unicef | for every child
Office of Research-Innocenti

Covid-19 & Children

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

Lynne M. Mofenson MD, Priscilla Idele PhD, David Anthony MSc,
Jennifer Requejo PhD, Danzhen You PhD, Chewe Luo PhD, Stefan Peterson PhD

UNICEF Office of Research | Innocenti Working Paper

WP-2020-07 | January 2021

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

Lynne M. Mofenson MD, Priscilla Idele PhD, David Anthony MSc Jennifer Requejo PhD, Danzhen You PhD, Chewe Luo PhD, Stefan Peterson PhD

25 January 2021

Abstract: The initial impression that paediatric SARS-CoV-2 infection is uncommon and generally mild has been replaced by a more nuanced understanding of infectious manifestations in children and adolescents across low-, middle-, and high-income countries, with recognition of a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 continue to hinder 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-mobridities, 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 is updated through January 25 2021 to cover new data since the last update in September.

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.

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

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. There has been a shift in age over time in COVID-19 cases in many pandemic settings to younger individuals, including adolescents and young adults.

- 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.

- Alarmingly, 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.

- 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 (1). 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 over the past year, 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 year 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 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 and the changing age-related demographics of SARS-CoV-2.
- 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, including 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 December 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 December 2020, two groups were conducting ongoing systematic reviews of journal articles on COVID-19 and maternal and child health: the American Academy of Pediatrics (2) and The Johns Hopkins Center for Humanitarian Health (3). These ongoing systematic review sites are reviewed for additional papers that would address the focus noted above.

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.

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

Twelve months after COVID-19 first appeared, a clear understanding of how it affects children and adolescents is still lacking; the dominant narrative has remained 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 (4,5).

However, as the pandemic has matured, demographic profiles are noted to 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.

A new UNICEF analysis of the Max Planck Institute database as of November 2020 from 87 countries (accounting for 54 percent of global infections) with age-disaggregated data shows that children and adolescents account for 11 per cent of the reported COVID-19 infections in these 87 countries (*https://www.unicef.org/reports/averting-lost-generation-covid19-world-childrens-day-2020-brief*) (6). Among 25.72 million total cases from these countries, 2.77 million (10.8 per cent) were in children and adolescents under age 20 years. Among high and upper middle-income countries, 17.13 million cases disaggregated by age were reported from 55 countries; 1.8 million (10.5 per cent) were in children and adolescents under age 20 years. Among low and lower middle-income countries, 8.58 million cases disaggregated by age were reported from 32 countries; 968,207 (11.3 per cent) were in children and adolescents under age 20 years. Of these cases, 68 per cent occurred among adolescents ages 10–19, and 32 per cent among children ages 0–9 years (*see Table 1*).

Table 1. COVID-19 cases in children and adolescents under age 20 years

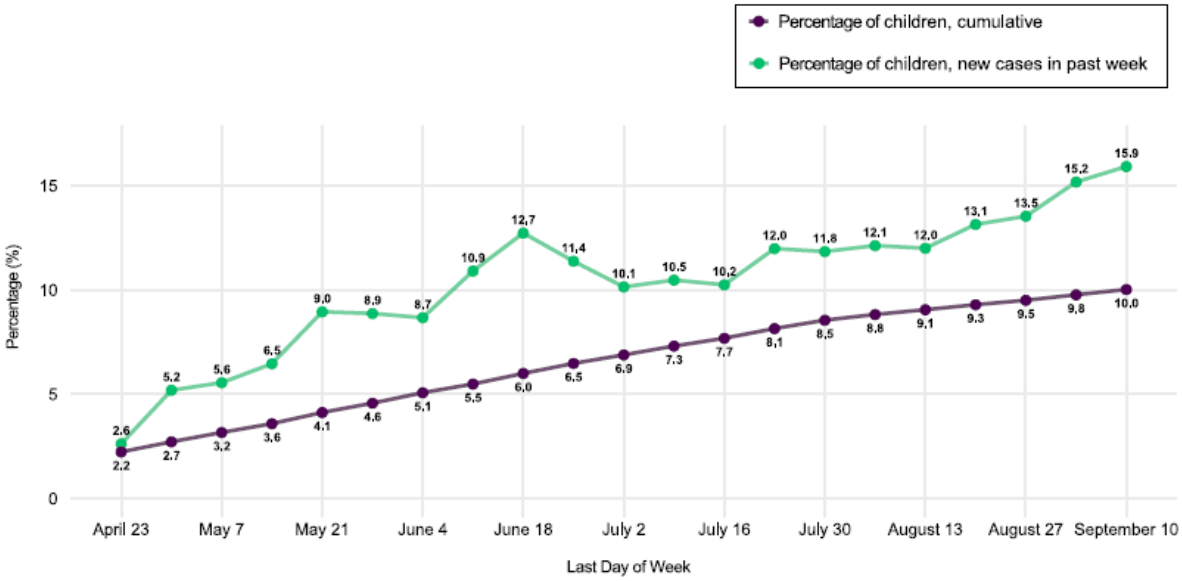
Age group (years)	Total	High/Upper Middle-Income Country	Low/Lower Middle- Income Country
<5 years	400,492 (14.5%)	260,390	140,102
5–9 years	479,026 (17.3%)	294,646	184,380
10–19 years	1,886,825 (68.2%)	1,243,100	643,725
Total <20 years	2,766,343	1,798,136	968,207

However, there is a broad spectrum of COVID-19 burden among those <20 years as a share of national caseloads in these 87 countries, ranging from 1.1 per cent in Botswana to 30 per cent in Israel. 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.

A demographic shift in age distribution of cases to younger age populations is occurring in many countries in which an older age predominance was present initially.

While data from additional countries, mainly high-income, continue to report lower numbers of children and adolescents diagnosed with COVID-19 than adults, there has been a demographic shift in the age distribution in COVID-19 cases to younger age populations in a number of countries. In the United States, the proportion of COVID-19 cases in the pediatric age group has risen substantially; in April 2020, the weekly per cent of COVID-19 cases in those age 0-18 years was 2.6%, rising to 15.9% by September 2020 (*see Figure 1*) (7). In an analysis of temporal trends in COVID-19 cases by age in "hotspot" counties in the United States, transmission among young adults, adolescents and children preceded transmission among older adults (8). A similar shift in demographics of COVID-19 has been described in Germany, Spain and India, with an increase in prevalence among children, adolescents and young adults over time (9-11).

Figure 1. Proportion of COVID-19 case in children, cumulative and per week, United States



Source: Sisk B et al. Pediatrics. 2020 Sept 29;e2020027425

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. However, while children and adolescents constitute a growing percentage of confirmed cases, hospitalization and death due to COVID-19 remain uncommon in this age group (7).

The exact incidence of COVID-19 in children, however, is difficult to ascertain. Despite being nearly a year into the pandemic, 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. Additionally, there may be 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. 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) (12,13). 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 first reports on pediatic COVID-19 cases in Africa were only recently published in November, eleven months into the pandemic (14-16).

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, China and Europe (multinational, multicenter), all from earlier in the pandemic (17-19) (*see Table 2*). 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 2: COVID-19 Cases in Children by Age Category

Country	Total Number of Paediatric Cases	Age Breakdown of Cases (Years)				
USA [1]	2,572 (Feb 12–Apr2)	<1 398 (15%)	1–4 291 (11%)	5–9 388 (15%)	10–14 682 (27%)	15–17 813 (32%)
China [2]	731 (Jan 16–Feb 8)	<1 86 (12%)	1–5 137 (19%)	6–10 171 (23%)	11–15 180 (25%)	16–18 157(21%)
Europe[3]	582 (Apr 1–24)	<2 270 (40%)	2–5 62 (11%)	5–10 94 (16%)	>10 196 (34%)	-

		(<1 month 40 (7%)				

[1] CDC COVID-19 Response Team. MMWR 2020 Apr 6 [2] Dong Y et al. Pediatrics. 2020 Mar 16 [3]Gotzinger F et al. Lancet Child Adoles Health 2020 Sept

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, with major differences in populations, epidemic time-points and methodologies, and conflicting results.

Viner and colleagues conducted a systematic review and meta-analysis of 32 studies including 41,640 children and adolescents and 268,945 adults, including 18 contact tracing studies and 14 population-based screening or seroprevalence studies (20). Findings from population-based screening were heterogeneous and a meta-analysis was not able to be performed for these studies.

Lower seroprevalence was identified in children, and in some studies adolescents, compared with adults in a number of studies, including a nationally representative study in Spain (ENE-COVID), a Dutch nationally representative study (PIENTER Corona study), and city or regional studies from Iran, the US, Switzerland, and Japan (21–25), but no difference by age was found in a serosurvey in 133 sentinel cities in 26 Brazilian states (26). Two community-based studies following local outbreaks found lower seroprevalence in children and adolescents in Italy and Germany, while a second study in Germany showed no overall assocation with age (27–29).

Of five seroprevalence studies that differentiated children from adolescents, most reported lower seroprevalence in chidren younger than age 10 years compared with adults, while seroprevalence in adolescents aged 10 to 19 years appeared similar to adults.

Table 3 shows 8 population-based studies including $\geq$100 children that have been published since the Viner review; studies continue to be very heterogeneous and have conflicting findings. A national serosurvey using residual laboratory specimens in the U.S., where overall seroprevalence was <10 per cent, reported lower seroprevalence among children <18 years than adults. A national serosurvey using residual laboratory samples in Greece found very low seroprevalence overall, 0.4 per cent, with no seropositive tests in indivudals <40 years (30, 31). Regional or city-specific serosurveys in Norway and Austria also found lower prevalence in children and adolescents than adults (32, 33). In contrast, regional studes in Italy and Dominican Republic found seroprevalence among adolescents and young adults similar (34, 35) and studies from Spain (household contacts) and China (city-wide screening) reported similar seroprevalence in children, adolescents and adults (36, 37).

Table 3. Seroprevalence Studies (since Viner meta-analysis) with Pediatric Age Data

Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Brotons P, *Clin Infect Dis* Barcelona, Spain	• Household contact cross-sectional seroprevalence study, enrolling 381 families with ≥ 1 adult positive by rtPCR and ≥ 1 child aged <15 years under strict home quarantine • 672 children age <15 years, 335 adult contacts	• Children had similar probability as adults to become infected in quarantined family households. • SARS-CoV-2 seroprevalence rates were 17.6 per cent (118/672) in children and 18.7 per cent (77/335) in adult contacts (p=0.64).
Pan Y, *Clin Microbiol Infect* Wuhan, China	• City-wide screening of 61, 437 residents in Wuchang District, Wuhan China • Included 1,601 children age ≤9 years and 3,593 age 10-19 years	• Children had similar positive seroprevalence as adults 20-40 years, with highest prevalence in oldest adults. • IgM and/or IgG positivity in children ≤9 years 1.5 per cent and 10-19 years 1.2 per cent , similar to adults aged 20-29 and 30-39 years (0.9 and 1.5 per cent); highest seroprevalence in age ≥70 years (3.9 per cent)
Bogoglannidou Z, *Euro Surveill* Greece	• Geographically stratified test 6,586 leftover blood samples March-April 2020 (during lockdown) • 490 children, adolescents, young adults age 0-29 years	• Low rates seropositivity overall (prevalence 0.24 per cent). • No seropositive tests in individuals <40 years, for those 50->70 range 0.29-0.54 per cent.
Bajema KL, *JAMA Intern Med* US national	• Repeated cross-sectional national survey using 177,919 residual blood samples from 2 commercial lab during 4 periods from Jul-Sept 2020 • 26,716 children/adolescents <18 years	• Seroprevalence among children lower than adults >18 years. Was more varied compared with adults and likely affected by differences in exposure risk across regions. • Seroprevalence in children/adolescents <18 years varied between 13.8-17.3 per cent across the 4 period; highest among young adults age 18-49 years (29-31 per cent); between 26-27 per cent for age 50->65 years.
Vos, ERA, *J Epidemiol Community Health.* Norway	• Cross-sectional survey of participants in prior serosurvey • 427 children age 2-12 years, 129 age 13-17 years	• Seroprevalence among children/adolescents <18 years lower than adults age >18 years. • Seroprevalence 0.9 per cent age 2-12 years, 0.8 per cent age 13-17 years vs 2.6-5.3 per cent in adults age 18-49 years.
Stefanelli P, *Clin Microbiol Infect* Trento municipalities, Italy	• Serosurvey of 6,098 volunteers age >10 years in 5 municipalities with high incidence COVID-19. • 667 adolescents age 10-<20 years	• Seroprevalence among adolescents similar to adults • Adjusted seroprevalence 27.9 per cent in adolescents 10-<20 years and range 20-29.4 per cent in those >20 years
Paulino-Ramirez R, *Am J Trop Med Hyg* 10 provinces Dominican Republic	• Serosurvey 12, 897 persons between Apr-June 2020 • 379 children/adolescents age 0-17 years	• Seroprevalence highest in older adults, but adolescent and young adult prevalence similar • IgG seroprevalence 8.6 per cent among children age 0-9 years, 3.9 per cent age 10-19 years vs 4.6 per cent age 20-29 years, 5.1 per cent age 30-39 years, and 6.0 per cent or higher among those age >40 years
Knabl L, *Medrxiv* Ischgl, Austria	• Cross-sectional household survey in ski-resort city that was center of outbreak; 1,543 individuals from 478 households participated • 101 children age <10 years, 113 age 10-17 years	• Seroprevalence lower in children/adolescents than adults. • Seroprevalence 27.1 per cent in children/adolescent age <18 years vs 45 per cent in adults.

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 (38,39).

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 recent or past infection. Additionally, there are multiple SARS-CoV-2 rtPCR and antibody tests, with varying sensitivity (40,41), and the sensitivity, specificity and predictive value of the individual 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 (42–46). A household study in Tennessee and Wisconsin evaluated 191 household contacts of 101 index patients identified less than 7 days after symptom onset; the overall secondary infection rate was 53 per cent, and were similar in children <12 years (57 per cent), 12–17 years (47 per cent) and older adults (43–59 per cent) (47). A second household transmission study in Wisconsin and Utah evaluated 188 household contacts of 58 index patients identified less than 10 days after diagnosis. The secondary infection rate was 28% in pediatric and 30% in adult contacts (48).

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. The Viner meta-analysis included 18 contact tracing studies. Overall, the pooled odds of secondary infection following exposure to an index case in children and adolescents (<20 years) compared with adults was 0.56, with significant heterogeneity (20). In analysis of contact tracing studies with sufficient age breakdown to differentiate children and adolescents, the pooled odds of becoming infected after contact with an infected individual was 0.52 (95 per cent confidence interval, 0.33–0.82) among children under age 10 years compaerd to those >20 years; in contrast, for adolescents, secondary infections were not significantly different than adults (odds ratio 1.23, 95 per cent confidence interval 0.64–2.36).

Table 4 provides a brief summary of 11 of the larger contact tracing studies (including 40 or more children/adolescent contacts) that have been published or are in pre-print since the Viner meta-

analysis, including details on type of study, pediatric age breakdown and numbers included in the study and key findings (47–57).

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 (58).

Six of the studies suggest lower rates of secondary infection in children, and among those with further breakdown by age, acquisition was lowest among young children under age 10–12 years; three of these studies, however, reported similar rates of acquisition among adolescents and adults. In contrast, five studies suggest similar rates of secondary infection in children, adolescents and adult.

Thus, findings from the the contact tracing and the population-based studies are inconsistent. There remain 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 susceptiblity between younger children and older children/adolescents. For example, data from a review of 22,333 SARS-CoV-2 rtPCR tests conducted at a teritary 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) (59).

Table 4. Contact Tracing Studies (since Viner meta-analysis) with Pediatric Age Data

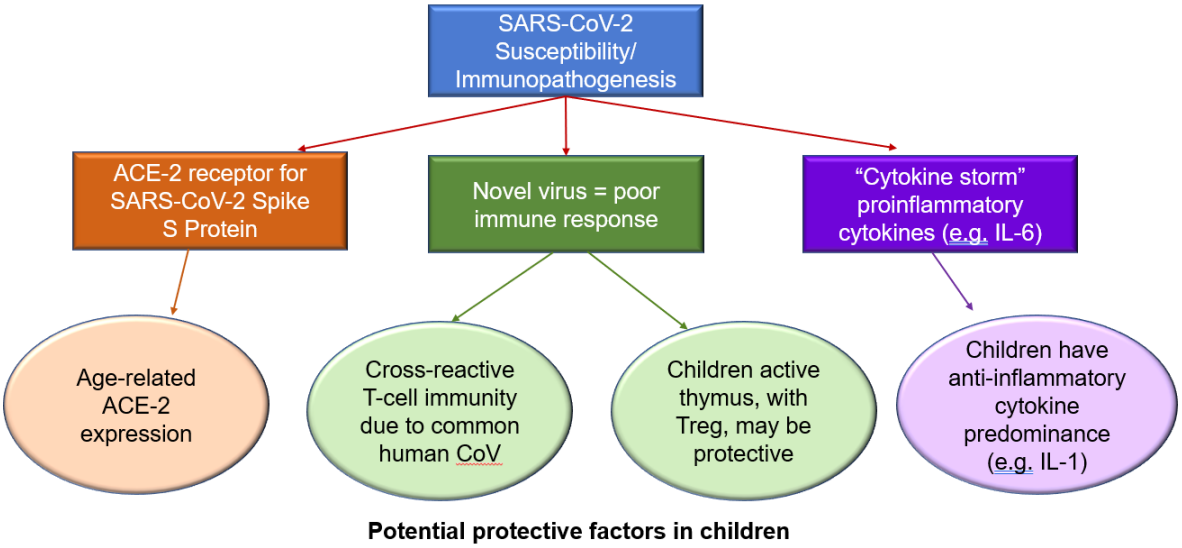
Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Fateh-Moghadam, *MedRxiv* Italy	• Community and household contacts • Pediatric age breakdown: 0–14 years (N=1,024)	• While children had lower risk of acquiring infection (8.4 per cent) than 4,730 adults (13.4 per cent), they had a higher risk of transmitting infection to others than other age groups • Workplace contacts at higher risk of infection; no difference by gender
Somekh E, *Pediatr Infect Dis J* Israel	• Household contacts in 13 families • Pediatric age breakdown: 0–4 years (N=18) and 5–17 years (N=40)	• Young children <5 years at lowest 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, *Osong Pub Health Res Perspect* Korea	• "Close contacts" • Pediatric age breakdown: 0–9 years (N=88) and 10–19 years (N=67)	• 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) • Male sex and household contact associated with infection
Zhang W, *Emerg Infect Dis* Guangzhou, China	• Contact of persons with pre-symptomatic infection • Pediatric age breakdown: 0–17 years (N=46)	• No significant difference 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.
Maltezou H, *J Med Virol* National registry Greece	• Household contacts, 23 families with at least one child and COVID-19 case • Pediatric age breakdown: 0–18 years (N=43)	• Similar 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, no cases of transmission from an infected child (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, *J Med Virol* Zhejiang Province China (included Madewell paper)	• Household contacts, 314 families with COVID-19 case and children • Pediatric age breakdown: ≤14 years (N=325)	• Lower 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.
Luo L, *Ann Int Med* Guangzhou China	• Close contacts 391 index cases • Pediatric age breakdown: 0–17 years (N=357)	• Secondary infection rate similar 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.
Grijalva CG, *MMWR* Tennessee, Wisconsin - US	• Household contact study of 101 index cases with 191 household contacts • Pediatric age breakdown 0-17 years (N=16 index cases, N=62 exposures)	• Secondary infection rate similar in children age <12 years (57 per cent) and 12-17 years (47 per cent) as adults 49 per cent age 18-49 years and 43 per cent age >50 years) • Transmission rate similar from index case age <12 years (53 per cent) and index case age 18-49 years (55 per cent)

Author/Journal/Location	Type Study and Pediatric Age Category	Key Findings
Kuwelker K, *MedRxiv* Norway	• Pediatric age breakdown: 0-19 years (N=52; N=28 age 0-12 years, N=24 age 13-19 years)	• Secondary infection rate (rtPCR positivity) similar in adolescents (40 per cent) and adults age 20-59 years (45 per cent) but lower in children <12 years (0.09 per cent) and highest in adults age ≥60 years (89 per cent). • IgG seropositivity was similar children <12 years (43%) and adults age 20-59 (46 per cent)
Laws RL, *Pediatrics* Utah, Wisconsin - US	• Household contact study of 58 index cases with 188 household contacts • Pediatric age breakdown: 0-17 years (N=68; N=10 age <5 years, N=34 age 5-12 years, N=24 age 13-17 years)	• Secondary infection rate similar in children, adolescents and adults (28 per cent in children and adolescents and 30 per cent in adults) • Of 10 households with the potential for transmission from a child index case to an adult, 2 represent possible child to adult transmission. Of 6 households with potential child-child transmission, one had possible transmission between children.
Park YJ, *Emerg Infect Dis* South Korea	• National contact tracing results for 5,706 index cases (153 in children 0-19 years) • Pediatric age breakdown 0-19 years • (N=694; N=237 age 0-9 years, N=457 age 10-19 years)	• Among household contacts, secondary infection rate lowest in children age 0-9 years (5.3 per cent) compared to adolescents age 10-19 years (18.6 percent); secondary infection in adolescents similar to adults (range 7.0-18.0 per cent). • Among non-household contacts, secondary infection rates in children and adolescents (1.1 and 0.9 per cent, respectively) were similar to those in adults 20-39 years (1.1 per cent); rates highest in older adults.

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

There have been a number of hypotheses for why children may have lower susceptibility to SARS-CoV-2 infection and milder disease than adults (*see Figure 2*) (60–62).

Figure 2: Possible factors associated with differences in SARS-CoV-2 susceptibility in children



Age-related changes to host cell susceptibility to SARS-CoV-2

One hypothesis for lower susceptibility to SARS-CoV-2 infection in children is potential age-related differences in cellular expression of factors related to SARS-CoV-2 infection. 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 (63). 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 (64). 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 (65). 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 (66). 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 verus females but no significant male-female differences in young children (67).

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 (68). 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.

Pre-existing human coronavirus immune response due to frequent childhood common human coronavirus infections

A second hypothesis is that human coronaviruses (hCoV)associated with the frequent common colds seen in young children may offer some protection due to cross-reactive T-cell immunity between SARS-CoV-2 and other hCoV. Mateus and colleagues evaluated blood samples collected prior to 2019 and found memory CD4 cells that react to SARS-CoV-2 epitopes that cross react with corresponding homologous sequences common to circulating common hCoV (69). A study in SARS-CoV-2 unexposed healthy blood donors also reported finding SARS-CoV-2 spike glycoprotein-reactive CD4 cells in healthy donors, primarily against C-terminal epitopes that show higher homology to spike glycoproteins of endemic hCoV (70). A separate study found SARS-CoV-2 specific Tcells in uninfected donors that targeted nucleoprotein epitopes (71). However, the presense of pre-existing cross-reactive immune memory does not necessarily correlate with protective immunity to disease, and such cells could eithe ameliorate or worse COVID-19 disease (72). In contrast, neutralizing antibodies are human coronavirus species-specific and do not show cross reactivity against SARS-CoV-2 (69).

Age-related differences in innate and adaptive immunity between children and adults

Infants and young children have higher thymic activity, higher levels of regulatory T cells and more diverse T cell pools compared with adults (61,73). The thymus begins to shrink after birth, continuing activity until adolescence and then decreases in both function and activity with involution in adults (74). The loss of T-cell regulatory function with aging may result in difficulty in control of the immune response , resulting in increased inflammation as seen with the “cytokine storm” in severe COVID-19, and may serve a protective function against disease in children.

Finally, children may be less likely to mount the pro-inflammatory reponse observed with severe COVID-19 disease because children have higher baseline levels of anti-inflammatory cytokines, such as IL-2, and lower levels of pro-inflammatory cytokines, such as IL-6, compared with adults (75,76). Aging itself is associated with increase in pro-inflammatory cyokines, which may contribute to the greater severity of COVID-19 disease in the elderly.

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 (77). 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 majorty were free of symptoms. The children who did not have symptoms had viral loads as high or higher than symptomatic children or adults (78). Similarly, a study of pediatric hospital-based screening in France found that among 22 infected children, the median SARS-CoV-2 rtPCR cycle thresold was similar in children with (n=11) or without (n=10) clinical symptoms (79). 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 (80). Finally, in a study of 178 nasopharyngeal samples from infected children children in the U.S., SARS-CoV-2 viral load did not differ by age group or the presense or absence of symptoms (81).

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 (82).

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 (83,84). 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 (85-87). 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 (86).

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 of 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 (45).

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 (87). In a survey of 144 houshold 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 (88). 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 (89). 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. Three of the household contact tracing studies in *Table 3* reported on transmission from children to adults; one reported no cases of transmission from children to adults (53), while two studies reported similar or higher risk of transmission from children than adults to adults (47,49).

Two outbreaks involving infants in daycare, one in Poland and one in the U.S., illustrate that transmission can occur both infant-infant and infant-adult in childcare settings and that such transmission may extend into the community. In a nursery care setting for children age 1-2 years, following notification that a staff member was exposed to SARS-CoV-2, rtPCR testing was conducted among infants, staff and family members of infants and staff. The outbreak resulted in 29 confirmed infections, representing 27 per cent of persons tested, including eight infants age 1-2 years (who were asymptomatic) and 12 family members who had no direct exposure to the nursery (90). In the U.S., 12 children in three child care facilities acquired SARS-CoV-2 infection after exposure to index cases in adults, with transmission documented from these children to at least 12 of 46 (26 per cent) non-facility household and non-household contacts, with one parent hospitalized for COVID-19 (91). These reports suggest that SAS-CoV-2 can be transmitted efficiently among children once they become infected.

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 (92). 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

Data on transmission of SARS-CoV-2 in the school setting are conflicting and difficult to interpret given that 1) transmission risk may differ between younger and older school-age children; 2) risk may vary based on overall community-level transmission; 3) some of the reported contact tracing studies related to schools tested only symptomatic contacts and will therefore underestimate the number of potentially infected children; and 4) reopening of many schools has been dependent upon having extensive mitigation procedures in place to prevent transmission from occurring. A review of reported school outbreaks through September 2020 concluded that as schools open, outbreaks that occurred

are likely due failure to adhere to appropriate mitigation procuedures, and outbreaks in schools were also more likely in locales with a high community transmission rate (93).

Differences in infection rates between younger and older school-age children have been seen. In an analysis of trends among 277,285 school-age children with COVID-19 in the U.S. between March and September 2020, monthly COVID-19 incidence increased approximately three-fold after May, when community migitation measures were relaxed in some areas during the summer. COVID-19 incidence among adolescents age 12-17 years was approximately twice that of children aged 5-11 years (94). If younger children are less susceptible to infection, the risk of transmission in a primary school setting may be different than in a high school setting.

A number of studies have suggested that children have not played a significant role in school transmission of SARS-CoV-2 (95). 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, but only symptomatic contacts received virologic testing (96).

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 (97). However, 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 quarentine and monitoring for symptoms of all students from the same class following detection of an index case.

In Australia, virologic and serologic screening of 663 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) (98). In Finland, no secondary cases were identified in contact tracing and testing of 89 of 121 contacts of a 12 year old infected child who had attended school (99). South Korea analyzed national data from pediatric patients with confirmed COVID-19 and association of infections with school reopening policies (100). They reported no sudden increase in pediatric cases after school reopening, and of 45 children diagnosed with COVID-19 after in-person classes started, most were infected by family members. More than 11,000 students and staff were tested in contact investigations and only one additional student was found infected in the same classroom.

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. 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 (101). 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. 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) (101). Additionally, 87 confirmed SARS-CoV-2 infections occurred among non-school close contacts of these cases. Most cases among students were mild or asymptomatic.

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 (102).

Thus, 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 appears rare

While most infants born to infected mothers test negative for SARS-CoV-2, a small number have tested positive (103). However, determining if a positive virologic or serologic test represents true infection of the infant, and characterizing the timing of such infection, has been challenging. Pathogens with a primary route of infection via the respiratory route, like SARS-CoV-2, are not easily transmitted *in utero*. There were no documented cases of *in utero* transmission for other severe coronavirus infections (SARS-CoV-1 or Middle East Respiratory Syndrome) (104,105). Human metapneumovirus and parainfluenza virus are widely prevalent pathogenic RNA respiratory viruses that have no documented cases of maternal-fetal transmission (106). Respiratory syncytial virus, a common seasonal respiratory virus, has been associated with one case of suspected intrauterine transmission (Manti). Influenza viruses, causing millions of infections annually, have been very rarely reported to possibly cause *in utero* infection, with only eleven case reports (106).

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) (108,109), 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 (110-117). SARS-CoV-2 viremia is more frequent in individuals with severe COVID-19 disease and correlates with highly elevated levels of IL-6 (118,119). Thus, it would be anticipated that viremia might 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 (120-122). 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 (123,124). 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 in rectly reach fetal tissues without requiring placental infection (125). SARS-CoV-2 can be associated with hyper-coagulopathy in pregnant women and abnormal placental pathology has been described COVID-19 positive women, with the most common finding being vascular malperfusion (126). In a systematic review, histopathologic placenta findings of fetal and maternal vascular malperfusion were seen in ≥35 per cent of placentas (127). With ischemic injury to the placenta, SARS-CoV-2 could reach the fetus without requiring placental cell infection. However, placental disruption may not be accompanied by transmission; in a study of placentas from 20 women with SARS-CoV-2 infection in New York City, 50 per cent of placentas showed placental/fetal vascular malperfusions, but all infants tested negative for the virus and were asymptomatic (128).

SARS-CoV-2 IgM has been thought to represent fetal immune response to in utero infection, as maternal IgM dose not cross the placenta unless there is placental disruption. However, the sensitivity and specificity of IgM tests vary and usually are less reliable than molecular diagnostic tests based on nucleic acid amplification and detection (129). A positive serological test always requires confirmatory testing. In the few cases of SARS-CoV-2-specific IgM detection in neonates, a single sample was obtained, and in six cases in which serial testing was done, there was a rapid drop in IgM, with repeatedly negative infant SARS-CoV-2 NP RT PCR tests in all (130-133).

Intrapartum transmission requires infant exposure to the infectious pathogen through contact with pathogen in maternal blood, vaginal secretions, or feces during the birth process, and for the pathogen to be able to reach an appropriate host cell to result in infection of the newborn. SARS-CoV-2 appears to only rarely be detected in vaginal swabs in pregnant women (133-137). However, SARS-CoV-2 is frequently identified in the feces of infected individuals (138). Fecal contamination of the vaginal canal during childbirth could potentially allow SARS-CoV-2 viral contamination of the neonatal oro-nasopharynx during vaginal delivery (139). There may also be viral contamination in the environment during labor or shortly after birth which can lead to iatrogenic viral acquisition by the infant immediately following birth (140). This may make it difficult to distinguish infant viral acquisition during passage through the birth canal from horizontal acquisition in the immediate postnatal environment, and hence only peripartum infection (intrapartum and immediate postnatal) would be able to be determined.

Postnatal transmission during the neonatal period occurs following childbirth and can occur from an infected mother to her infant via infectious secretions, skin-skin contact, or through contact with the pathogen in the neonate's environment; postnatal transmission through breastfeeding requires infant exposure to breast milk containing a replicative and infectious pathogen, and infectious virus being able to reach target sites in the infant through the oral/gastrointestinal route and overcome infant defense systems (141). While SARS-CoV-2 has been detected by rt-PCR in breast milk, it appears to be uncommon and no replication competent virus has been detected to date (141-143). SARS-CoV-2-specific IgG, IgM and IgA have been detected in breast milk; it is unknown if these antibodies would be

protective in a breastfeeding infant against infection (144-147). 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.

To date postnatal acquisition of SARS-CoV-2 appears to account for the majority of infections reported in neonates, likely representing environmental exposure. Raschetti and colleagues conducted a meta-analysis of 176 published cases of neonatal SARS-CoV-2 infections, defined by at least one positive nasopharyngeal swab and/or the presence of specific IgM, using the classification system of Shah et al to classify infection timing and certainty (148,149). They found that the majority of infections, 70.5 per cent, were likely transmitted postpartum, due to environmental exposure (6.6 per cent considered 'confirmed' and 63.9 per cent 'probable' postpartum acquired). Of the 29.5 per cent of cases that were considered vertical transmission from mother to child, over half were considered transmission that occurred intrapartum (17.3 per cent classified as intrapartum transmission and 12.2 per cent *in utero*). However, only 9 per cent had sufficient information to classify the infections as 'confirmed' (5.7% 'confirmed' *in utero* and 3.3 percent 'confirmed' intrapartum infection), with the remainder classified as possible or probable vertical infection. Thus, the majority, 91 per cent, of reported neonatal SARS-CoV-2 infections lacked sufficent data to enable classification as proven confirmed transmission.

In summary, while vertical mother-to-child transmission of SARS-CoV-2 is possible during pregnancy and delivery, it has only been confirmed in a few cases. 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.

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 (150,151). Similarly, in the United Kingdom COVID-19 is more common among Black and ethnic minority individuals (152,153). 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 (154-157).

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) (158). 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 (159-162). 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 (163). 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.

Similar data have been reported for children presenting with multisystem inflammatory syndrome in children temporally associated with SARS-CoV-2 (MIS-C), where population-based data demonstrated a disproportionate burden of both COVID-19 hospitalizations and cases of MIS-C among Black and Hispanic children in New York City (164). Finally, in a national surveillance study in the United Kingdom of SARS-CoV-2 infection in neonates under age 28 days, of the 66 neonates identified, a disproportionate percentage of infected neonates were from Black or other ethnic miniority groups (44 per cent) (165).

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

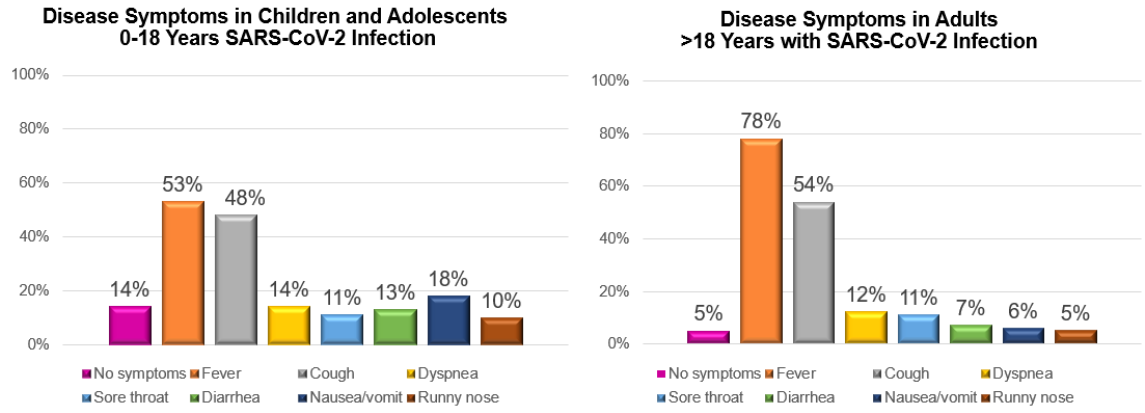
Experience with other severe coronavirus infections, Serious Acute Respiratory Virus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome coronavirus (MERS), suggested SARS-CoV-1 and MERS infections occurred less commonly and less severely in children than adults (166).

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) (167). 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 (168). Similarly, hospitalization rates in children are lower than in adults; in the United States, an evaluation of hospitalizaton 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 $\geq$65 years (169).

Clinical findings

A 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) (170). 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.

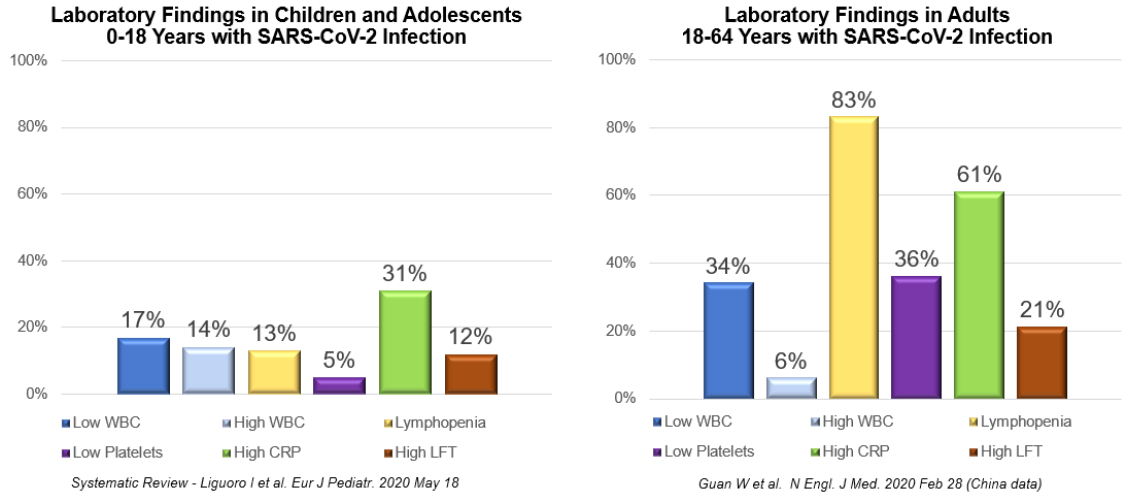
Figure 3: Symptoms of SARS-CoV-2 in children and adolescents compared with adults
(Jutzeler et al. Travel Med Infect Dis 2020;37:101825)



Laboratory findings

Laboratory findings in children were reported in the systematic review from Liguoro et al, with data from 655 children from 38 studies (167). 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***) (168). 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

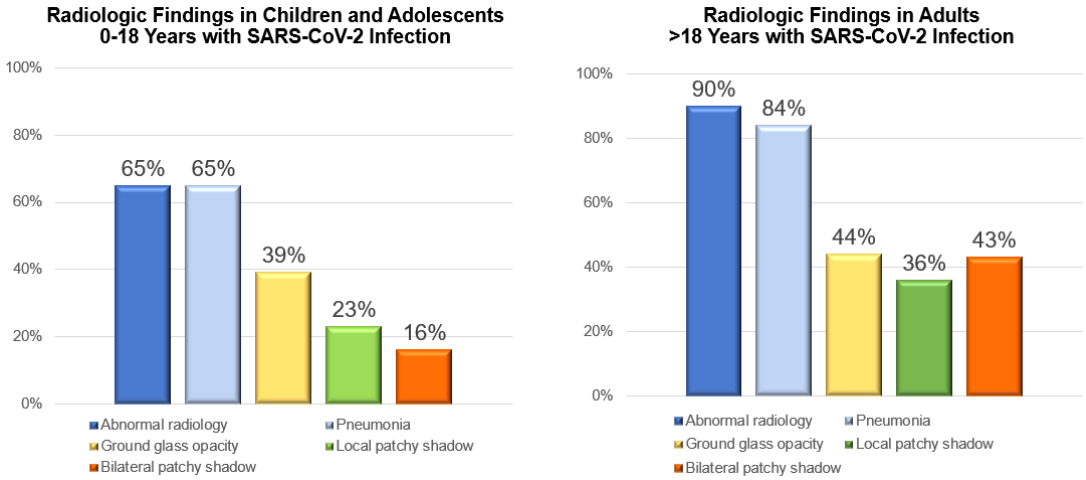


Radiologic findings

Comparison of radiologic findings between children/adolescents and adults was available from the Jutzeler systematic review, including 313 children/adolescents and 7,780 adults (170).

Radiologic abnormalities in children and adolescents were similar to those in adults, but were lower in frequency in children (*see 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

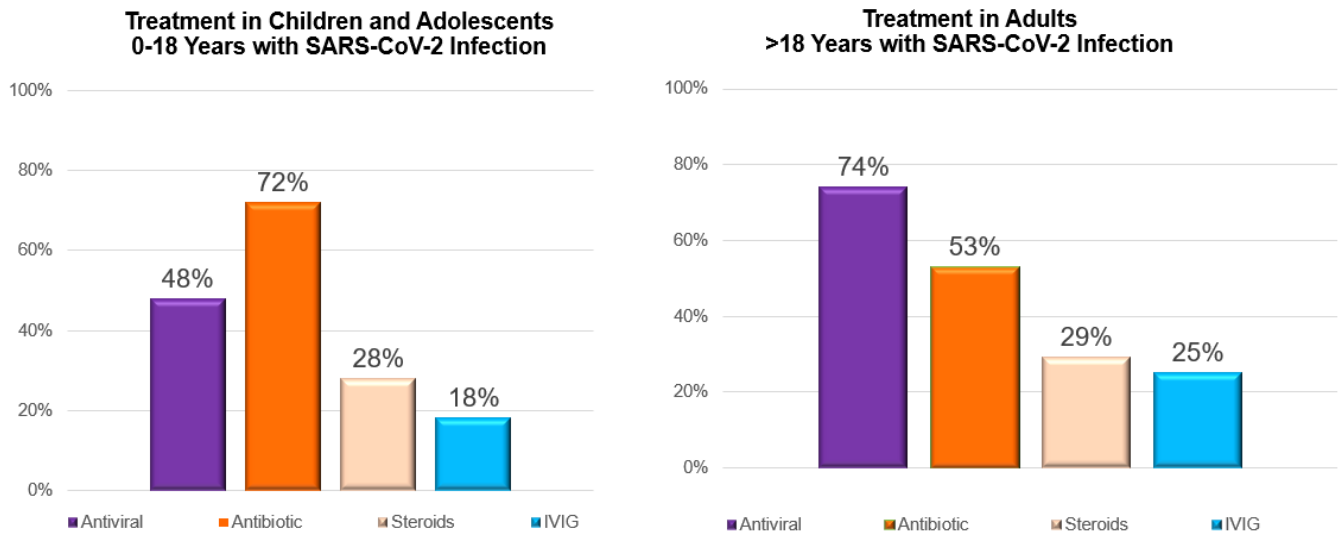
While hospitalization rates in children/adolescents are lower than adults, once admitted to the hospital, children have similar rates of ICU admission as adults; in the US, 33 per cent of hospitalized children/adolescents and 32 per cent of adults required ICU admission (158, 169, 171).

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 (158,171).

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 (170) ***(Figure 6***). Children/adolescents were somewhat less likely to receive antivirals (48 per cent) and more likely to receieve antibotics (72 per cent) than were adults (74 per cent and 53 per cent, respectively) (170). Use of corticosteroids and intravenous immunoglobulin was relatively similar.

Mortality was significantly lower in hospitalized children/adolescents , 0.5 per cent, compared to hosptialized adults, 17 per cent (158,171).

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



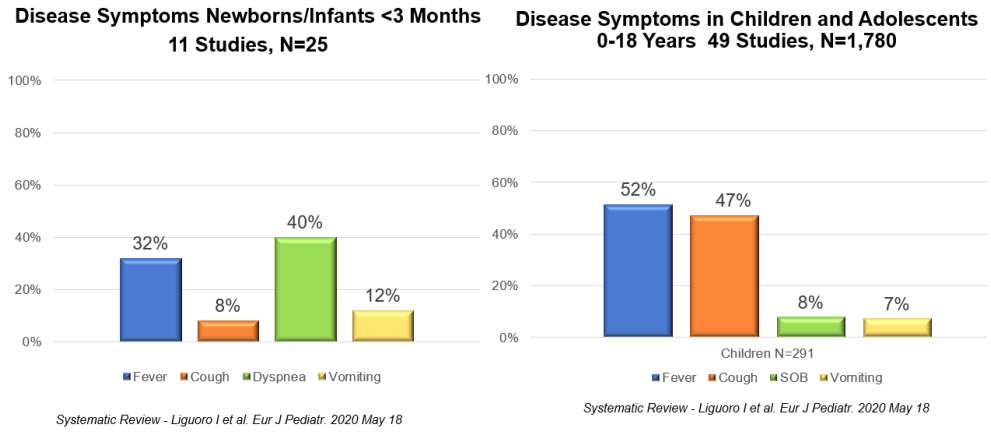
Newborns/infants age <3 months compared with all children and adolescents

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 (167). 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).

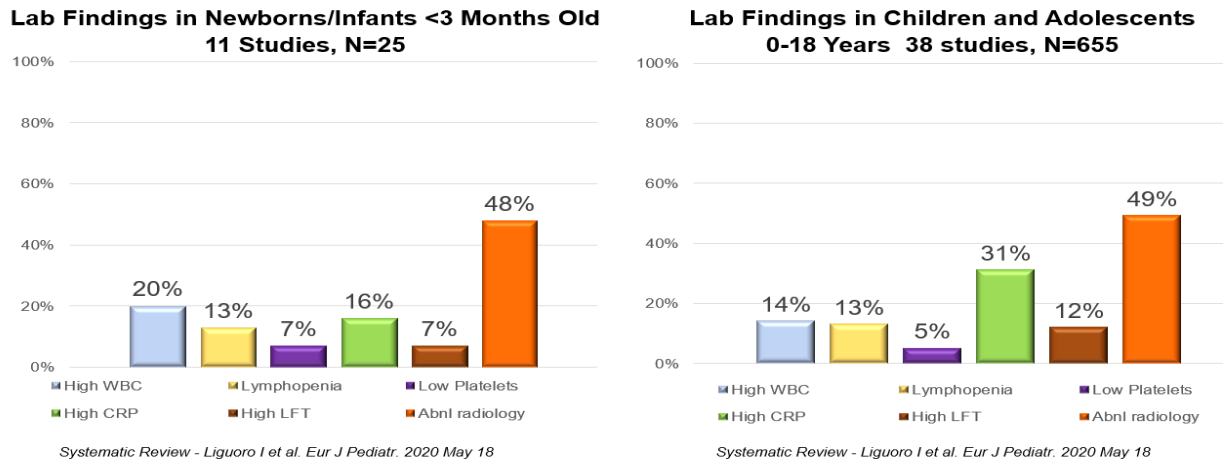
In contrast to the overall group of children, more newborns/infants had reported dyspnea (shortness of breath) and few had a cough (*see Figure 7).* Fever was observed in only 32 per cent of infants versus 52 per cent of all children. Gastrointestinal symptoms were somewhat more likely in newborns/infants. 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



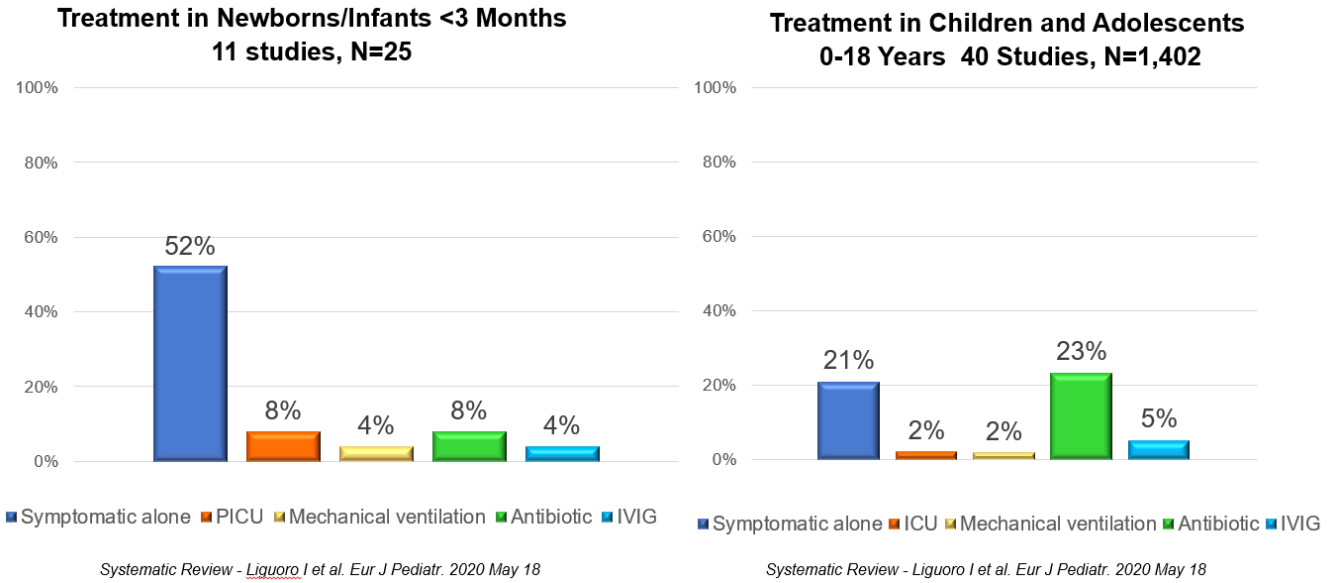
Laboratory findings demonstrated more leukocytosis (elevated white cell count) in newborns/infants than overall children and they had elevated CRP levels; 64 per cent of neonates had a chest radiograph, and abnormal findings were observed in 48 per cent, similar to overall children (***Figure 8***). 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 (*see 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 (172). 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 was published there are been several additional case series published on infants/neonates with SARS-CoV-2.

A retrospective single-center study in New York compared clinical characteristics between febrile infants age <57 days seen between March 1-April 30 of 2018 (n=38), 2019 (n=33) and 2020 (n=53) (173). During 2020, fewer febrile infants had a bacterial infection or positive respiratory viral panel; of 30 infants tested for SARS-CoV-2 in 2020, 20 tested positive. Comparing the 20 SARS-CoV-2 positive infants to the 81 without SARS-CoV-2, infected infants were more likely Hispanic, have public insurance, have symptoms of lethargy, feeding difficulties and lower white blood cell, neutrophil and lymphocyte counts. None of the infants with SARS-CoV-2 had concurrent infections and disease was mild and self-limited.

A populaton-based active national surveillance study in the United Kingdom examined the outcomes of infants with confirmed SARS-CoV-2 in the first 28 days of life who received inpatient care (165). Of 66 neonates with confirmed SARS-CoV-2 infection, 16 (24 per cent) were preterm and 28 (42 per cent) had severe neonatal infection. Only two infants had possible vertical infection, with positive testing at age <12 hours; most infection was postnatal. Eight infants had nosocomially-acquired infection (all

preterm) and 34 (52 per cent) had immediate family or close contacts with signs or symptoms consistent with SARS-CoV-2 infection. The most common signs at presentation were hyperthermia and poor feeding or vomiting. Coryza, respiratory signs and lethargy were common; 7 infants (11 per cent) were asymptomatic. Twenty-four infants (36 per cent) received care in a neonatal or pediatric intensive care unit; 22 (33 per cent) required one or more types of respiratory support, three of whom required invasive ventilation. Short-term outcomes were good, with 88 per cent of neonates discharged home, seven still in hospital and there was one death from an unrelated cause.

A national epidemiologic study including 21 hospitals in Spain between April 3 and May 18 2020 identified of 40 neonates with SARS-CoV-2 infection; 26 were community-acquired and 14 nosocomially-acquired (174). Ten neonates were asymptomatic; in those with symptoms, clinical manifestations were generally mild, including upper respiratory airways infection, febrile syndrome or acute gastroenteritis. Twenty of the 26 community-acquired cases were admitted to the hospital; clinical manifestations were generally mild; five infants required non-invasive respiratory suppport, with the most severe manifestations in two 23-week preterm infants and a neonate with concurrent rhinovirus co-infection. Of the 14 nosocomial cases, median age at diagnosis was 14.5 days; COVID-19 related non-invasive respiratory support was required in only one case.

Eighty-three neonates were screened for SARS-CoV-2 at admission to a tertiary pediatric hospital in Bangladesh between March 29-July 1, 26 testing positive at a median age of eight days (175). Most were admitted with diagnoses unrelated to SARS-CoV-2, with 11 having serious non-communicable diseases primarily pror to surgery, seven with early-onset sepsis, five with late-onset sepsis, and two with pneumonia. Of nine caregivers tested, eight had positive rtPCR. There was a wide range of presenting symptoms, including fever, respiratory distress, gastrointestinal symptoms and a range of non-communicable morbidities such as perinatal asphyxia; only two presented with respiratory symptoms that might be typical of COVID-19. Of 23 neonates with follow-up, eight died (six with serious comorbidities that may be the primary cause of death and two for which SARS-CoV-2 was a likely contributor to mortality).

Thus, SARS-CoV-2 infection in young infants and neonates, as in older children, is generally mild, requiring supportive treatment only, but serious, life-threatening illness was seen in a small minority of children, with mortality being rare.

SARS-CoV-2 in African children

Most reports on SARS-CoV-2 infection have been from high-resource settings, with minimal data reported from children in low-resource settings where there is a high burden of tuberculosis and HIV infection. A few reports from Africa have been published but it is difficult to draw conclusions given the limited data. While most studies report a high percentage of asymptomatic and mild disease, data from South Africa suggest infants under age one year are at highest risk of severe disease.

South Africa

The largest cohort of infected children in Africa reported to data is from South Africa, including 159 children aged <13 years with laboratory-confirmed SARS-CoV-2 presenting to Tygerberg Hospital, Cape

Town, South Africa between April and July 2020 (14). The median age was 48 months; 62 children (39 per cent) were hospitalized. Two were HIV-infected (1.3 per cent) and 13 were HIV-exposed but uninfected. Children under age one year were most likely to require hospitalization, presenting with severe respiratory illness requiring significant respiratory support, while older children had a more varied clinical presentation, including gastrointestinal symptoms.

Ten (16 per cent) of the 62 hospitalized children were asymptomatic and tested for other reasons. Most hospitalized children (82.3 per cent) were symptomatic; lower respiratory tract infection was most common, particularly in children age under three months (68.8 per cent), while gastrointestinal symptoms were most common in hospitalized children over age 5 years. Four children with a positive SARS-CoV-2 test were initially diagnosed with acute appendicitis; three had an appendectomy and were subsequently diagnosed with MIS-C while one was managed non-surgically and did not have MIS-C (176). Six children hospitalized children presented with seizures and one with a stroke. Weight for age for hospitalized children did not show evidence of malnourished or overweight.

Both age and pre-existing medical conditions were associated with the need for hospitalization. The median age of hospitalized children was 13.5 months compared to 81 months in those not hospitalized; of the 41 children under age one year, 30 (48.4 per cent) required hospitalization. Pre-existing medical conditions were noted in 33 children (20.8 per cent), 29 of whom required hospitalization. Pre-existing conditions included sickle cell anemia, aplastic anemia, asthma, prematurity and tuberculosis; seven children had a recent or current diagnosis of tuberculosis; two children were on anti-tuberculosis treatment at presentation and an additional four children received a new tuberculosis diagnosis during this admission. Two children were HIV-infected, while 11 were HIV-exposed but uninfected.

Oxygen supplementation was required in 49 per cent of hospitalized children; the need for respiratory support was highest (81.3 per cent) among infants under age three months. Intensive care admission was required in 21.6 per cent; four children required mechanical ventilation. Median length hospital stay was five days and despite severity, there were no deaths in chldren admitted to the ICU; there was one death in a five week-old infant who was HIV-exposed but uninfected, felt secondary to sepsis and not directly due to SARS-CoV-2 infection.

Nigeria

A study in Bauchi State in north-east Nigeria evaluated lab-confirmed SARS-CoV-2 cases reported between March and June 2020 (15). Of 495 cases, 89 (18 per cent) were children between age 0-18 years; most were identified through contract tracing, while 25 per cent presented at health facilities. Complete data were available on 53 cases; mean age was 12.6 years and 81 per cent were adolescents. Sixty per cent were asymptomatic, with the percentage asymptomatic higher among adolescents (60 per cent) compared to children under age 10 years (30 per cent). Of those with symptoms, all had either mild or moderate diseases., with most commonly reported symtpoms cough (21 per cent), fever (17 per cent), sneezing (15 per cent), and headache (11 per cent). There were no deaths.

Ethiopia

A single hospital prospective study of 90 consecutively admitted children with positive SARS-CoV-2 rtPCR with at least three months follow-up between June-September 2020 were reported. Median age was 15 years (range 6 months-18 years) (16). Only three children had a history of pre-existing co-morbidity. The majority (81 per cent) had mild disease at admission (with most being asymptomatic) and the rest moderate disease; children with one or more symptoms, particularly fever, cough, sore throat, or headache were more likely to have moderate disease. None required admission to the intensive care unit and there were no deaths.

Democratic Republic of the Congo (DRC)

A retrospective cohort study of 766 confirmed COVID-19 cases admitted to seven hospitals in Kinshasa, DRC; overall mortality was 13. 2 percent (177). Thirty-four (4.5 per cent) of patients were under age 20 years, with 11 younger than 10 years. Four adolescents (11.8 per cent) died (age 16, 17, 17 and 19 years); three of the four had severe/critical disease and one had moderate disease at hospital admission and three had no underlying comorbidity. Mortality was highest among patients under age 20 years or 60 years or older compared to those aged 20-39 years.

Uganda

In a report on the first 56 patients admitted to two hospitals in Uganda, the median age was 33 years, younger than reported initially reported in most high-income country settings (178). Most patients had asymptomatic or mild disease with only two having moderate disease. Eight (14.6 per cent) were under the age of 18 years, with the youngest patient age nine months. However, symptoms and outcomes were not reported by age. There were no admissions to the intensive care unit and no deaths.

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 (158). 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. 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 in observed for hospitalized adults (158). Children admitted to pediatric intensive care units with significant COVID-19 disease have a high rate of co-morbidities as well as mortality. In an analysis of 121 SARS-CoV-2-associated deaths in persons age under 21 years in the United States between February and July 2020, 70 per cent were in adolescents aged 10-20 years, with a disproportinate percentage among Hispanics (45 per cent), non-Hispanic Black (29 per cent) and Native Americans (4 per cent); 75 per cent had an underlying medical condition (179).

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 (180). 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 (180). 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 occuring 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 (181). 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) (182). 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 $\leq$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 (183). 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.

Comparison of severity with SARS-CoV-2 versus influenza and other respiratory viral infections

In a cross-sectional study of national data from Brazil between January 1 and July 14 2020, the rate of mortality was compared between 2,570 children with laboratory-confirmed SARS-CoV-2 infection, 659 with influenza and 1,555 with other respiratory viruses (e.g., respiratory syncytial virus, rhinovirus, meta-pneumovirus, adenovirus, etc) (184). Children with SARS-CoV-2 had a significantly increased risk of mortality despite similar rates of admission to the PICU (15.1 per cent for SARS-CoV-2, 4.8 per cent for influenza, 3.6 per cent for other respiratory viruses). The presence of comorbidities significantly increased the risk of death in all groups.

In a multi-national cohort study using routinely collected primary care and hospital electronic medical records, hospital billing data and insurance claims from 19 databases from the United States, Europe

(Netherlands, Spain, United Kingdom, Germany and France) and Asia (South Korea and China), 55,270 children age <18 years diagnosed with SARS-CoV-2 between January-June 2020 (3,693 hospitalized) was compared to 1,956,358 children diagnosed with seasonal influenza in 2017-2018 (185). Among children with SARS-CoV-2 infection, comorbidities including neurodevelopmental disorders, heart disease and cancer were more common among those hospitalized. Dyspnea, bronchiloities, anosmia, and gastrointestinal symptoms were more comon among these with SARS-CoV-2 than seasonal infuenza, and respiratory complications such as pneumonia and acute respiratory distress syndrome were significantly higher in children with SARS-CoV-2 than influenza. Hospitalization rates were between five to 13-fold higher among those diagnosed with SARS-CoV-2 than seasonal influenza in prior years. However, mortality secondary to SARS-CoV-2 or influenza was rare, with under five deaths per database.

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 (186). 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 (186).

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 (187). The most common co-morbidity was immunosuppressive condtions, 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 (*see Table 5*) (158).

Table 5. 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 (%)
Any underlying condition	*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%)

A systematic review and meta-analysis evaluated the effects of pediatric comorbidities on COVID-19 disease severity in 42 studies including 275,661 children without comorbidities and 9,353 children with comorbidities (188). Severe COVID-19 disease was reported in 5.1% of children with comorbidities and 0.2% of those without comorbidities, and there was a 2.8-fold relative risk of COVID-19-associated mortality in children with underlying conditions. Childhood obesity in particular was associated with a 2.9-fold relative risk of severe COVID-19 disease compared to non-obese children.

Nutrition/Obseity 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) (189). 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 (188,190-193). 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 (160). 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 (194,195).

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 (159).

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 (181).

In a prospective cohort of 382 children and adolescents with a SARS-CoV-2-infected close contact, 293 (77 per cent) were found to be SARS-CoV-2-infected. SARS-CoV-2-infected children were significantly less likely to have a history of provider-diagnosed asthma compared to those who were uninfected (81). Similarly, 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 (196). 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 (197).

Cancer/Immune Suppresion and SARS-CoV-2

SARS-CoV-2 infection in children with cancer has similar clinical presentation and most have mild disease, as in the general pediatric population. However, severe disease can also be seen.

The largest cohort of children with cancer and SARS-CoV-2 infection comes from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project, a national hospital-based registry of pediatric patients with cancer with confirmed SARS-CoV-2 infection (198). All children and adolescents <16 years with cancer in the United Kingdom are managed at 20 principal treatment centers in the country. Each participating center collects information on an child with cancer who is diagnosed with SARS-CoV-2, reporting to the Project database. Through 31 July 2020, 54 children age <16 years with cancer had data submitted, with nearly all having a minimum of four weeks of follow-up from the initial positive test. Median age at time of SARS-CoV-2 diagnosis was five year (range 10 months to <16 years); the most common cancer was acute lymphoblastic leukemia (44 per cent). The children were on a range of chenmotherapy treatments in the 4 weeks preceding their infection, including more intensive chemotherapy regimens. The majority of children had asymptomatic or mild infection and 85 per cent were not admitted to the hospital for their SARS-CoV-2 infection; only five had more than mild disease (one moderate, one severe, three critical); all five have recovered. There was one death in a child from their primary cancer. The data suggest that children with cancer are at no greater risk of severe disease than the general pediatric populaton.

Similar data, reporting primarily mild disase among children with cancer, have been reported from other countries, including Spain, Italy, United States, France and Egypt (199-205). For example, the French Society of Pediatric Oncology conducted a study of pediatric cancer patients follwed in a French pediatric oncology/hematology wards through May 2020; 37 pediatric patients with cancer (17 solid tumor, 16 hematologic malignancy, four stem cell transplant) with SARS-CoV-2 were identified. Nine were asymptomatic while 28 had symptoms, most commonly fever and cough (206). Overall, 20 patients were hospitalized at diagnosis but most of them did not require hospitalization specifically for COVID-19 disease. Most patients had asymptomatic to moderate forms of infection; however, five patients (13.5 per cent) required intensive care and one died (2.7 per cent).

The European Rare Kidney Disease Reference Network has a ongoing survey of 16 pediatric nerphology centers across 11 countries to report outcomes among children with kidney diease 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 (207).

The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) analyzed data from two international databases, identifying 209 children and adolescents with inflammatory bowel disease (IBD) and SARS-CoV-2 infection. (208) The most common IBD treatment was tumor necrosis factors antagonist monotherapy (48 per cent). Only 14 children (7 per cent) required hospitalization and only two mechanical ventilation (1 per cent); there were no deaths. Thus, pediatric IBD patients appeared at relatively low risk of severe disease even when receiving biologic and/or other immunosuppressive therapies.

Congential 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 (209). 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 arrthymias and evidence of myocardial inflammation were noted. The majority of cases (five of seven) were under age one year.

Hemoglobinopathy and SARS-COV-2

In a systematic review of SARS-CoV-2 in patients with a hemoglobinopathy, nine papers including 121 pediatric patients with sickle cell disease (SCD) and SARS-CoV-2 were identified (210). Seventy-four patients (61.2 per cent) were hospitalized while 47 were not. The main clinical manifestations at/during hospitalization were vaso-occlusive crisis (VOC) (41 patients) and acute chest syndrome (ACS) (27 patients) or both (two patients). Fourteen of 119 pediatric patients with data required the intensive care unit (11.8 per cent), with two requiring mechanical ventilation (1.7 per cent). Red blood cell or exchange transfusion were performed in 30 of 101 patients with data available (29.7 per cent). One adolescent died with SCD (mortality 0.82 per cent), while the remainder recovered. The authors

concluded that pediatric patients with SCD and COVID-19 have a low mortality rate when compared to adults, however this is higher than the global pediatric population with COVID-19 (0–0.67 per cent) and more pediatric patients required intensive care thant the global pediatric population (~3.3 per cent)

HIV and SARS-CoV-2

A systematic review of COVID-19 in adults with HIV infection reported on 252 coinfected patients from 25 studies, the vast majority from high or middle-income countries with one case report from Uganda (211). 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 antiretoviral 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 occured 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 (212-214). 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 (215,216).

Importantly, there are, however, are minimal data on children, adolescents and pregnant women with HIV infection and SARS-CoV-2/COVID-19 to date. In the report on COVID-19 in 159 children in South Africa, two (1.3 per cent) were HIV-infected and 13 (8.2 per cent) were HIV-exposed but uninfected. (14). Neither of the HIV-infected children died; there was one death in a five week-old infant who was HIV-exposed but uninfected, felt secondary to sepsis and not directly due to SARS-CoV-2 infection.

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

The emergence of multi-system inflammatory syndrome in children and its relation to SAR-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 (217). 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 (218).

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 (219). 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 (220). With increasing cases being reported globally, the World Health Organization published a scientific brief on MIS-C and requested global reporting (221).

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 6***).

Table 6. Definitions of Pediatric Multisystem Inflammatory Syndrome: Europe, U.S., WHO

Preliminary Royal College of Paediatrics and Child Health, UK, case definition Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PMIS-TS) • 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 imagining and ECG features (children fulfilling full or partial criteria for Kawasaki disease may be included) and • **And** inflammation (neutrophilia, elevated CRP and lymphopaenia) • **And e**xclusion 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.
CDC: Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- 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 rtPCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

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

WHO: Preliminary case definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- Children and adolescents 0–19 years of age with fever ≥ 3 days
- **And** two (or more) of the following:
    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 (rtPCR, 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 (223). 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 protoein, 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.

A scoping review through October 2020 identified 57 studies of MIS-C patients confirmed to have positive testing or an epidemiologic link to SARS-CoV-2 (224). These studies identified a total of 875 patients from 15 countries including the United States, United Kingdom, France, Italy, Switzerland, Brazil, Chile, Saudi Arabia, Iran, Belgium, Norway, Czech Republic, Poland, Spain and India. Median age was 9 years, ranging from 6 months to 21 years. Forty-five per cent had underlying comorbidities, including obesity and lung disease. Fever, gastrointestinal symptoms, and mucocutaneous symptoms (conjunctivitis, rash) were common. Most MIS-C patients had high biomarkers of inflammation including D-dimer, erythrocyte sedimentation rate, C-reactive protein, white blood cell, interleukin 6, procalcitonin, and ferritin, as well as biomarkers of cardiac dysfunction such as troponin I and N-terminal prohormone of B-type natriuretic peptide. The treatment for most patients included IVIG and inotropic support; fatality was 2.5 per cent.

A spectrum of MIS-C is now being identified. A retrospective review of data from children meeting the case definition of MIS-C between March 1 and June 15 from 13 participating European, Asian and American countries identified 183 children (225); 114 (62.3 percent) had documented evidence SARS CoV 2 infection. Children with MIS-C presented with a wide clinical spectrum including Kawasaki Disease-like syndrome; life-threatening shock; and milder forms with mainly fever and inflammation. The mean age was seven years, ranging from age 1.2 months to 18 years; 30.6 per cent were Black race, 26.2 per cent had obseity as a comorbidity. Over 40 per cent presented with shock; they had higher levels of NT-pro-BNP, d-Dimer, CRP and ferritin and developed more cardiac complications including pericardial effusion, valvulitis and left ventricular dysfunction; their hospital stay was longer and required more inotropic support and mechanical ventilation. A minority, 27 patients (14 per cent), fulfilled criteria for Kawasaki disease; these children were younger with no shock, fewer symptoms, less inflammation, and few cardiac complications other than coronary artery aneurysms. Their hospital stay was shorter with less need for intensive care, inotropic support and mechanical ventilation, although one child experienced sudden death in the setting of multiple giant coronary aneurysms. The remaining MIS-C pateints without shock experienced fever and inflammation; they had a higher rate of cornonary artery aneuryms but less other cardiac complications, and generally had better outcome.

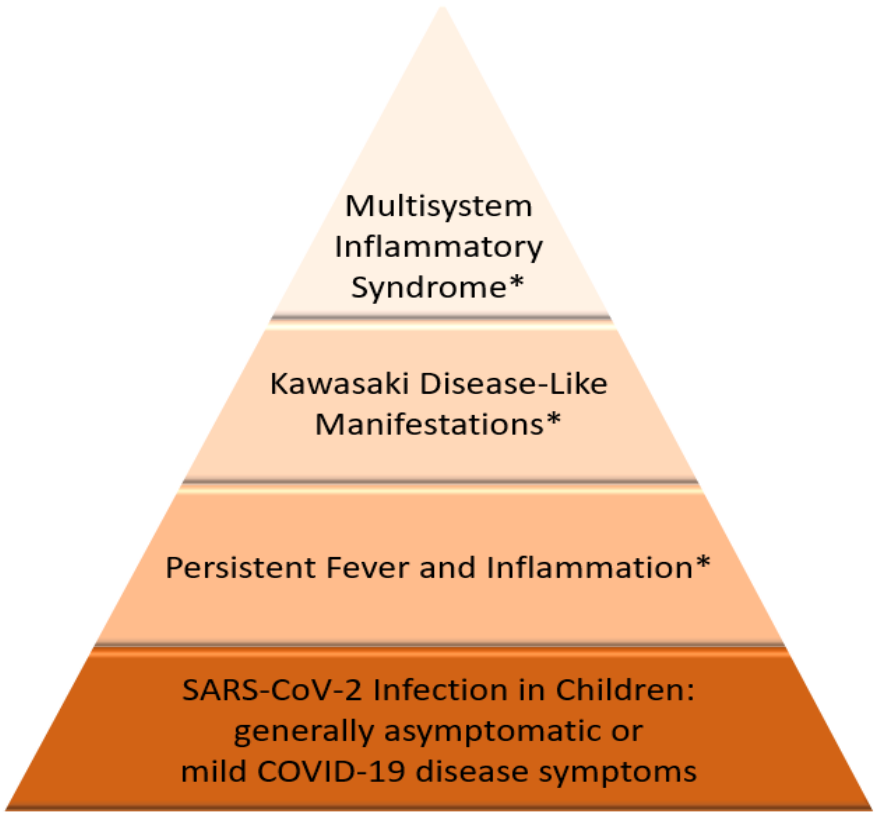
With the more recent expansion of the pandemic, MIS-C cases are now being reported from Africa, although due to limitations in SARS-CoV-2 testing, proven exposure has been documented in only a few (226). Webb and colleagues reported on 23 cases of MIS-C treated at two pediatric hospitals in Cape Town, South Africa; mean age was 6.6 years. The authors note that due to poor access to rtPCR and antibody testing, most children (70 per cent) did not have documentation of infection, but all children met clinical diagnositic criteria, and had likely community contact with infected individuals. All had multi-system organ dysfunction, including cardiac involvement in 91 per cent, and 30 per cent met complete and 39 per cent complete Kawasaki diagnositic criteria. Fifty-two per cent required intensive care admission primarily because of cardiac dysfunction; two had surgery for suspected appendicitis. All children received intravenous immunoglobulin, and 15 received additional drugs such as steroird or tocilzumab. There were no deaths.

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 (227). 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. A wide range of possible mechanisms underlying MIS-C have been postulated: a possible consequence of a person's initial innate immune response to infection with SARS-CoV-2, which sets the stage for all that follows; an autoimmune response resulting from cross-reactivity between viral antigens and host antigens; a response to ongoing viral replication in unrecognized viral reservoirs; a response to a viral superantigen; and/or the influence of genetic or epigenetic susceptibilities (228).

It is hypothesized that there is a widening spectrum of SARS-CoV-2-related disease in children (***Figure 10***). 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 10: Spectrum of Disorders in Children with SARS-CoV-2 Infection



*Temporally associated with recent SARS-CoV-2 infection

Modified from figure by Dr. Michael Levin, Imperial College, London

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 (221,222).

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 early narrative, 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**. Demographic structures as well as testing strategies 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) (229,230). 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.

- **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.

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.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395 (10223):497-506.
2. Boast A, Munro A, Goldstein H. An evidence summary of paediatric COVID-19 literature, don't forget the bubbles. 2020. URL: http://doi.org/10.31440/DFTB.24063, 27 June 2020.
3. Johns Hopkins University Center for Humanitarian Health. COVID-19, maternal and child health, nutrition. URL: http://hopkinshumanitarianhealth.org/empower/advocacy/covid-19/covid-19-children-and-nutrition/, 27 June 2020
4. Pan A, Liu L, Wang C, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA. 2020;323:1-9.
5. Zhang Y; the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus disease (COVID-19) – China, 2020. Chinese J Epidemiol. 2020 Feb 10;41:145-51.
6. UNICEF. Averting a lost COVID generation – a six-point plan to respond, recover and reimagine a post-pandemic world for every child. World Children's Day 20 November. UNICEF, New York; 2020 Nov 19. URL https://www.unicef.org/reports/averting-lost-generation-covid19-world-childrens-day-2020-brief.
7. Sisk B, Cull W, Harris JM, et al. National trends of cases of COVID-19 in children based on US State Health Department data. Pediatrics. 2020 Dec;146 (6):e2020027425.
8. Oster AM, Caruso E, DeVies J et al. Transmission dynamics by age group in COVID-19 hotspot counties – United States, April-September 2020. MMWR Morb Mortal Wkly Rep. 2020 Oct 16;69 (41):1494-
9. Goldstein E, Lipsitch M. Temporal risk in the proportion of younger adults and older adolescents among coronavirus disease (COVID-19) cases following the introduction of physical distancing measures, Germany, March to April 2020. Euro Surveill. 2020;25 (17):pii=2000596.
10. De Salazar PM, Gomez-Barroso D, Pampaka D, et al. Lockdown measures and relative changes in the age-specific incidence of SARS-CoV-2 in Spain. Epidemiol Infect. 2020 Oct 21;148, e268.
11. Laxminarayan R, Wahl B, Dudala SR et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science. 2020 Nov 6;370:691-7.
12. Diop BZ, Ngom M, Biyong CP et al. The relatively young and rural population may limit the spread and severity of COVID-19 in Africa: a modeling study. BMJ Glob Health. 2020 May;5 (5):e002699.
13. Ayoub HH, Chemaitelly H, Seedat S, et al. Age could be driving variable SARS-CoV-2 epidemic trajectories worldwide. PlosOne. 2020 Aug 20;15 (8):e0237959.
14. Van der Zalm MM, Lishman J, Verhagen LM, et al. Clinical experience with SARS-CoV-2-related illness in children – hospital experience in Cape Town South Africa. Clin Infect Dis. 2020 Nov 10;ciaa 1666.
15. Adedeji IA, Abdu YM, Bashir MF et al. Profile of children with COVID-19 infection: a cross-sectional study fron North-East Nigeria. Pan African Med J. 2020;35 (2):145.
16. Leulseged TW, Hassen IS, Maru EH et al. COVID-19 in hospitalized Ethiopian children: characteristics and outcome profile. MedRxiv. 2020 Nov 4. Doi: 10/1101/2020/10/30/20223115.
17. CDC COVID-19 Response Team. Coronavirus disease 2019 in children – United States, February 12-April 2, 2020. Morbid Mortal Wkly Rpt. 2020 Apr 10;69 (14):422-6.
18. Dong Y, Mo X, Hu Y et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020 Jun;145 (6):e20200702.
19. Gotzinger F, Santiago-Garcia B, Noguera-Julian A et al. COVID 19 in children and adolescents in Europe: a multinational, multicentre study. Lancet Child Adolesc Hdealth. 2020;4 (9):653.
20. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents as compared with adults – a systematic review and meta-analysis. JAMA Pediatr. 2020 Nov. doi:10/1001/jamapediatrics.2020.4573.
21. Pollan M, Perez-Gomez B, Pastor-Barriuso R et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 2020;396:535-44.
22. Shakiba M, Hashemi Nazari SS, Mehrabian F, et al. Seroprevalence of COVID-19 virus infection in Guilan province, Iran. MedRxiv. Preprint posted online May 1, 2020. Doi:10.1101/2020.04.26.20079244.
23. Biggs HM, Harris JB, Breakwell L et al. Estimated community seroprevalence of SARS-CoV-2 antibodies-two Georgia counties, April 28-May 3 2020. 2020 Jul 21;69:

24. Stringhini S, Wisniak A, Piuratti G et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396:313-19.
25. Nawa N, Kuramochi J, Sonoda S, et al. Seroprevalence of SARS-CoV-2 IgG Antibodies in Utsunomiya City, Greater Tokyo, after first pandemic in 2020 (U-CORONA): a household- and population-based study. MedRxiv. Preprint posted online July 26, 2020. doi:10.1101/2020.07.20.20155945
26. Hallal P, Hartwig F, Horta B, et al. Remarkable variability in SARS-CoV-2 antibodies across Brazilian regions: nationwide serological household survey in 27 states. MedRxiv. Preprint posted online May 30, 2020. doi:10.1101/2020.05.30.20117531
27. Pagani G, Conti F, Giacomelli A, et al. Seroprevalence of SARS-CoV-2 IgG significantly varies with age: results from a mass population screening (SARS-2-SCREEN-CdA). MedRxiv. Preprint posted online August 28, 2020. doi:10. 1101/2020.06.24.20138875
28. Weis S, Scherag A, Baier M, et al. Seroprevalence of SARS-CoV-2 antibodies in an entirely PCR-sampled and quarantined community after a COVID-19 outbreak—the CoNAN study. MedRxiv. Preprint posted online July 17, 2020. doi:10.1101/2020.07.15.20154112
29. Streeck H, Schulte B, Kuemmerer B, et al. Infection fatality rate of SARS-CoV-2 infection in a German community with a super-spreading event. MedRxiv. Preprint posted online June 2, 2020. doi: 10.1101/2020.05.04.20090076
30. Bajema KL, Wiegand RE, Cuffe K et al Estimated SARS-CoV-2 seroprevalence in the US as of September 2020. JAMA Intern Med. 2020 Nov 24. Doi: 10.1001/jamainternmed.2020.7976
31. Bogoglannidou Z, Vontas A, Dadouli K et al. Repeated leftover serosurvey of SARS-CoV-2 antibodies, Greece, March and April 2020. Euro Surveill. 2020;15 (31):pii=2001369.
32. Vos ERA, den Hartog G, Schepp RM et al. Nationawide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave. J Epidemiol Community Health. 2020 Nov 28;jech-2020-215678.
33. Knabl L, Mitra T, Kimpel J et al. High SARS-CoV-2 seroprevalence in children and adults in the Austrian resort Ischgl. MedRxiv. 2020 doi: 10.1101/2020.08.20.20178533.
34. Stefanelli P, Bella A, Fedele G et al. Prevalence of SARS-CoV-2 IgG antibodies in an area of north-eastern Italy with a high incidence of COVID-19 cases: a population-based study. Clin Microbiol Infect. 2020 Nov 27;S1198-743X(20)30709-6.
35. Paulino-Ramirez R, Baez AA, Degaudenzi AV et al. Seroprevalence of specific antibodies against SARS-CoV-2 from hotspot communities in the Dominican Republic. Am J Trop Med Hyg. 2020 Dec;103 (6):2343-6.
36. Brotons P, Launes C, Buetas E et al. Susceptibility to SARS-CoV-2 infection among children and adults: a seroprevalence study of family household in the Barcelona metropolitan region, Spain. Clin Infect Dis.
37. Pan Y, Li X, Yang G, et al. Seroprevalence of SARS-CoV-2 immunoglobulin antibodies in Wuhan, China: part of a city-wide massive testing campaign. Clin Micrbiol Infect. 2020 doi:10/1016/j.cmi.2020.09.044.
38. Davies NG, Klepac P, Liu Y et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nature Med. 2020 June 16 (epub)
39. Zhang J, Litvinova M, Liang Y et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. Science. 2020;368:1481-6
40. Whitman JD, Mowery CT, Shy BR et al. Test performance evaluation of SARS-CoV-2 serological assays. MedRxiv version 2. 2020 May 17:2020.04.25.20074856.
41. Lieberman JA, Pepper G, Naccache SN, Huang M-L, Jerome KR, Greninger AL. Comparison of commercially available and laboratory-developed assays for in vitro detection of SARS-CoV-2 in clinical laboratories. J Clin Microbiol. 2020 Apr 29;JCM.00821-20.
42. Wolf GK, Glueck T, Huebner J et al. Clinical and epidemiological features of a family cluster of symptomatic and asymptomatic SARS-CoV-2 infection. J Pediatr Infect Dis Soc. 2020 May 22;piaa060.
43. Qian G, Yang N, Ma AHY et al. A COVID-19 transmission within a family cluster by pre-symptomatic infections in China. Clin Infect Dis. 2020 Mar 23:ciaa316..
44. Mao L-J, Xu J, Xu Z-H et a. A child with household transmitted COVID-19. BMC Infect Dis. 2020;20:329.
45. Posfay-Barbe KM, Wagner N, Gauthey M et al. COVID-19 in children and dynamics of infection in families. Pediatrics. 2020 May 26:e20201576.
46. Chan J F-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-person transmission: a study of a family cluster. Lancet 2020;395:514-23.

47. Grijalva CG, Rolfes MA, Zhu Y et al. Transmission of SARS-CoV-2 infections in households – Tennessee and Wisconsin, April-September 2020. 2020 Oct 30;6.
48. Laws RL, Chancey RJ, Rabold EM et al. Symptoms and transmission of SARS-CoV-2 among children – Utah and Wisconsin, March-May 2020. Pediatrics. 2020 Oct 8:e2020027268.
49. Fateh-Moghadam P, Bas L, Molinaro S et al. Contact tracing during Phase I of the COVID-19 pandemic in the Province of Trento, Italy: key findings and recommendations. MedRxiv. 2020 July 29. Preprint doi.org/10.1101/2020.07.16.20127357.
50. Somekh E, Gleyzer A, Heller E, et al. The role of children in the dynamics of intra-family coronavirus 2019 spread in densely populated area. Pediatr Infect Dis J. 2020 Aug;39 (8): e202-4
51. COVID-19 National Emergency Response Center, Korea Centers for Disease Control and Prevention. Coronavirus disease-19: summary of 2,370 contact investigations of the first 30 cases in the Republic of Korea. Osong Pub Health Res Perspect. 2020;11 (2):81-4.
52. Zhang W, Cheng W, Luo L et al. Secondary transmission of coronavirus disease from pre-symptomatic persons, China. Emerg Infect Dis. 2020;26 (8).
53. Maltezou HC, Vorou R, Papadima K et al. Transmission dynamics of SARS-CoV-2 within families with children in Greece: a study of 23 clusters. J Med Virol. 2020 Aug 7. Doi: 10.1002/jmv.26394.
54. Hua C-Z, Miao Z-P, Zheng J-S et al. Epidemiological features and viral shedding in children with SARS-CoV-2 infection. J Med Virol. 2020 Jun 15;10.1002/jmv.26180.
55. Luo L, Liu D, Liao X-L et al. Modes of contact and risk of transmission of COVID-19 among close contacts. MedRxiv. 2020 Mar 24. Pre-print doi:10.1101/2020/03/24/20042606.
56. Kuwelker K, Zhou F, Blomberg B et al. High attack rates of SARS-CoV-2 through household transmission-a prospective study. MedRxiv. 2020 Nov 4. Doi:10.1101/2020.11.20224485.
57. Park YJ, Choe YJ, Park O et al. Contact tracing during coronavirus disease outbreak, South Korea, 2020. Emerg Infect Dis. 2020. Doi: 10.3201/eid2610.201315.
58. Madewell ZJ, Yang Y, Longini IM, Halloran E, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. JAMA Netw Open.2020 Dec 1;3 (12):e2031756.
59. Chhibber AV, Muttaiyah S, McAuliffe G et al. Age-related differences in SARS-CoV-2 testing in the Northern Region of New Zealand. N Z Med J. 2020 Jul 31;133 (1519):89-94.
60. Singh T, Heston SM, Langel SN et al. Lessons from COVID-19 in children: key hypotheses to guide preventive and therapeutic strategies. Clin Infect Dis. 2020 Oct 15;71 (8):2006-13.
61. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child. 2020 Dec 1:archdischild-2020-320338.
62. Steinman JB, Lum FM, Ho PP-H, et al. Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics. Proc Natl Acad Sci USA. 2020 Oct 6;117 (40):24620-6.
63. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA. 2020 2020 Jun 16;323 (23):2427-9.
64. Sharif-Askari NS, Sharif-Askari FS, Alabed M et al. Expression of SARS-CoV-2 receptor, ACE 2, and TMPRSS2 in the lung airways is lower in children compared to adults and increases with smoking. Molec Therapy-Methods Clin Develop. 2020 May 22;18:1-6.
65. Radzikowska U, Tan G, Traidl-Hoffmann C et al. Distribution of ACE2, CD147, CD26 and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID 19 risk factors. Allergy. 2020 Jun 4:10.1111/all.14429.
66. Sward P, Edsfeldt A, Reepalu A et al. Age and sex differences in soluble ACE2 may give insights for COVID-19. Critical Care. 2020;24:221.
67. Pavel AB, Guttmann-Yassky E. SARS-CoV-2 receptor ACE2 protein expression in serum is significantly associated with age. Allergy. 2020 Jul 29. Doi:10.1111/all.14522.
68. Patel AB, Verma A. Nasal ACE2 levels and COVID-19 in children. JAMA. 2020 Jun 16;323 (23):2386-7.
69. Mateus J, Grifoni A, Tarke A et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. Science. 2020 Oct;370 (6512):89-94.
70. Braun J, Loyal L, Frentsch M et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020 Nov;587 (7833):270-4.

71. Le Bert N, Tan AT, Kunasegaran K et al. SARS-CoV-2 specific T-cell immunity in cases of COVID-19 and SARS and uninfected controls. Nature. 2020 Aug;584 (7821):457-62.
72. de Vries RD. SARS-CoV-2 specific T-cells in unexposed humans: presence of cross-reactive memory cells does not equal protective immunity. Signal Transduct Target Ther. 2020 Oct 6;5 (10):224.
73. Gunes H, Dincer S, Acipayam C et al. What chances do children have against COVID-19 – is the answer hidden within the thymus? Eur J Pediatr. 2020 Oct 13;1-4. Online ahead of print: doi:10.1007/s00431-020-03841-y.
74. Palmer DB. The effect of age on thymic function. Front Immunol. 2013 Oct 7;4:316.
75. Valiathan R, Ashman M, Asthana D. Effects of ageing on the immune system: infants to elderly. Scand J Immunol. 2016 Apr;83 (4):255-66.
76. Gasparoni A, Ciardelli L, Avanzini A et al. Age-related changes in intracellular Th1/Th2 cytokine production, immunoproliferative T lymphocyte response and natural killer cell activity in newborns,children and adults. Biol. Neonate. 2003;84:297-303.
77. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr. 2020 Jul 30. Doi: 10/1001/jamapediarics.2020.3651.
78. Jones TC, Muhlemann B, Veith T et al. An analysis of SARS-CoV-2 viral load by patient age. MedRxiv. 2020.06.08.20125484. doi: 10.1101/2020.06.08.20125484.
79. Poline J, Gaschignard J, Leblanc C, et al. Systematic SARS-CoV-2 screening at hospital admission in children: a French prospective multicenter study. Clin Infect Dis. 2020 Jul 25:ciaa1044.
80. Baggio S, L'Huillier AG, Yerly S et al. SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19. Clin Infect Dis 2020 Aug 6;ciaa1157.
81. Hurst JH, Heston SM, Chambers HN et al. SARS-CoV-2 infections among children in the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) study. Clin Infect Dis. 2020 Nov 3;ciaa1693.
82. L'Huillier AG, Torriani G, Pigny F, Kaiser L, Eckerle I. Culture-competent SARS-CoV-2 in nasopharynx of symptomatic neonates, children and adolescents. Emerg Infect Dis. 2020 Jun 30;26 (10). Doi: 10.3201/eid2610.202403.
83. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA. 2020;323:1406-7.
84. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Pre-symptomatic Transmission of SARS-CoV-2 – Singapore, January 23-March 16 2020. MMWR Morb Mortal Wkly Rep. 2020;69:411-5.
85. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020;382(12):1177-9.
86. Kam KQ, Yung CF, Cui L et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. Clin Infect Dis. 2020 Feb 28 (epub)
87. Cai J, Xu J, Lin D et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020 Feb 28 (epub).
88. Teherani MF, Kao CM, Camacho-Gonzalez A et al. Burden of illness in households with SARS-Cov-2 infected children. J Pediatr Infect Dis Soc. 202 Aug 11;piaa092.
89. Zhu Y, Bloxham CJ, Hulme KD et al. Children are unlikely to have been the primary source of household SARS-CoV-2 infections. MedRxiv preprint. doi: 10.1101/2020.03.26.20044826.
90. Okarska-Napierala M, Mandziuk J, Kuchar E. SARS-CoV-2 cluster in nursery, Poland. Emerg Infect Dis. 2020 Oct 9;27 (1). On-line ahead of print: doi:10.3201/eid2701.203849.
91. Lopez AS, Hill M, Antezano J et al. Transmission dynamics of COVID-19 outbreaks associated with child care facilities – Salt Lake City, Utah, April-July 2020. MMWR Morb Mort Wkly Rpt. 2020 Sept 18;69 (37):1319-23.
92. Szablewski CM, Chang KT, Brown MM et al. SARS-CoV-2 transmission and infection among attendees at an overnight campe – Georgia, June 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 7;69 (31):1023-5.
93. Grech V, Grech E, Myatt JB. Holidays over: a review of actual COVID-19 school outbreaks up to September 2020. Early Hum Dev. 2020 Oct 1;105206. Online ahead of print: doi:10/1016/jearlhumdev.2020.105206.

94. Leeb RT, Price S, Kimball A et al. COVID-19 trends among school-aged children – United States, March 1-September 19, 2020. MMWR Morbid Mort Wkly Rpt. 2020 Oct 2;69 (39):1410-5.
95. European Centre for Disease Prevention and Control. COVID-19 in children and the role of school settings in COVID-19 transmission, 6 August 2020. Stockholm: ECDD, 2020. URL: https://www.ecdc.europa.eu/en/publications-data/children-and-school-settings-covid-19-transmission
96. Heavy L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland. Euro Surveill. 2020 May;25 (21):2000903.
97. Yung CF, Kam K-q, Nadua KD, et al. Novel coronavirus 2019 transmission in educational settings. Clin Infect Dis. 2020 Jun 25:ciaa794.
98. Macartney K, Quinn HE, Pillsbury AJ et al. Transmission of SARS-CoV-2 in Australian education settings: a prospective cohort study. Lancet Child Adolesc Health. 2020 August 3.
99. Dub T, Erra E, Hagberg L, Sarvikivi E, Virta C, Jarvinen A, et al. Transmission of SARS-CoV-2 following exposure in school settings: experience from two Helsinki area exposure incidents. medRxiv. 2020:2020.07.20.20156018.
100. Yoon Y, Kim K-R, Park H, Kim S-y, Kim Y-J. Stepwise school opening on-line and off-line and an impact on the epidemiology of COVID-19 in the pediatric population. MedRxiv. 2020 Aug 3. Doi: 10.1101/2020.08.03.20165589.
101. Stein-Zamir C, Abramson N, Shoob H et al. A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. Euro Surveil. 2020 Jul 23;25 (29):pii=2001352.
102. Torres JP, Pinera C, De La Maza V, et al. SARS-CoV-2 antibody prevalence in blood in a large school community subject to a COVID-19 outbreak: a cross-sectional study. Clin Infect Dis. 2020 Jul 10;ciaa955.
103. Woodworth KR, Olsen EO, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy – SET-NET, 16 jurisdictions, March 29-October 14 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 6;69 (44):1635-40.
104. Schwartz DA, Graham AL. Potential maternal and infant outcomes from coronavirus 2019-nCoV (SARS-CoV-2) infected pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses. 2020 Feb 10;12 (20):194.
105. Galang RR, Chang K, Strid P et al. Severe coronavirus infections in pregnancy: a systematic review. Obstet Gynecol. 2020 Aug;136 (2):262-72.
106. Schwartz DA, Dhaliwal A. Infections in pregnancy with COVID-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: experiences with coronaviruses, HPIV, hMPV, RSV and influenza. Arch Pathol Lab Med. 2020 Apr 27;144:920-8.
107. Manti S, Cuppari C, Lanzafame A et al. Detection of respiratory syncytial virus (RSV) in a newborn with respiratory distress. Pediatr Pulmonol. 2017 Oct;52 (10):E81-4.
108. Ng EKO, Hui DS, Chan A et al. Quantitative analysis and prognostic implication of SARS coronavirus RNA in the plasma and serum of patients with severe acute respiratory syndrome. Clin Chem. 2003;49:12.
109. Kim SY, Park SJ, Cho SY et al. Viral RNA in blood as an indicator of severe outcomes in Middle East Respiratory Syndrome coronavirus infeciton. Emerg Infect Dis. 2016;22:1813-6.
110. Ling Y, Xu S-B, Lin Y-X et al. Peristance and clearance of viral RNA in 2019 novel cornavirus disease rehabilitation patients. Chin Med J. 2020;133:1039-43.
111. Xie C, Jiang L, Huang G et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. Int J Infect Dis. 2020;93:264-7.
112. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323:1843-4.
113. Wu J, Liu J, Li S et al. Detection and analysis of nucleic acid in various biological samples of COVID-19 patients. Travel Med Infect Dis. 2020 Apr 18:101673.
114. Young BE, Ong SWx, Kalimuddin S et al. Epidemiologic features and clinicalcourse of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020;323:1488-94.
115. Chen W et al. Emerg Microb Infect. 2020;9:469-73.
116. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
117. Chang JF-W, Yuan S, Kok K-H et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-person transmission: a study of a family cluster. Lancet. 2020;395:514-23.

118. Xu D, Zhou F, Sun W et al. Relationship between serum SARS CoV 2 nucleic acid (RNAemia) and organ damage in COVID-19 patients: a cohort study. Clin Infect Dis. 2020 Jul 28;ciaa1085.
119. Chen X, Zhao B, Qu Y et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID 19 patients. Clin Infect Dis. 2020 Apr 17;ciaa449.
120. Li M, Cheng L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLosOne. 2020;15:e020295.
121. Weatherbee BAT, Glover DM, Zernicka-Goetz M. Expression of SARS-CoV-2 receptor ACE2 and the protease TMPRSS2 suggests susceptibility of the human embryo in the first trimester. Open Biol. 2020;10:200162.
122. Pique-Regi R, Romero R, Tarca AL et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? Elife. 2020 Jul 14;9:358716.
123. Wang Q, Qiu Y, Li J-L, Zhou Z-J, Liao C-H, Ge X-Y. A unique protease cleavage site predicted in the spike protein of the novel pneumonia coronavirus (2019-nCoV) potentially related to viral transmissibility. Virologica Sinica. 2020;35:337-39.
124. Jaimes JA, Millet JK, Whittaker GR. Proteolytic cleavage of the SARS-CoV-2 spike protein and the role of the novel S1/S2 site. iScience. 2020 Jun 26;23 (6):101212.
125. Mahyuddin AP, Kanneganti A, Wong J et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2. Prenat Diagn. 2020 Jun 12;10.1002/pd.5765.
126. Komine-Aizawa S, Takada K, Hayakawa S. Placental barrier against COVID 19. Placenta. 2020;99:45-49.
127. Sharps MC, Hayes DJL, Lee S et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta. 2020 Aug 23;101:13-29.
128. Baergen RN, Heller DS, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol. 2020 Jul 7;154 (2):279.
129. Kimberlin D W, Stagno S. Can SARS-CoV-2 infection be acquired in utero? More definitive evidence is needed. JAMA. 2020 May 12;323 (18):1788-9.
130. Zeng H, Xu C, Fan J et al. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA May 12;323 (18):1848-9.
131. Dong L, Tian J, He S et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020 May 12;323 (18):1846-8.
132. Gao J, Li W, Hu X, et al. Disappearance of SARS-CoV-2 antibodies in infants born to women with COVID-19 in Wuhan China. Emerg Infect Dis. 2020 Oct;26 (10).
133. Fenizia C, Biasin M, Cetin I et al. In utero mother to child SARS-CoV-2 transmission: viral detection and fetal immune response. MedRxiv preprint. 2020 Jul 10. Doi: 10.1101.2020.07.09.20149591.
134. Qiu L, Liu X, Xiao M et al. SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection. Clin Infect Dis. 2020 Jul 28;71 (15):813-7
135. Aslan MM, Yuvaci HU, Kose O et al. SARS-CoV-2 is not present in the vaginal fluid of pregnant women with COVID-19. J Matern Fetal Neonatal Med. 2020 Jul 16;1-3.
136. Schwartz DA, Mohagheghi P, Beigi B et al. Spectrum of neonatal COVID-19 in Iran: 19 infants with SARS-CoV-2 perinatal infections with varying test results, clinical findings and outcomes. J Matern Fetal Neonatal Med. 2020 Aug 12;1-10.
137. Vivanti AJ, Vauloup-Fellous C, Prevot S et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020 Jul 14;11 (1):3572.
138. van Doorn AS, Meijer B, Frampton CMA et al. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. Aliment Pharmacol Ther. 2020 Aug 27. Doi: 10.1111/apt.16036.
139. Carosso A, Cosma S, Borella F et al. Pre-labor anal swab for SARS-CoV-2 in COVID-19 pregnant patients: is it time to think about it? Eur J Obstet Gynecol Reprod Bio. 2020 Jun;98-99.
140. Hermesch AC, Horve PF, Edleman A et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) environmental contamination and childbirth. Obstet Gynecol. 2020 Oct;136 (40:827-9.
141. World Health Organization. (2020). Breastfeeding and COVID-19: scientific brief, 23 June 2020. World Health Organization. https://apps.who.int/iris/handle/10665/332639.

142. Centeno-Tablante E, Medina-Rivera M, Finkelstein JL et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Ann N Y Acad Sc. 2020 Aug 28. Doi:10.1111/nyas.14477.
143. Chambers C, Krogstad P, Bertrand K et al. Evaluation for SARS-CoV-2 in breast milk from 18 infected women. JAMA. 2020 Aug 19;e2015580.
144. Lackey KA, Pace RM, Williams JE et al. SARS-CoV-2 and human milk: what is the evidence? Matern Child Nutr. 2020 May 30:e13032
145. Fox A, Marino J, Amanat F et al. Robust and specific secretory IgA against SARS-CoV-2 detected in human milk. iScience. 2020 Nov 20;23 911):101735.
146. Demers-Mathieu V, Do DM, Mathijssen GB et al. Differences in levels of SARS-CoV-2 S1 and S2 subunits- and nucleocapsid protein-reactive SIgM/IgM, IgG, and SIgA/IgA antibodies in human milk. J Perinatol. 2020 Sep1;1-10.
147. Gao X, Wang S, Zeng W et al. Clinical and immunologic features among COVID-19-affected mother-infant pairs: antibodies to SARS-CoV-2 detected in breast milk. New Microbes New Infect. 2020 Sep;37:100752
148. Raschetti R, Vivanti AJ, Vauloup-Fellous C et al. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun. 2020 Oct 15;11 (1):5164.
149. Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand. 2020 May;99(5):565-568.
150. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. N Engl J Med. 2020 May 27 (epub).
151. Moore JT, Ricaldi JN, Rose CE et al. Disparities in incidence of COVID-19 among underrepesented racial/ethnic groups in counties identified as hotspots during June 5-18 wowo – 22 states, February-June 2020. MMWR Morbid Mort Wkly Rpt. 2020 Aug 14;60:early release
152. De Lusignan S, Dorward J, Correa A et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis. 2020 May 15 (epub).
153. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of COVID-19? Brit Med J. 2020;369:m1548.
154. Bhala N, Curry G, Martineau AR, Agyemang C, Bhopal R. Sharpening the global focus on ethnicity and race in the time of COVID-19. Lancet. 2020 May 8 (epub).
155. Tal Y, Adini A, Eran A, Adini I et al. Racial disparity in COVID-19 mortality rates – a plausible explanation. Clin Immunol. 2020;217:108481.
156. Yaya S, Yeboah H, Charles CH, Out A, Labonte R. Ethnic and racial disparities in COVID-19-related deaths: counting the trees, hiding the forest. BMJ Global Health. 2020 Jun;5 (6):e002913.
157. Hooper MW, Napoles AM, Perez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA May 11
158. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 – COVID-NET, 14 states, March 1-July 25 2020. MMWR Morbid Mort Wkly Rep. 2020 Aug 7;69 early release.
159. Bandi S, Nevid MZ, Mahdavinia M. African American children are at higher risk for COVID-19 infection. Pediatr Allergy Immunol. 2020 May 29 (epub).
160. Zachariah P, Johnson CL, Halabi KC et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr. 2020 June 3 (epub)
161. Chao JY, Derespina KR, Herold BC et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. J Pediatr. 2020 May (epub).
162. Harman K, Verma A, Cook J et al. Ethnicity and COVID-19 in children with co-morbidities. Lancet Child Adolesc Health. 2020 May 28 (epub).
163. Goyal MK, Simpson JN, Boyle MD et al. Racial/ethnic and socioeconomic disparities of SARS-CoV-2 infection among children. Pediatrics. 2020 August epub. doi:10.1542/peds.2020-009951.

164. Lee EH, Kepler KL, Geevarughese A et al. Race/ethnicity among children with COVID-19-associated multisystem inflammatory syndrome. JAMA Network Open. 2020 Nov 2;3 (11):e2030280.
165. Gale C, Quigley MA, Placzek A et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health. 2020 Nov 9. On line ahead of print: doi: 10.1016/52352-4642(20)30342-4.
166. Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect Dis J. 2020;39(5):355-368.
167. Liguoro I, Pilotto C, Bonanni M, et al. SARS-CoV-2 infection in children and newborns: a systematic review. Eur J Pediar. 2020 May 18:1-18.
168. Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
169. Garg S, Kim L, Whitaker M et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 states, March 1-30, 2020. MMWR Morb Mortal Wkly Rpt. 2020 Apr 17;69 (15):458-64.
170. Jutzeler CR, Bourguignon L, Weis CV et al. Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020 Aug 4;37:101825.
171. Kim L, Garg S, O'Halloran A et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis. 2020 Jul 16;ciaa1012.
172. Trad ATA, Ibirogba ER, Elrefaei A et al. Complications and outcomes of SARS-CoV-2 in pregnancy: where and what is the evidence? Hypertension in Pregnancy. 2020 May 26 (epub).
173. Leibowitz J, Krief W, Barone S et al. Comparison of clinical and epidemiologic characteristics of young febrile infants with and without SARS-CoV-2 infection. J Pediatr. 2020 Oct 9;S0022-3476(20)31264-6.
174. Fernandez-Colomer B, Sanchez-Luna M, de Alba Romero C et a. Neonatal infection due to SARS-CoV-2: an epidemiologic study in Spain. Front Pediatr. 2020 Oct 23;8:580584.
175. Saha S, Ahmed NU, Sarkar PK, et al. The direct and indirect impact of SARS-CoV-2 infection on neonates: a series of 26 cases in Bangladesh. Pediatr Infect Dis J. 2020 Dec;39 (12):e398-405.
176. Lishman J, Kohler C, de Vos C, van der Zalm MM, Itana J, Redfern A, Smit L RH. Acute appendicitis in MIS-c and COVID-19. Pediatr Infect Dis J. 2020 Dec;39 (12):e472-3.
177. Nachega JB, Katuashilshoso D, Otokoye JO et al. Clinical characteristics and outcomes of patients hospitalized for COVID-19 in Africa: early insights from the Democratic Republic of the Congo. Am J Trop Med Hyg. 2020. Doi: 10.4269/ajtmh.20-1240.
178. Kirenga B, Muttamba W, Kayongo A et al. Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda. BMJ Open Resp Res. 20207:e000646.
179. Bixler D, Miller AD, Mattison CP et al. SARS-CoV-2-associated deaths among persons aged <21 years – United States, February 12-July 31 2020. 2020 Sept 18;69 (37):1324-9.
180. Shekerdemiaden LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 admitted to US and Canadian pediatric intensive care units. JAMA. 2020 May 11 (epub).
181. DeBiasi RL, Song X, Delaney M et al. Severe COVID-19 in children and young adults in the Washington DC Metropolitan region. J Pediatr. 2020 May 13 (epub).
182. Oualha M, Bendavid M, Berteloot L et al. Severe and fatal forms of COVID-19 in children. Arch Pediatr. 2020 Jul;27 (5):235-8.
183. Gonzalez-Dambrauskas S, Vasquez-Hoyos P, Camporesi A et al. Pediatric critical care and COVID 19. Pediatrics. 2020 Jun 9;e20201766.
184. Sousa BLA, Sampaio-Carneiro M, de Carvalho WB et al. Differences among severe cases of SARS-CoV-2, influenza and other respiratory viral infections in pediatric patients: symptoms, outcomes and preexisting comorbidities. Clinics (Sao Paolo). 2020 Nov 30;75;e2273.
185. Duarte-Salles T, Vizcaya D, Pistillo A et al. Baseline charactertistics, management and outcomes of 55,270 children and adolescents diagnosed with COVID-19 and 1,952,693 with influenza in France,

Germany, Spain, South Korea, and the United States: an international network cohort study. MedRxiv. 2020 Oct 29. Doi: 10.1101/2020.10.29.20222083.
186. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of underlying health conditions among patients with coronavirus disease 2019 – United States, February 12-March 28 2020. Morbid Mort Wkly Rpt. 2020 March 31;69 (early release)
187. Hoang A, Chorath K, Moreira A et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinical Medicine. 2020 June 23. Doi:10.1016/jeclinm.2020.100433.
188. Tsankov BK, Allaire JM, Irvine MA et al. Severe COVID-1 i infection and pediatric comorbidities: a systematic review and meta-analysis. Int J Infect Dis. 2020 Nov 20;S1201-9712(20)32475-9.
189. Briguglio M, Pregliasco FE, Lombardi G, Perazzo P, Banfi G. The malnutrition status of the host as a virulence factor for new coronavirus SARS-CoV-2. Front Med. 2020 Apr 23:146.
190. De Carvalho Sales-Peres SH, Azevedo-Silva LJ, Bonato RCS, et al. Coronavirus (SARS-CoV-2) and the risk of obesity for critical illness and ICU admission: meta-analysis of the epidemiological evidence. Obes Res Clin Prac. 2020 Aug 3;S1871-403X(20)30555-X.
191. Steinberg E, Wright E, Kushner B. In young adults with COVID-19, obesity is associated with adverse outcomes. West J Emerg Med. 2020 Jun 15;21 (4):752-5.
192. Tartof SY, Qian L, Hong V et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. Ann Int Med. 2020 Aug 22. Doi: 10.7326/M20-3724.
193. Kass DA. COVID-19 and severe obesity: a big problem? Ann Int Med. 2020 Aug 22 doi:10.7326/M20-5677.
194. Korakas E, Ikonomidis I, Kousathana F et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab. 2020 May 27 (epub).
195. Green WD, Beck MA. Obesity altered T cell metabolism and the response to infection. Curr Opin Immunol. 2017;46:1-7.
196. Li X, Xu S, Yu M et al. Risk factors for severity and mortality in adults COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020 Apr 12:S0091-6749(20)30495-4.
197. Jackson DJ, Busse WW, Bacharier LB et al. Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol. 2020 April 22:S0091-6749(20)30551-0.
198. Millen GC, Arnold R, Cazier J-B, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Brit J Cancer. 2020 Dec 10.
199. de Rojas, T., Pérez-Martínez, A., Cela, E., Baragaño, M., Galán, V., Mata, C. et al. COVID-19 infection in children and adolescents with cancer in Madrid. Pediatr. Blood Cancer 67, e28397 (2020).
200. Cesaro S, Compagno F, Zama D, et al. Screening for SARS-CoV-2 infection in pediatric oncology patients during the epidemic peak in Italy. Pediatr Blood Cancer. 2020 Jun 15;e28466.
201. Bisogno G, Provenzi M, Zama D et al. Clinical characteristics and outcome of SARS-CoV-2 infection in Italian pediatric oncology patients: a study from the Infectious Disease Working Group of the AIEOP. J Pediatr Infect Dis Soc. 2020 Jul 11;piaa088.
202. Ferrari, A., Zecca, M., Rizzari, C., Porta, F., Provenzi, M., Marinoni, M. et al. Children with cancer in the time of COVID-19: an 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. Pediatr. Blood Cancer 67, e28410 (2020).
203. Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in children with cancer in New York City. JAMA. 2020 May 13:e202028.
204. André, N., Rouger-Gaudichon, J., Brethon, B., Phulpin, A., Thébault, É., Pertuisel, S. et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: high risk of severe forms? Pediatr. Blood Cancer 67, e28392 (2020).
205. Ebeid FSE, Ragab IA, Elsherif NHK et al. COVID-19 in children with cancer: a single low-middle income center experience. J Pediatr Hematol Oncol. 2020 Dec 7. Online ahead of print
206. Rouger-Gaudichon J, Thebault E, Felix A et al. Impact of the first wave of COVID-19 on pediatric oncology and hematology: a report from the French Society of Pediatric Oncology. Cancers. 2020;12:3398.
207. Marlais M, Wlodkowski T, Vivarelli M et al. The severity of COVID-19 in children on immunosuppressive therapy. Lancet Child Adolesc Health. 2020 Jul;4 (7):e17-18.

208. Brenner EJ, Pigneur B, Foccht G et al. Benign evolution of SARS-CoV-2 infections in children with inflammatory bowel disease: results from two international databases. Clin Gastroenterol Hepatol. 2020 Oct 12;S1542-3565(20)31399-9.
209. Simpson M, Collins C, Nash DB, Panesar LE, Oster ME. COVID-19 in children with pre-existing heart disease. J Pediatr. 2-2- Jul 27;S0022-3476(20)30969-9.
210. De Souza Vilela T, Braga JAP, Loggetto SR. Hemoglobinopathy and pediatrics in the time of COVID-19. Hematol Transfus Cell Ther. 2020 Dec 2. Doi: 10.1016/j.htct.2020.11.002. Online ahead of print.
211. Mirzaei H, McFarland W, Karamousian M, Sharifi H. COVID-19 among people living with HIV: a systematic review. AIDS Behav. 2020 Jul 30;1-8. Doi: 10.1007/s10461-020-02983-2.
212. Nordling L. HIV and TB increase death risk from COVID-19, study finds – but not by much. Science. 2020 June. doi:10.1126/science.abd3406
213. Bhekisisa Webinar. When epidemics collide: TB, HIV and COVID-19. June 11, 2020. URL: https://bhekisisa.org/multimedia/2020-06-09-standing-by-when-epidemics-collide-does-hiv-tb-cause-worse-covid-19/
214. Boulle A, Davies M-A, Hussey H et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. Clin Infect Dis. 2020 Aug 29;ciaa1198.
215. Geretti AM, Stockdale AJ, Kelly SH et al. Outcomes of COVID-19-related hospitalization among people with HIV in the ISARIC WHO Clinical Characterization Protocol UK Protocol: prospective observational study. MedRxiv. 2020 Aug 7. Doi: 01.1101/2020.08.07.20170449.
216. Bhaskaran K, Rentsch CT, MacKenna B et al. HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. MedRxiv. 2020 Aug 7. Doi: 10.1101/2020.08.07.20169490
217. European Centre for Disease Prevention and Control. Rapid risk assessment: Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. May 15 2020 URL: https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment
218. Whittaker E, Bamford A, Kenny J et al. Clinical characteristics of 58 children with a pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2. JAMA. 2020 June 8 (epub)
219. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). May 2020 URL: https://www.cdc.gov/mis-c/hcp/
220. Godfred-Cato S, Bryant B, Leung J et al. COVID-19-associated Multisystem Inflammatory Syndrome in children – United States, March-July 2020. MMWR Morbid Mort Wkly Rep. 2020 Aug 7;69 early release
221. https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
222. https://www.who.int/maternal_child_adolescent/research/covid-19/en/
223. Shulman ST. Pediatric COVID-associated multi-system inflammatory syndrome (PMIS). J Pediatr Infect Dis Soc. 2020 May 22 (epub).
224. Panigrahy N, Policarpio J, Ramanathan R. Multisystemc inflammatory syndrome in children and SARS-CoV-2: a scoping review. J Pediatr Rehab Med. 2020;13:301-316.
225. Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC et al. Multisystem inflammatory syndrome in children: an international survey. Pediatrics. 2020 Nov 24;e2020024554.
226. Webb K, Abraham DR, Faleye A et al. Multisystem inflammatory syndrome in children in South Africa. Lancet Child Adolesc Health. 2020 Oct;4 (10):e38.
227. Diamanti AP, Rosado MM, Piloi C, Sesti G, Lagana B. Cytokine release syndrome in COVID-19 patients, a new scenario for an old concern: the fragile balance between infections and autoimmunity. Int J Molec Sci. 2020 May 8 (epub).
228. Martinez OM, Bridges ND, Goldmuntz E, Pascual V. The immune roadmap for understanding multi-system inflammatory syndrome in children: opportunities and challenges. Nature Med. 2020 Dec;26:1819-24.
229. Hwang TJ, Randolf AG, Bourgeois FT. Inclusion of children in clinical trials of treatment for coronavirus disease 2019 (COVID-19). JAMA. 2020 May 7 (epub).
230. Whitehead CL, Walker SP. Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. Lancet. 2020 May 13 (epub).