CDC) issued a surveillance definition for what they called multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2, and a request for reporting of cases (CDC). As of August 6, 2020 CDC had received reports of 570 cases of MIS-C in 40 state health departments, District of Columbia and New York City, with 10 deaths (Godfred-Cato). With increasing cases being reported globally, the World Health Organization published a scientific brief on MIS-C and requested global reporting (WHO).

The case definitions for PIMS-TS/MIS-C in Europe, US and from WHO have a few minor differences, but all require evidence of fever, organ dysfunction, laboratory evidence of inflammation in a child where other etiologies are ruled out and there is a positive diagnosis of SARS-CoV-2 or recent contact with an individual with SARS-CoV-2 infection (*Table 5*).

Table 5. Definitions of Pediatric Multisystem Inflammatory Syndrome: Europe, U.S., WHO

<p><u>Preliminary Royal College of Paediatrics and Child Health, UK, case definition Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PMIS-TS)</u></p> <ul style="list-style-type: none"> • A child presenting with persistent fever • And evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other additional clinical, laboratory or imaging and ECG features (children fulfilling full or partial criteria for Kawasaki disease may be included) and • And inflammation (neutrophilia, elevated CRP and lymphopaenia) • And exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus. • And SARS-CoV-2 PCR testing positive or negative.
<p><u>CDC: Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)</u></p> <ul style="list-style-type: none"> • An individual aged <21 years presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours). • And evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological). • And laboratory evidence of inflammation (Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin). • And no alternative plausible diagnoses. • And positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms. <p>Additional comments: Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C; consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection</p>
<p><u>WHO: Preliminary case definition for Multisystem Inflammatory Syndrome in Children (MIS-C)</u></p> <ul style="list-style-type: none"> • Children and adolescents 0–19 years of age with fever ≥ 3 days • And <u>two</u> (or more) of the following: <ol style="list-style-type: none"> 1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). 2. Hypotension or shock. 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), 4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers). 5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). • And elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. • And no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. • And evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

While many cases resemble Kawasaki Disease (KD), MIS-C has distinct features (Shulman). Children with MIS-C are older: in KD, 50 per cent of children affected are <24 months and 80 per cent <5 years, compared to mean age 8–10 years, including adolescents, with MIS-C. The inflammation with MIS-C appears far greater than that observed with KD, with elevated markers of hyperinflammation including ferritin, d-dimers, IL-6 and c-reactive protein, and clinical features of MIS-C include more impressive abdominal pain, diarrhea, vomiting and multi-organ involvement including acute kidney injury. Cardiac features of MIS-C show moderate to severe myocardial involvement (as documented by imaging and very high NT-pro-BNP and troponin levels) that is greater than that seen with KD or KD shock syndrome. Additionally, KD is more frequent in Asian countries but MIS-C has not yet been reported in Asia. In several series, MIS-C seemed more common in children of African ancestry. Finally, laboratory features are distinct from KD, with elevated markers of hyperinflammation including ferritin, D-dimers, IL-6, and CRP as well as lymphopenia and thrombocytopenia.

Cases of MIS-C have been reported in multiple case series from the United States, United Kingdom, Italy, France, and Spain as well as numerous case reports from other countries including Iran, Israel, India, Pakistan, Brazil, and Ecuador. *Table 6* shows demographic, clinical, laboratory, treatment and outcome data from 780 children hospitalized with MIS-C from eight studies in seven countries; the largest non-duplicative studies were chosen for each country.

The median age ranges from 6 to 10 years, although there have been case reports of MIS-C in infants as well as older adolescents/young adults (Del Barba, Giacomet, Kesici, Craver, Ng J, Gnechhi, Trogen). A relatively high proportion of cases have occurred among black or Hispanic children in countries that have reported

race/ethnicity (Godfred-Cato, Pouletty, Toubiana, Davies). The majority of children are previously healthy without co-morbidities. Most patients have antibodies against SARS-CoV-2, with viral detection in a smaller proportion. Multi-system organ system dysfunction is evident, most commonly gastrointestinal (abdominal pain, diarrhea, vomiting) and cardiovascular systems, with mucocutaneous involvement also frequent; renal, neurologic, and respiratory system involvement has also been reported. New neurologic manifestations involving both the peripheral and central nervous system, including abnormalities on brain magnetic resonance imaging, were reported in 14.8 per cent of 27 children with MIS-C in the United Kingdom (Abdel-Mannan). Coagulopathy has been rarely reported including venous thrombosis and pulmonary emboli (Feldstein, Davies). Features associated with KD (rash, mucous membrane changes/conjunctivitis, peripheral extremity edema and erythema, cervical lymphadenopathy) are common, although all diagnostic criteria may not be met. Elevations in inflammatory markers are near universal, with frequent elevation in markers of cardiac damage (troponin, brain natriuretic peptide (BNP) or N-terminal proBNP) and lymphopenia.

Critical illness with shock leading to intensive care develops in a majority of patients, with need for invasive mechanical ventilation in 20 to 60 per cent. Prominent cardiac involvement, including the development of coronary artery dilatation and more rarely coronary artery aneurysms, is observed. While children with MIS-C can be critically ill, the majority have recovered with intensive care support and anti-inflammatory treatment including steroids, intravenous immunoglobulin and/or IL-1 or IL-6 blockers such as anakinra, sarilumab or tocilizumab (Viner Lancet, Shulman). Mortality appears rare although it can occur – in the 780 children included in *Table 6*, there were 13 deaths, 1.7 per cent.

Table 6: Multisystem Inflammatory Syndrome in Children Temporally Associated with COVID-19 – Characteristics, Treatment, Outcomes (Large Studies)

	Godfred-Cato US (national data)	Pouletty <i>Ann Rheum Dis</i> Paris France (7 hospitals)	Toubiana <i>BMJ</i> Paris France (separate hospital)	Davies <i>Lancet Child Adolesc Health</i> UK (23 Ped ICUs)	Verdoni <i>Lancet</i> Bergamo, Italy (single hospital)	Moraleda <i>Clin Infect Dis</i> Spain (41 hospitals)	Belhadjer <i>Circulation</i> France/ Switzerland (13 hospitals)	Dhanalakshmi <i>Indian Ped</i> India (single hospital)
N	570	16	21	78	10	31	35	19
Age: median	8 years	10 years	7.9 years	11 years	7.5 years	7.6 years	10 years	6 years
IQR	4–12	4.7–12.5	3.7–16.6	8–14	2.9–16.0	4.5–11.5	2–16	1–16.5
Race/ethnicity: Black	153 (33%)	10 (62%)	12 (57%)	37 (47%)	NP	NP	NP	NP
Hispanic	187 (41%)	-	-	-	-	-	-	-
White non-Hispanic	61 (13%)	4 (25%)	6 (29%)	17 (22%)	-	-	-	-
Asian	13 (3%)	0	2 (10%)	22 (28%)	-	-	-	-
Other/unknown	156 (17%)	2 (12%)	1 (5%)	2 (3%)	-	-	-	-
Gender: Female	254 (45%)	8 (50%)	12 (57%)	26 (33%)	3 (30%)	13 (42%)	17 (49%)	11 (58%)
Male	316 (55%)	8 (50%)	9 (43%)	52 (67%)	7 (10%)	18 (58%)	18 (51%)	8 (42%)
Comorbidity			NP		NP			
None	376 (66%)	10 (63%)	-	61 (78%)	-	21 (68%)	25 (72%)	18 (95%)
Yes	194 (34%)	6 (37%)	-	17 (21%)	-	10 (32%)	10 (28%)	1 (5%)
<i>Comorbidity Types</i>			NP		NP			1 (5%)
Respiratory	48 (8%)	2	-	-	-	4	3	-
Cardiac	-	-	-	-	-	1		-
Immunologic	-	-	-	-	-	2	1	-
Obesity	146 (26%)	4	-	-	-	3	6	-
Other	-	-	-	-	-	-	-	1 neurologic
SARS-CoV-2 diagnostics								
Positive rtPCR or antibody	565 (99%)	15/16 (94%)	19 (90%)	41 (53%)	8 (80%)	30 (97%)	31 (89%)	11 (58%)
rtPCR	302 (53%)	12 (75%)	8 (38%)	17 (22%)	2 (20%)	17 (55%)	14 (40%)	4 (21%)
antibody	418 (73%)	8 (50%)	19 (90%)	33/35 (94%)	8 (80%)	19/21 (90%)	30 (86%)	8 (42%)
Positive rtPCR and antibody	155 (27%)	5 (31%)	8 (38%)	9/10 (90%)	2 (20%)	7/21 (33%)	-	1 (5%)
Hx contact	5 (1%)	12 (75%)	-	8 (10%)	5 (50%)	16 (52%)	13 (35%)	-
Other							2 (CT finding)	-
Coinfection	NP	0/11	0/19	3 (4%) (2 bacterial, 1 viral)	0/10	3/21 (14%) (1 viral, 1 mycoplasma)	NP	NP
Organ system involvement								

Gastrointestinal	518 (91%)	13 (81%)	21 (100%)	70 (90%)	6 (60%)	27 (87%)	29 (83%)	8 (42%)
Cardiovascular	493 (87%)	11 (69%)	16 (76%)	28 (36%)	6 (60%)	25 (80%)	35 (100%)	12 (63%)
Hematologic	421 (74%)	-	-	[3 (4%) thrombi]	-	29 (97%) (‘coagulopathy’)	-	NP
Mucocutaneous/skin	404 (71%)	15 (94%)	17 (81%)	35 (45%)	8 (80%)	21 (67%)	31 (89%)	14 (74%)
Pulmonary	359 (63%)	2 (12%)	8/18 (44%)	-	5 (50%)	11 (36%)	12 (34%)	8 (42%)
Musculoskeletal	-	1 (6%)	2 (10%)	-	-	5/28 (18%)	-	-
Renal	105 (18%)	9 (56%)	11 (52%)	-	-	4 (13%)	-	3 (16%)
Neurologic	218 (38%)	9 (56%)	18 (86%)	-	4 (40%)	10 (34%)	11 (31%)	6 (31%)
Symptoms Fever	186 (100%)	16 (100%)	21 (100%)	78 (100%)	NP	30 (97%)	35 (100%)	19 (100%)
Gastrointestinal	518 (91%)	13 (81%)	21 (100%)	70 (90%)	6 (60%)	27 (87%)	29 (83%)	8 (42%)
Rash	315 (55%)	13 (81%)	16 (76%)	35 (45%)	7 (70%)	23 (74%)	20 (57%)	12 (63%)
Bilateral Conjunctivitis	276 (48%)	15 (94%)	17 (81%)	23 (29%)	8 (80%)		31 (89%)	9 (47%)
Mucus membrane changes	201 (35%)	14 (87%)	16 (76%)	-	6 (60%)	-	19 (54%)	9 (47%)
Peripheral extremity changes	-	11 (68%)	-	-	5 (50%)	-	-	10 (53%)
Neurologic	218 (38%)	9 (56%)	18 (86%)	-	4 (40%)	10 (34%)	11 (31%)	6 (31%)
Cervical lymphadenopathy	76 (13%)	6 (37%)	12 (57%)	-	1	4 (13%)	21 (60%)	6 (32%)
Respiratory signs	359 (63%)	2 (12%)	-	-	-	-	23 (65%)	8 (42%)
Respiratory insufficiency	34 (6%)	-	-	-	-	-	-	-
Shock at presentation	202 (35%)	11 (69%)	-	68 (87%)	5 (50%)	15 (48%)	28 (80%)	10 (53%)
Meet complete KD criteria	28 (5%)	10 (62%)	11 (57%)	66 (61%)	5 (50%)	-	0 (0%)	7 (37%)
Laboratory Neutrophilia	-	-	21 (100%)	78	8 (80%)	-	-	13 (69%)
Lymphopenia	202 (35%)	-	17 (81%)	78	8 (80%)	-	-	7 (37%)
Elevated inflammatory markers	-	16/16 (100%)	21 (100%)	78 (100%)	10 (100%)	31 (100%)	35 (100%)	19 (100%)
Elevated troponin	176 (31%)	11/11 (100%)	17 (81%)	-	5/9 (56%)	-	35 (100%)	1/6 (17%)
Elevated BNP or NT-proBNP	246 (43%)	11/11 (100%)	14/18 (78%)	-	10 (100%)	22 (71%)	5/5 (100%)	3/4 (75%)
Elevated CRP	-	16/16 (100%)	21 (100%)	-	9 (90%)	31 (100%)	35 (100%)	19 (100%)
Elevated fibrinogen	-	-	-	-	9 (90%)	-	-	7/9 (78%)
Elevated ferritin	-	12/14 (86%)	-	-	5/9 (56%)	29 (93%)	-	1 (21%)
Elevated D-dimer	344 (61%)	-	19/20 (95%)	-	8 (80%)	30 (97%)	20/20 (100%)	13/14 (93%)
Elevated IL6	-	6/6 (100%)	21 (100%)	-	4 (40%)	23 (74%)	13/13 (100%)	-
Chest XR Abnormal	-	5 (31%)	8/18 (44%)	-	5 (50%)	-	-	5/15 (33%)
Cardiac ECHO abnormal	207/510 (41%)	11 (69%)	8 (38%)	28 (36%)	6/10 (60%)	19 (61%)	31 (89%)	3 [0]

Arrhythmia	-	-	2/16 (13%)	-	-	7 (23%)	1 (3%)	-
Coronary dilation or aneurysm [aneurysm]	106 (19%) [-]	3 (19%) [0]	8 (38%) [0]	28 (36%) [18]	2 (20%) [2]	3 (10%) [1]	6 (17%) [0]	3 [0]
Myocarditis	130 (23%)	7 (44%)	16 (76%)	-	-	-	-	-
Pericarditis	-	4 (25%)	-	-	-	6 (19%)	-	-
Hospitalization ICU	364 (64%)	7 (44%)	17 (81%)	78 (100%)	NP	20 (65%)	35 (100%)	12 (63%)
Non-invasive ventilation	132 (23%)	3 (19%)	-	5 (6%)	NP	-	11 (28%)	NP
Invasive mechanical ventilation	69 (13%)	2 (13%)	11 (52%)	36 (46%)	NP	6 (19%)	22 (62%)	NP
ECMO	-	-	-	3 (4%)	NP	-	10 (28%)	NP
Treatment								
Vasoactive support	221 (42%)	6 (38%)	15 (71%)	65 (83%)	2/10 (20%)	-	28 (80%)	6 (32%)
Steroids	331 (63%)	4 (25%)	10 (48%)	57 (73%)	8/10 (80%)	21 (68%)	12 (34%)	11 (58%)
IVIg	424 (81%)	15 (93%)	21 (100%)	59 (76%)	10 (100%)	20 (65%)	25 (71%)	15 (79%)
Immune modulators*	119 (23%)	2 (12%)	-	17 (22%)	-	-	3 (8%)	1 (5%)
Anticoagulation	233 (44%)	8 (50%)	21 (100%)	-	-	-	23 (66%)	-
Aspirin	309 (59%)	-	-	39 (50%) (aspirin)	10 (100%)	-	-	16 (84%)
Antiviral	NP	0	NP	1 (5%) (remdesivir)	NP	9 (29%) (2 remdesivir, 7 LPV/r)	NP	NP
Antibiotics	NP	NP	18 (86%)	NP	NP	NP	NP	NP
Outcome Discharge	-	16 (100%)	21 (100%)	75 (96%)	10 (100%)	30 (97%)	28 (80%)	19 (100%)
Still hospitalized	-	-	0	1 (1%)	-	-	7 (20%)	-
Death	10 (2%)	0	0	2 (3%)	0	1 (3%)*	0	0

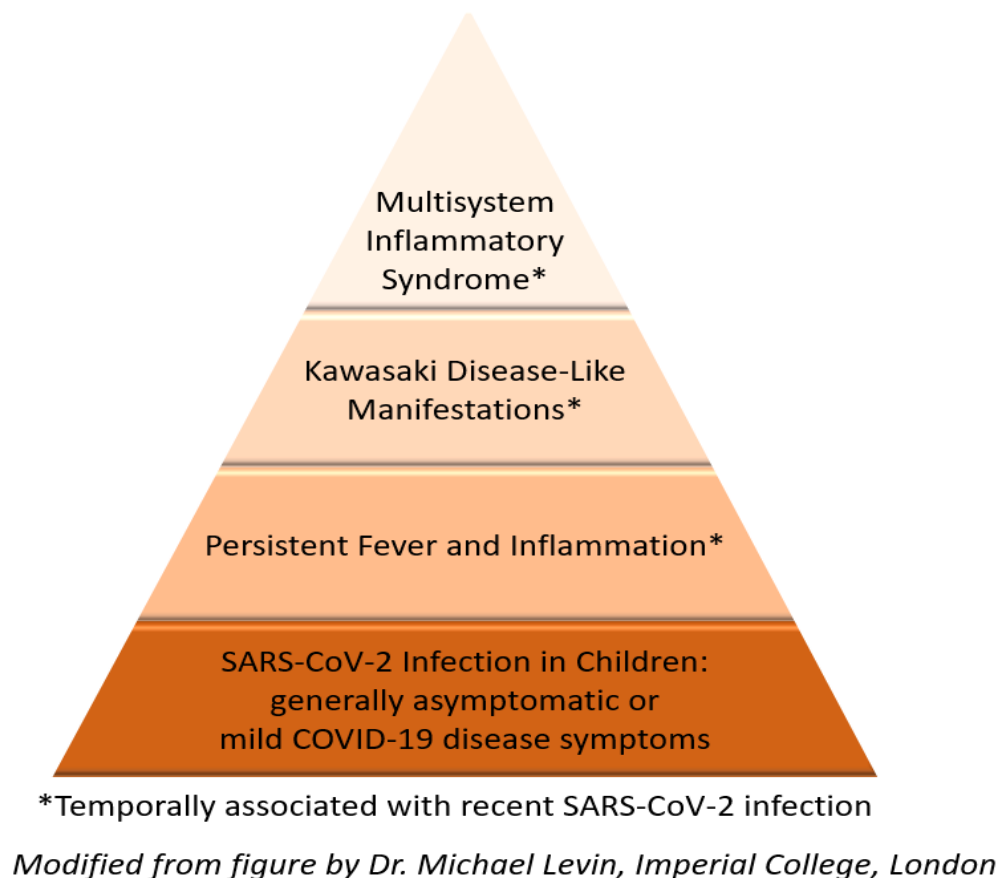
*Anakinra, Tocilizumab, Infliximab, Siltuximab

ages 10-16 years; 2 underlying conditions; 3 received ECMO support *underlying condition acute leukemia and bone marrow transplant

The clinical picture of MIS-C has been thought to resemble that of the later phase of severe adult COVID-19 that is felt to be secondary to an exaggerated host immune system response to infection characterized by cytokine storm, hyperinflammation, multi-organ damage including severe myocarditis and acute kidney injury (Diamanti). This suggests that MIS-C may be a post-infectious inflammatory process precipitated by prior SARS-CoV-2 infection and may be immune complex-mediated.

It is hypothesized that there may be a widening spectrum of SARS-CoV-2-related disease in children (*Figure 9*). The majority of children will have asymptomatic or mild infection; a small proportion may develop a post-infection inflammatory condition with persistent fever and signs of inflammation; a small proportion of these developing post-infection Kawasaki Disease-like syndrome; and a smaller minority developing the paediatric inflammatory multisystem syndrome.

Figure 9: Spectrum of Disorders in Children with SARS-CoV-2 Infection



Although the current incidence of multi-system inflammatory syndrome (MIS-C) is still low, the potential association of MIS-C with SARS-CoV-2 infection has stimulated intensive research interest in Europe and the United States with several research studies underway (e.g., the Overcoming COVID-19 study in the US; DIAMONDS study in Europe; multi-country Best Available Therapy Study[BATS]). International

discussions, led by the World Health Organization, are underway to facilitate standardized approaches to define and investigate the condition and its management and a global clinical data platform has been set up to facilitate reporting (WHO website references).

6. Summary

There is much remaining to be learned about SARS-CoV-2 in children and adolescents. The initial impression that paediatric COVID-19 disease is uncommon and generally mild has been replaced by a more nuanced understanding of infectious manifestations in children across countries and by income group, with recognition of a widening disease spectrum. Critical knowledge gaps remain that have significant public policy and programme implications. For example, if children are less susceptible to infection and/or less likely to transmit, the effectiveness of school closures to reduce viral spread may be limited. Should mother-to-child viral transmission occur, long-term effects on the child will need evaluation. As the spectrum of disease in children becomes better elucidated, it will be important to understand geographic and racial/ethnic differences, including variances in disease risk and health outcomes in low- and middle-income countries where co-morbidities and other vulnerabilities are more frequent among children than in high-income countries.

The following are the conclusions and data and research needs derived from this paper.

- **In contrast to the dominant narrative up to August, COVID-19 disease could have an important epidemiological impact on children, largely depending on where they live and how vulnerable they are to disease and ill health.** This is evidenced by the higher share of cases among children and young people in low- and middle-income countries which have youthful population structures (e.g. 23 per cent in Paraguay compared to 1 per cent in Spain), suggesting that demographic structures might contribute to the age distribution of reported cases. This fact alone should propel us to far greater vigilance in generating and monitoring age-disaggregated data on the pandemic in all countries.
- **There is no single place to obtain country comparable age-related data.** Global data are not readily available disaggregated by age, and available country data likewise lack age breakdowns or may only provide aggregate data for those <20 years. Data on the proportional age breakdown between 0–19 years is limited, and existing reports often use different and overlapping age categories. Acquisition of age-disaggregated data is critical to assess age-related differences in infection and whether SARS-CoV-2 infection and disease manifestations in children differ

geographically or based on other characteristics such as ethnicity, gender and socioeconomic status. Geographic disparities in pediatric SARS-CoV-2 infection and prevalence of different disease manifestations (e.g., MIS-C in Europe/US vs Asia/Africa) is still unclear and urgently needs to be monitored and assessed.

- **Critical knowledge gaps remain for LMICs as most studies and data are from HICs.** Insufficient availability of disaggregated data by age, geography and race/ethnicity are hindering efforts to fully assess incidence of infection and disease in children and adolescents and their role in transmission, especially during this phase of school re-openings in different countries and income settings.
- **The role of children in transmission of SARS-CoV-2 infection requires rapid evaluation.** A clear understanding of the transmission risk from children to other children, adolescents to adolescents, and children/adolescents to adults would provide needed information for guiding policies around school re-opening.
- **Predictors of disease progression and severe morbidity and mortality in children need to be determined, and whether these vary based on socio-economic determinants.** For example, are children in low- and middle-income countries, where poor nutritional and health conditions and other vulnerabilities are more frequent among children than in higher-income settings at greater risk of infection and disease severity? Children with co-morbidities appear over-represented in those with more severe disease. Better delineation of which co-morbidities and vulnerabilities put children at greatest risk of severe disease needs to be evaluated,

including potential role of malnutrition and non-infectious and infectious co-morbidities (e.g. Malaria, HIV, Pneumonia, TB, Cancer, diabetes, hypertension, obesity, severe underweight).

- **Potential biologic differences in susceptibility to infection between children and adults needs to be examined.** Children of all ages can be infected by SARS-CoV-2, but the incidence of infection among children appears to be much lower than in adults. Pediatric SARS-CoV-2 infection appears to be more likely to be asymptomatic or associated with mild disease and have less typical symptoms than in adult populations. But severe cases of SAR-CoV-2 have been reported among children, particularly among those with co-morbidities. Whether this lower infection incidence is due to decreased biologic susceptibility to the virus (and whether this might vary by age), or lower exposure to the virus than adults given mitigation/suppression efforts is unclear and needs to be examined. More data are needed on the paediatric population before conclusions can be drawn about the direct effects of SARS-Cov-2 on children and adolescents.
- **Optimal treatment of the most severe manifestations of SARS-CoV-2 in children must be evaluated, with inclusion of children in clinical therapy and vaccine trials.** Clinical trials of treatment for COVID-19 have excluded children to date, resulting in a recurring lost opportunity to generate data in a timely fashion to guide treatment of a new disease in children (and similarly in pregnant women) (Hwang, Whitehead). It will be particularly important to ensure inclusion of children and pregnant women in

planned future SARS-CoV-2 clinical and vaccine trials.

- **To evaluate the potential for mother-to-child SARS-CoV-2 transmission**, appropriate specimens (including amniotic fluid, placenta, neonatal blood and respiratory secretions) must be obtained with suitable timing, including birth specimens. More work is needed on transmission via breastfeeding and whether SARS-CoV-2 in breast milk in the presence of antibody is infectious.

7. Recommendations for policy, programmes and data and research

- UN agencies especially WHO and UNICEF should take the lead to advocate to governments, especially in LMICs to make age disaggregated data publicly available to inform policy and programme strategies that are context specific. Data disaggregated by age, sex, race/ethnicity, geography and by co-morbidities need to be collected and made publicly accessible. A global database allowing easy public access will help to facilitate context specific policy and programme design, including for studies and research on children and adolescents.
- UNICEF and WHO, through regional and country offices to support countries to strengthen monitoring and reporting of disaggregated data by age and co-morbidities and vulnerabilities e.g. malaria, HIV, TB, pneumonia, malnutrition, poverty—to better understand the intersections between them and to inform context-specific policy and programme design for children and adolescents.
- Where feasible, testing strategies should include children and adolescents whether asymptomatic or symptomatic, especially where an adult household member is infected to better inform prevention measures especially during school re-openings in different settings.
- More and improved quality data and research targeting children and adolescents are required to achieve a better understanding on the evolving nature of SARS-CoV-2 infection in this population and its effect, particularly in low- and middle-income countries.
- Countries, UN agencies, public health communities, donors and academia need to coordinate the efforts and work collectively to close the data and knowledge gaps and make data publicly available for better evidence to guide policy and programme decision-making for children and young people and SARS-CoV-2 infection/COVID-19 disease.

The recent emergence of multi-system inflammatory syndrome in children (MIS-C) with SARS-CoV-2 infection (either current infection or infection in recent past) demonstrates how disease due to SARS-CoV-2 in children remains yet to be defined. Disease pathogenesis and optimal treatment need to be defined, including in LMICs. Additionally, research into the pathogenesis of pediatric MIS-C will help to better illuminate the pathogenesis of SARS-CoV-2 in humans overall.

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Annex 1: List of Countries in the Analysis and COVID-19 Data Source

Country	Code	Region	Income Level Classification	COVID-19 Data Source and Dashboard	Data Last Update
Argentina	ARG	Latin America and Caribbean	High-income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Argentina#By_gender_and_age	14/06/2020
Australia	AUS	East Asia and Pacific	High-income	https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers#cases-and-deaths-by-age-and-sex	14/06/2020
Belgium	BEL	Europe and Central Asia	High-income	https://epistat.wiv-isp.be/Covid/covid-19.html	14/06/2020
Brazil	BRA	Latin America and Caribbean	Low- and middle-income	https://covid.saude.gov.br/	20/05/2020
Canada	CAN	North America	High-income	https://www.statista.com/statistics/1107149/covid19-cases-age-distribution-canada/	14/06/2020
Chile	CHL	Latin America and Caribbean	High-income	https://www.minsal.cl/nuevo-coronavirus-2019-ncov/informe-epidemiologico-covid-19/	11/06/2020
China	CHN	East Asia and Pacific	Low- and middle-income	https://www.statista.com/statistics/1095024/china-age-distribution-of-wuhan-coronavirus-covid-19-patients/	11/02/2020
Costa Rica	CRI	Latin America and Caribbean	Low- and middle-income	https://www.ministeriodesalud.go.cr/index.php/centro-de-prensa/noticias/741-noticias-2020/1532-lineamientos-nacionales-para-la-vigilancia-de-la-infeccion-por-coronavirus-2019-ncov	14/06/2020
Cyprus	CYP	Europe and Central Asia	High-income	https://covid19.ucy.ac.cy/	14/06/2020
Czech Republic	CZE	Europe and Central Asia	High-income	https://onemocneni-aktualne.mzcr.cz/covid-19	14/06/2020
Denmark	DNK	Europe and Central Asia	High-income	https://www.statista.com/statistics/1103966/number-of-coronavirus-covid-19-cases-in-denmark-by-age-and-gender/	10/06/2020
El Salvador	SLV	Latin America and Caribbean	Low- and middle-income	https://covid19.gob.sv/	14/06/2020
Estonia	EST	Europe and Central Asia	High-income	https://koroona kaart.ee/en	14/06/2020
Ethiopia	ETH	Sub-Saharan Africa	Low- and middle-income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Ethiopia#Total_confirmed_cases_by_gender_and_age	17/05/2020
Finland	FIN	Europe and Central Asia	High-income	https://www.statista.com/statistics/1103926/number-of-coronavirus-cases-in-finland-by-age-group/	14/06/2020
Germany	DEU	Europe and Central Asia	High-income	https://www.statista.com/statistics/1105465/coronavirus-covid-19-cases-age-group-germany/	2/06/2020
Guatemala	GTM	Latin America and Caribbean	Low- and middle-income	https://www.mspas.gob.gt/index.php/noticias/covid-19/casos	14/06/2020
Haiti	HTI	Latin America and Caribbean	Low- and middle-income	https://msp.gov.ht/site/downloads/63%20nouvo%20ka%20konfime%20ak%20yon%20nouvo%20lanm%C3%B2%20anba%20COVID-19%20nan%20peyi%20Dayiti%20nan%20dat%2018%20me%202020%20an..pdf	14/06/2020
Hong Kong	HKG	East Asia and Pacific	High-income	https://www.chp.gov.hk/files/pdf/local_situation_covid19_en.pdf	14/06/2020
India	IND	South Asia	Low- and middle-income	https://www.statista.com/statistics/1110522/india-number-of-coronavirus-cases-by-age-group/	26/04/2020

Italy	ITA	Europe and Central Asia	High-income	https://www.statista.com/statistics/1103023/coronavirus-cases-distribution-by-age-group-italy/	9/06/2020
Jamaica	JAM	Latin America and Caribbean	Low- and middle-income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Jamaica#Statistics	12/06/2020
Kenya	KEN	Sub-Saharan Africa	Low- and middle-income	https://www.health.go.ke/wp-content/uploads/2020/06/Kenya-SITREP-090-15-Jun-2020.pdf	15/06/2020
Mexico	MEX	Latin America and Caribbean	Low- and middle-income	https://coronavirus.gob.mx/datos/	14/06/2020
Moldova	MDA	Europe and Central Asia	Low- and middle-income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Moldova	13/06/2020
Montenegro	MNE	Europe and Central Asia	Low- and middle-income	https://www.coronainfocg.me/	14/06/2020
Netherlands	NLD	Europe and Central Asia	High-income	https://www.rivm.nl/documenten/epidemiologische-situatie-covid-19-in-nederland-19-mei-2020	14/06/2020
New Zealand	NZL	East Asia and Pacific	High-income	https://www.statista.com/statistics/1108939/new-zealand-number-of-coronavirus-cases-by-age-group/	2/06/2020
Nigeria	NGA	Sub-Saharan Africa	Low- and middle-income	https://ncdc.gov.ng/diseases/sitreps/?cat=14&name=An%20update%20of%20COVID-19%20outbreak%20in%20Nigeria	13/06/2020
Norway	NOR	Europe and Central Asia	High-income	https://www.statista.com/statistics/1103986/number-of-coronavirus-covid-19-cases-in-norway-by-age-groups/	10/06/2020
Panama	PAN	Latin America and Caribbean	High-income	http://minsa.gob.pa/coronavirus-covid19	14/06/2020
Paraguay	PRY	Latin America and Caribbean	Low- and middle-income	https://www.mspbs.gov.py/reporte-covid19.html	14/06/2020
Philippines	PHL	East Asia and Pacific	Low- and middle-income	https://ncovtracker.doh.gov.ph/	14/06/2020
Portugal	PRT	Europe and Central Asia	High-income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Portugal	14/06/2020
Puerto Rico	PRI	Latin America and Caribbean	High-income	https://bioseguridad.maps.arcgis.com/apps/opsdashboard/index.html#/d7308c1abb4747e584329adf1215125e	14/06/2020
Republic of Korea	KOR	East Asia and Pacific	High-income	https://www.statista.com/statistics/1102730/south-korea-coronavirus-cases-by-age/	8/06/2020
Romania	ROU	Europe and Central Asia	Low- and middle-income	https://www.statista.com/statistics/1104592/romania-covid-19-infections-by-age-group/	14/06/2020
South Africa	ZAF	Sub-Saharan Africa	Low- and middle-income	https://www.nicd.ac.za/wp-content/uploads/2020/05/COVID19-Daily-Report-National-18-May-2020_public.pdf	18/05/2020
Spain	ESP	Europe and Central Asia	High-income	https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_68_COVID-19.pdf	06/04/2020
Sweden	SWE	Europe and Central Asia	High-income	https://fohm.maps.arcgis.com/apps/opsdashboard/index.html#/68d4537bf2714e63b646c37f152f1392	14/06/2020
United Kingdom	GBR	Europe and Central Asia	High-income	https://www.statista.com/statistics/1115083/coronavirus-cases-in-england-by-age-and-gender/	14/06/2020
United States	USA	North America	High-income	https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html	14/06/2020