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

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Abstract: The initial impression that paediatric SARS-CoV-2 infection is uncommon and generally mild has been replaced by a more nuanced understanding of infectious manifestations in children and adolescents across low-, middle-, and high-income countries and by demographic structure, with recognition of a widening disease spectrum. Critical knowledge gaps, especially in low- and middle-income countries remain, that have significant public policy and programme implications. Insufficient data disaggregated by age, geography and race/ethnicity are hindering efforts to fully assess prevalence of infection and disease in children and adolescents and their role in transmission. Potential biologic differences in susceptibility to infection and transmissibility between children and adults need to be assessed. Determination of mother-to-child SARS-CoV-2 transmission during pregnancy or peripartum 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 particularly as the pandemic moves to low- and middle-income countries, where poor nutritional and health conditions and other vulnerabilities are more frequent among children than in higher-income settings. 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, comorbidities, transmission, income-level, demographics, testing, data, disaggregated.

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**KEY FINDINGS AND RECOMMENDATIONS**

- Contrary to the current narrative, the risks of COVID-19 disease in children and young people depend largely on where individuals live and how vulnerable they are to disease and ill health. This is evidenced by the higher proportion of COVID-19 cases among the under-20s in low- and middle-income countries: around 11 per cent of the national caseload, compared with 7 per cent in high-income countries. This figure varies widely across countries, from 23 per cent of the national COVID-19 caseload in Paraguay to 0.82 per cent in Spain.

- Some studies have found the susceptibility to COVID-19 disease 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.

- 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 malnutrition – may increase the severity of COVID-19 disease and mortality in children especially in low- and middle-income countries where underlying child vulnerabilities and poor health conditions are prevalent.

- Alarmingly, in some countries like the United States of America and the United Kingdom of Great Britain, these risks 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 in transmission of SARS-CoV-2 infection requires rapid evaluation. Available evidence suggests transmission risk from children to other children and adults could be small. Therefore, the impact of school closing on mitigating SARS-CoV-2 infection and COVID-19 disease in the community may be minimal and could make guidance for school re-opening less complex.

- Modelling scenarios have found a high risk of indirect health and social impacts of the pandemic on child, adolescent and maternal health:
  - About 9.8 to 44.7% increase in under-five deaths and up to 8.3 to 38.6% increase in maternal deaths per month across 118 countries due to disruptions in essential maternal and child health interventions.
  - About 100% or more mother-to-child transmission (MTCT) of HIV in some countries, due to a 6-month disruption in all prevention of MTCT services.
  - Up to 20% increase in Tuberculosis deaths, due to reductions in timely diagnosis and treatment.
  - Up to 36% increase in Malaria deaths, due to reduced prevention activities.
• The newly emerging multisystem inflammatory syndrome (MIS-C) further underscores the need for better reporting, monitoring and analysis to understand the COVID-19 disease health risks for children and young people. There may be a widening spectrum of COVID-19-related disease in children, ranging from asymptomatic to post-infection conditions including MIS-C.

• But critical knowledge gaps persist, especially in low- and middle-income countries. This research brief 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, income, geography and intersections with co-morbidities and underlying vulnerabilities.

• The authors therefore 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, adolescents and young people.

1. Introduction

In December 2019, a novel coronavirus - Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in Wuhan City, China, causing a cluster of cases of severe pneumonia (Huang C). The coronavirus virus rapidly spread, resulting in an epidemic throughout China and evolving into a global pandemic with increasing number of cases worldwide. In February 2020, the World Health Organization designated the disease caused by SARS-CoV-2 virus as COVID-19 disease (shorthand for Coronavirus Disease 2019). Individuals of all ages are susceptible to SARS-CoV-2 infection, but older age and underlying co-morbidities are known to be associated with increased risk of disease severity and mortality. However, despite the rapidly increasing amount of evidence on SARS-CoV-2 infection and COVID-19 disease, data and evidence on how it affects children (age <10 years) and adolescents (age 10-19 years) remain limited and conflicting, with an increased spectrum of disease manifestations emerging (e.g., multisystem inflammatory syndrome). There is a wide knowledge gap between high- and low-/middle-income countries (LMICs), both because the pandemic has emerged later among LMICs and the resources to conduct the needed epidemiologic and clinical studies are more limited in such settings. Critical data and research needs have emerged with important public policy and programme implications.

Given the rapid growth and evolving nature of evidence on paediatric SARS-CoV-2 and COVID-
19 disease, a scoping review of the scientific literature and data was conducted related to SARS-CoV-2/COVID-19 disease in children and adolescents. The paper reviews the epidemiology of SARS-CoV-2 infection in children and adolescents six months after the COVID-19 pandemic has started, susceptibility and transmissibility of infection in children and adolescents, potential for mother to child transmission during pregnancy, and clinical manifestations of disease (morbidity and mortality) in children and adolescents, including in relation to pre-existing co-morbidities and vulnerabilities. The paper uses data from published scientific literature and online data from 42 countries with such data publicly available online. The paper acknowledges the critical data and evidence gaps for children and adolescents due to lack of age disaggregation and limited public availability of comparable data, especially from low- and middle-income countries.

The review focuses on the following:

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

- The final section has the conclusions and policy, programme and data and research implications.

2. Literature and Data Scoping and Search Criteria

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

Given we are just six months into the pandemic and the urgent need for information, studies to date have been produced rapidly with varying quality, with most from high income countries (HICs). Some studies are small case series, and some reports have included suspected, as well as, confirmed cases. The scoping review tried to focus on studies with larger sample size that included individuals with laboratory-proven infection. However, for some topics, such as neonatal infection with SARS-CoV-2, case reports were included. A total of 1,132 papers
were reviewed, of which 148 were included in the scoping review.

There is no public global database with age disaggregated data, hence the COVID-19 disease caseload data for children and adolescents were accessed from 42 country-specific online databases, dashboards and published reports, where publicly available. While this review does not include the indirect health effects of SARS-CoV-2/COVID-19 on the paediatric and adolescent population, some examples of modelling possible indirect effects on their health is included and a list of additional models are in Annex 2.

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

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

It should be noted that there is a general possibility of underreporting of COVID-19 cases – as patients with mild symptoms, especially children and young people, 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 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 groups, and 0.9 per cent aged <10 years (12 per cent of the population), and no deaths in children age <10 years (Pan, Zhang Y).

Subsequent data from additional countries, mainly high income, continue to report low numbers of children diagnosed with COVID-19. Children continue to constitute a low proportion of those diagnosed with COVID-19 in reports from Europe and United States. However, the exact incidence of COVID-19 in children is difficult to ascertain. Global data are not readily available disaggregated by age, and country data likewise lack age breakdown or may only provide aggregate data for those <20 years. Data on the proportional age breakdown between birth to 19 years is limited, and existing reports or databases often use different and overlapping age categories.

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

The common narrative, at least for now, is that children and adolescents (0-19 years) have been largely spared the adverse direct effects of SARS-CoV-2 and COVID-19 disease on their own health and survival. This narrative is based predominantly on early data from the first affected countries of the virus, notably from China (Wuhan Province) and Italy in early 2020, and other high-income countries including the United States and European nations. But demographic profiles differ widely among countries, and assumptions and narratives made on evidence taken from ageing societies and mainly from high-income countries may not hold for more youthful and growing populations in low- and middle-income countries (LMICs). The vast majority of the world’s children, adolescents and young people live in LMICs, and with the observed upward trend in reported COVID-19 caseloads in these settings, it is
imperative to evaluate the direct effects of the disease on children and adolescents. The data below, despite the limitations, illustrate the contrast between the age cohort profiles of COVID-19 caseloads for Kenya and Italy (Figure 1), and suggests that children worldwide may be more affected by COVID-19 disease than the dominant narrative so far suggests. This contrasting pattern is observed for other countries as well, with available data.

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

![Graph showing COVID-19 cases by age in Italy and Kenya](image)

**Note:** *Age range is 10-18 years


Data from 42 country-specific publicly available online surveillance databases, dashboards and reports indicate that there is a broad spectrum of COVID-19 burden among those <20 years as a share of national caseloads, ranging from 23 per cent in Paraguay to just 1 per cent in Spain as of 15 June 2020 (Figure 2). This may be indicative of differences in demographic structures of high and low income countries or differing policies related to SARS-CoV-2 diagnostic testing; if testing is confined to individuals with severe disease, children may be less likely to be tested as they appear to have milder disease with infection. Accurate, age-disaggregated data are critical to better understand the geographic variations and age distribution in paediatric cases and for design of context specific policies and programmes.

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

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

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

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

¹ CDC COVID-19 Response Team. MMWR 2020 Apr 6  
² Dong Y et al. Pediatrics. 2020 Mar 16

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

Because surveillance data predominantly reflect individuals diagnosed with COVID-19 disease, there is concern that low case rates among children may reflect selective testing of only the most severely symptomatic individuals for SARS-CoV-2 infection. There is debate as to whether the low incidence of COVID-19 disease/SARS-CoV-2 infection is related to children being more likely asymptomatic or having atypical/mild symptoms compared with adults -- reducing the likelihood of them being tested for SARS-CoV-2 – or whether they are less likely to be exposed to infected individuals outside of the household given mitigation measures such as school closure, or whether it reflects a true lower susceptibility to infection (Davies, Zhang).

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

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

In a preprint systematic review and meta-analysis of contact tracing and population-screening studies to explore the issue of child susceptibility to infection, Viner and colleagues identified 18 studies (including unpublished pre-prints) (VinerMedRxiv). Their meta-analysis of nine contact tracing studies found children and adolescents <20 years had 56 per cent lower likelihood of a positive virologic test for SARS-CoV-2 after index exposure than adults >20 years (pooled odds ratio 0.44, 95 per cent confidence interval [CI] 0.29-0.69), with substantial between study heterogeneity (63 per cent). The authors noted there were insufficient data to do sensitivity analyses separating younger children from adolescents because few studies reported sufficient age disaggregation.

In an age-structured mathematical model using epidemic data from China, Italy, Japan, Singapore, Canada and South Korea, and including heterogeneous contact rates between age groups, Davies and colleagues from the London School of Hygiene and Tropical Medicine estimated that susceptibility to SARS-CoV-2 infection in children and adolescents <20 years was approximately half that of adults aged over 20 years – findings similar to the meta-analysis by Viner (Davies, Viner). They estimated the relative susceptibility to infection was 0.40 (Interquartile range (IQR) 0.25-0.57) in children aged 0-9 years and 0.38 (IQR 0.27-0.53) in adolescents aged 10-19 years compared to 0.88 (IQR 0.70-0.99) in those aged 60–69 years. The estimated probability of clinical symptoms also increased with age, with 21-29 per cent of those aged 0-29 years developing symptoms of disease (29 per cent of children age <10, 21 per cent of adolescents 10-19, and 27 per cent of young adults 20-29 years) compared to 63 per cent in those age 60-69 years.

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

With screening for SARS-CoV-2 predominantly based on symptoms of COVID-19 disease, the true extent of SARS-CoV-2 infections among children and the wider community is unknown. Information regarding SARS-CoV-2 infection requires population-based surveillance, which has been relatively limited. The Viner meta-analysis evaluated eight published/pre-print population prevalence studies (VinerMedRxiv). Because of significant differences in the populations studied (demography, exposure history, time-point in the epidemic) and differences in defining infection (virologic testing to evaluate incidence of current infection versus serologic testing to evaluate prevalence of past infection), a meta-analysis was not able to be done.

Four studies (two viral prevalence studies in Iceland and Italy and two seroprevalence studies from the Netherlands and Spain) suggested a lower SARS-CoV-2 seroprevalence in children than adults while four studies (two viral prevalence studies in Stockholm and United Kingdom and two serosurveys from Geneva and Gangelt, Germany) showed no difference in SARS-CoV-2 seroprevalence between children and adults.
The Geneva serosurvey data were published on June 11 including a larger number of individuals (2,766 participants from 1,339 households), and now report a lower seroprevalence, 0.8 per cent, among 123 children aged 5-9 years tested compared with those aged 10-64 years (relative risk 0.32, 95 per cent CI 0.11-0.63); seroprevalence in 332 adolescents age 10-19 years was 9.6 per cent and similar to 1,942 individuals age 20-64 years, 8.8 per cent (Stringhini). In contrast, updated data from the United Kingdom pilot national serosurvey of 9,912 households conducted between April 26 and June 18 2020 continues to report no difference in seroprevalence between children age 2-11 years (0.38 per cent, 95 per cent CI 0.16-0.75) seropositive), 12-19 years (0.30 per cent, 95 per cent CI 0.11-0.66), and those >20 years (ranging from 0.33-0.57 per cent) (UK ref).

Thus, findings from the population-based studies are inconsistent, and most had small numbers of children and adolescents included. There are currently insufficient data to draw definitive conclusions regarding SARS-CoV-2 infection incidence and prevalence in children and adolescents.

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

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

A separate study evaluated several public gene-expression datasets and found that gene expression for ACE-2 and TMPRSS2 in nasal tissue as well as bronchial tissue was lower in children compared to adults (Sharif-Askari). Lower ACE2 expression in the nasal epithelium of the upper respiratory tract – the first point of contact for the SARS-CoV-2 virus – and the lower respiratory tract could result in decreased susceptibility to acquisition of SARS-CoV-2 infection and/or lower levels of viral replication in children than adults (Patel). If confirmed, these findings could account for potential decreased susceptibility to SARS-CoV-2 acquisition and/or replication in children.

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

Data are also conflicting regarding the risk of SARS-CoV-2 transmission from children to adults. While data have indicated that children are more likely to have mild or asymptomatic disease, transmission has been demonstrated to occur from asymptomatic infected individuals within family clusters (Bai, Wei W). Additionally, studies of quantitative viral load in upper respiratory specimens have found similar viral load in asymptomatic and symptomatic patients, suggesting similar transmission potential regardless of symptoms (Zou L, Kam K, Huff). For example, an asymptomatic six-month old infant with SARS-CoV-2 infection had high viral load detected on nasopharyngeal testing, similar to that in his symptomatic mother, with the infant remaining positive for 17 days (Kam K).
Child-to-adult transmission has been documented in a few case reports including a small number of individuals. In a study of 10 paediatric cases of COVID-19 in China, a three month-old infant residing in an endemic area transmitted infection to both parents, who developed symptomatic COVID-19 a week after they cared for the sick infant without protection measures (Cai J). However, in a preprint review of 31 household transmission cluster studies, only three clusters (10 per cent) identified a child <18 years as the index case (Zhu Y). In a sensitivity analysis in which child with asymptomatic infection in any household with an adult index case was presumed to be the asymptomatic index case, then potentially six of 28 (21 per cent) clusters could be due to a child index case. The authors conclude that data to date suggest children have not played a substantial role in household transmission of SARS-CoV-2.

Three studies have reported on school-related contact tracing. In a contact investigation of 12 COVID-19 cases linked to a single case in the French Alps, one nine-year old child, who was coinfectected with other respiratory viruses (picornavirus and influenza A), attended three schools while mildly symptomatic but did not transmit the SARS-CoV-2, although there was a high proportion of picornavirus and influenza infection among school contacts (Danis K). In Australia, virologic and serologic screening of 863 school-related contacts of 18 COVID-19 cases (nine students, nine staff) identified secondary infection in only two students and no staff (New South Wales). In an evaluation of contact tracing records from children and adults in Ireland diagnosed with COVID-19 who attended a school setting prior to national school closures on March 12 2020, three paediatric (one primary and two secondary school attendance) and three adult cases of confirmed COVID-19 with a history of school attendance were identified; of 924 child and 101 adult contacts in schools that were evaluated, no confirmed cases of COVID-19 were identified, although only symptomatic contacts received virologic testing (Heavey).

These data suggest that children have not played a significant role in school transmission of SARS-CoV-2. However, news accounts of reopening of schools in Israel, France and South Korea following mitigation interventions for COVID-19 reported several clusters of school infections, including at least 130 cases at a single school in Israel, prompting re-closure of affected schools (NPR, Independent co UK, CNN).

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. Further evaluation is needed to determine whether children (and schools) will play a more substantive role once mitigation measures are eased, and whether children are less infectious than adults or less susceptible to infection.

The difference in transmissibility, if real, may be more likely in younger children. Reports have indicated the potential for rapid transmissibility of SARS-CoV-2 among adolescents and young adults. In a study in China, six of 15 classmates exposed to an initially asymptomatic 22-year-old index case were documented to have acquired COVID-19 disease within a median of 2 days of exposure (Huang L).

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

With the initial coronavirus SARS-CoV-1 and MERS epidemics, there were no confirmed cases of maternal-fetal vertical transmission
(Schwartz D). For in utero transmission, the pathogen must be present in blood and be able to cross the placenta and infect the fetus. Although SARS-CoV-1 and the MERS virus are detected relatively frequently in blood samples (33-78 per cent) (Ng, Kim SY), viremia secondary to SARS-CoV-2 appears much less frequent. In eight studies that have evaluated SARS-CoV-2 viremia in patients with COVID-19, viremia was detected in 21 of 587 samples, for a prevalence of 3.6 per cent, significantly lower than the other serious coronaviruses. (Ling Y, Xie C, Wang W, Wu J, Young B, Chen W, Huang C, Chang JF) The receptor for SARS-CoV-2, ACE2, has been identified in both placental and fetal tissues (Li M). 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.

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

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

There have been a small number of reports of SARS-CoV-2 detection in cord blood, placenta, and breast milk, or SARS-CoV-2 IgM antibody detection in neonatal blood; in all instances to date, the infants had negative nasopharyngeal tests, no symptoms, and/or IgM turned negative by 12-28 days (Buonsenso, Penfield, Algarroba, Baud, Dong L, Zeng, Wu). Additionally, the presence of SARS-CoV-2 RNA by rtPCR in human milk does not necessarily confirm the presence of infectious virus capable of replicating in host cells (Lackey, Widders).

In summary, while mother-to-child transmission of SARS-CoV-2 is possible, it has not yet been confirmed. 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 (Price-Haywood). Similarly, in the United
Kingdom COVID-19 is more common among black and ethnic minority individuals (de Lusignan, Khunti). This may reflect social determinants that make these populations more vulnerable to infection, such as economic insecurity, poor neighborhood and housing conditions, employment in occupations at higher risk of viral exposure, and availability of healthcare, as well as higher prevalence of chronic co-morbidities such as hypertension, diabetes and obesity among minority populations, or an undefined biologic factor (Bhala, Tal, Yaya, Hooper).

There have been limited data on COVID-19 and race/ethnicity in children, and most paediatric studies have not reported race/ethnicity data. In a study in a pediatric out-patient clinic at Rush University Medical Center in Chicago, 474 children were evaluated and tested for SARS-CoV-2 between March and April 2020; 25 (5.2 per cent) children had a positive test (Bandi). Adjusting for age and gender, minority race/ethnicity was significantly associated with a positive test result (6.8 per cent of 205 African American and 6.6 per cent of 117 Hispanic children vs 1.7 per cent of 119 non-Hispanic white children had a positive test). Of the five children needing hospitalization, four were African American. Studies from three hospitals in New York City 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 (Zachariah, Chao, Harman).

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

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

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

A systematic review of SARS-CoV-2/COVID-19 literature through 1 May 2020 identified 62 papers and three prior reviews covering 7,480 children and adolescents (0-18 years). The mean age of these children was 7.6 years and 52 per cent were male (Liguoro). The studies came primarily from Italy (44 per cent), the United States (34 per cent) and China (18 per cent), with a small percentage from South Korea (3 per cent), and under 1 per cent each from Spain, Vietnam, Malaysia, and Iran. The review only included children with laboratory-proven SARS-CoV-2 infection. A family history of contact with an infected person was present in 73 per cent of cases.

**Clinical findings**

Disease severity was assessed in the 1,780 children, primarily from Italy, United States and China. Fifty-seven 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). This contrasts with a study of 1,099 adults with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces in China, in whom severe/critical disease was
observed in 16 per cent of COVID-19 patients (Guan).

Clinical findings were available in the same 1,780 children across 49 studies. Figure 3 compares disease symptoms reported in these children to that in 10,944 adults aged 18-64 years in the United States with SARS-CoV-2 infection (CDCCOVID19). Fever, cough, and sore throat were the commonest symptoms in children, while dyspnea was rare. Lower rates of all symptoms were seen in children compared to adults.

**Figure 3:** Symptoms of SARS-CoV-2 in children and adolescents compared with adults

Laboratory and radiologic findings

Laboratory findings were reported in 655 children from 38 studies (Liguoro). White blood count was normal in most, with only 17 per cent demonstrating low white cell count and 5 per cent lymphopenia; in contrast, 34 per cent of adults in a large study of infected adults in China had low white cell count and 83 per cent lymphopenia (Figure 4) (Guan). Markers of inflammation were lower in children, with elevated c-reactive protein (CRP) observed in 31 per cent of children compared to 61 per cent of adults. Lymphopenia and elevated CRP are both associated with poorer prognosis among adults. Of 674 children with radiologic evaluation in 40 studies, 49 per cent had abnormal radiologic findings, including 15 per cent of 113 asymptomatic children (Liguoro). Radiologic abnormalities were observed in 59 per cent of adult patients (Guan).
Figure 4: Laboratory and Radiologic Findings of SARS-CoV-2 in children and adolescents compared with adults

![Laboratory Findings in 655 Children and Adolescents 0-18 Years with SARS-CoV-2 Infection vs Laboratory Findings in 1,099 Adults 18-64 Years in China with SARS-CoV-2 Infection](image)

**Treatment**

Two per cent of children in the studies required hospital admission compared to 5 per cent of adults (Figure 5) (Liguoro, Guan). Of these hospitalized cases, 2 per cent of both child and adult cases required mechanical ventilation. By contrast, non-invasive oxygen was required by 9 per cent of children compared with 41 per cent of adults. Use of antiviral agents was similar between children and adults, but use of antibiotics, steroids and intravenous immune globulin was less frequent in children.

Figure 5: Treatment of SARS-CoV-2 in children and adolescents compared with adults

![Treatment in 1,402 Children and Adolescents 0-18 Years with SARS-CoV-2 Infection vs Treatment in 1,099 Adults 18-64 Years in China with SARS-CoV-2 Infection](image)
**Newborns/infants age <3 months compared with all children and adolescents**

At the time of writing this report, there were data from 12 papers on 25 newborns and infants <3 months of age (Liguoro). Neonates (84 per cent) primarily underwent SARS-CoV-2 screening because of maternal COVID-19 disease. Given the small number of newborns/infants, caution is needed in interpreting comparisons with older children. Similar to older children, 88 per cent of newborns/infants had asymptomatic, mild, or moderate symptoms (20 per cent, 48 per cent and 20 per cent, respectively). However, a higher proportion of newborns/infants had severe illness (12 per cent) versus all children (2.7 per cent).

In contrast to the overall group of children, more newborns/infants had reported dyspnea (shortness of breath) and few had a cough (Figure 6). 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 6:** Symptoms of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents

<table>
<thead>
<tr>
<th>Disease Symptoms Newborns/Infants &lt;3 Months</th>
<th>Disease Symptoms in Children and Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 Studies, N=25</td>
<td>0-18 Years 49 Studies, N=1,780</td>
</tr>
<tr>
<td>32% Fever</td>
<td>52% Fever</td>
</tr>
<tr>
<td>8% Cough</td>
<td>47% Cough</td>
</tr>
<tr>
<td>40% Dyspnea</td>
<td>8% SOB</td>
</tr>
<tr>
<td>12% Vomiting</td>
<td>7% Vomiting</td>
</tr>
</tbody>
</table>

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 7). Given the small number of newborns/infants, caution is needed in interpreting comparisons with older children.
**Figure 7:** Laboratory and radiologic findings of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents

![Graph showing laboratory and radiologic findings](image)

More newborns/infants received only symptomatic treatment, 52 per cent, compared with 21 per cent for children overall. However, 8 per cent were admitted to the neonatal intensive care unit compared to 2 per cent pediatric intensive care for children overall (Figure 8). This may have been because infants born to mothers with COVID-19 disease are more likely to be born preterm or that they were admitted for observation because of COVID-19 disease in their mother (Trad). Again because of the small sample size for newborns/infants, caution should be exercised in interpreting results.

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

![Graph showing treatment](image)
Underlying medical conditions and outcomes in children and adolescents

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

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

Severe SARS-CoV-2 infection in children and adolescents

Children admitted to pediatric intensive care units with significant COVID-19 disease have a high rate of co-morbidities as well as mortality. In a study of 48 children admitted to 46 pediatric intensive care units (PICU) in Canada and the United States between March 14 and April 3, 2020, 31 (83 per cent) had significant pre-existing co-morbidities. Co-morbidities in these 31 children included medically complex conditions (children with a long-term dependence on technology support including tracheostomy associated with developmental delay or genetic abnormalities) in 19, immune suppression/malignancy in 11, obesity in 7, diabetes in 4, seizures in 3, congenital heart in 3, sickle cell disease in 2, chronic lung disease in 2, and other congenital abnormalities in 2 (Shekerdemian). Seventy-three per cent of children presented with respiratory symptoms, 38 per cent required mechanical ventilation, and their mortality rate was 4 per cent.

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

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.

Asthma and SARS-CoV-2

In a study at Rush University Medical Center in Chicago of 474 children <18 years who had virologic testing as out-patients for SARS-CoV-2 between March 12 and April 20 2020, 25 (5.2 per cent) were positive, and the prevalence of
pre-existing asthma did not differ significantly between those who were positive for SARS-CoV-2 and those who were negative (12 per cent vs 10.2 per cent, respectively). Among those children admitted to the hospital, only one had asthma and also had sickle cell acute pain crisis (Bandi).

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

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

**Nutrition 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 malnutrition (Briguglio). The lack of data is not surprising given that SARS-CoV-2 is just beginning to increase in low-and middle-income countries where malnutrition in children and adults is often more prevalent. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) conducted a survey among 102 affiliated centers in Europe on COVID-19 cases in children with inflammatory bowel disease (IBD) (Turner). Within Europe, seven children with IBD and COVID-19 have been reported. All had mild infection without the need for hospitalization despite treatment with immunosuppressive medication, steroid or biologics nor was there evidence of IBD disease worsening.

Obesity has been identified as a co-morbidity in both adults and children requiring hospitalization with SARS-CoV-2. In a report on 50 hospitalized children with COVID-19 in New York City, 22 per cent of all children and 67 per cent of children with severe disease were obese (Zachariah). Obesity is associated with chronic low-grade inflammation and a disrupted immune response, and has been shown to impair the adaptive immune response to infection through alterations in T-cell function secondary to perturbations in T-cell metabolism stemming from nutrient, hormone and adipokine dysregulation in obese individuals (Korakas, Green).

**Cancer and SARS-CoV-2**

There have been few reports of SARS-CoV-2 and cancer in children. A case of severe COVID-19, with concomitant influenza A, in a child undergoing myelosuppressive therapy for T-cell acute lymphocytic leukemia in China was reported (Sun). A survey on COVID-19 incidence was sent to pediatric hematology/oncology departments in Europe, with responses from 32 centers in 25 countries (Hrusk). Of >200 children tested for SARS-CoV-2, only nine cases of infection were identified; none required intensive care and they had mild, self-limited infection.
In Italy, 14 pediatric hematology-oncology centers adopted a policy to screen all childhood cancer patients for SARS-CoV-2 before starting chemotherapy or entering the hospital for supportive measures; 10 of 247 children tested positive, all in northern Italy where the epidemic was more prevalent (Cesaro). Among these children, eight were completely asymptomatic while two presented with mild fever; chemotherapy was paused until rtPCR tests turned negative and all children did well. Similarly, in Memorial Sloan Kettering Cancer Center in New York City, 20 childhood cancer patients with SARS-CoV-2 infection were identified of 178 tested. Only 5 per cent required hospitalization for symptoms of COVID-19 (Boulad). Results were similar in a prospective report on 800 adults age 18–80 years with a diagnosis of cancer and symptomatic COVID-19 in the United Kingdom Coronavirus Cancer Monitoring Project: 52 per cent had mild disease, 12 per cent did not require hospital admission, and only 7 per cent required intensive care (Lee). Mortality in adults was 28 per cent and was significantly associated with advancing patient age, being male and presence of other co-morbidities such as hypertension and cardiovascular disease. In an adjusted analysis, cancer patients on cytotoxic chemotherapy or other anticancer treatments were not at increased risk of mortality compared to those not on active treatment.

**HIV and SARS-CoV-2**

Table 2 shows data on 22 published reports of HIV and SARS-CoV-2 infection/COVID-19 disease in 182 persons living with HIV, all adults primarily from high-income settings. Of the 182 persons living with HIV, 98 per cent were receiving antiretroviral therapy (ART) with a variety of regimens (non-nucleoside reverse transcriptase, 9 per cent; protease inhibitors, 18 per cent; integrase inhibitors, 73 per cent). Only 10 had CD4 cell (white cells that fight infection) count <200 cells/mm³ with the majority having CD4 count >350 cells/mm³. Of those with viral load data, 94 per cent were suppressed, and 63 per cent had co-morbidities. Most had mild-moderate COVID-19 disease; 8 (4 per cent) required mechanical ventilation and there were 12 deaths (6.6 per cent). 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.

However, a preliminary analysis of public sector data in adults age >20 years by the Provincial Health Data Centre in the Western Cape, South Africa found that adults with HIV infection had a modestly higher risk of mortality from COVID-19 disease than HIV-uninfected individuals (hazard ratio 2.75, 95 per cent CI 2.09-3.61), with no significant difference by HIV viral suppression status (Nordling, Bhekisisa). 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.

Importantly, there are, however, no data on children with HIV infection and SARS-CoV-2/COVID-19 to date.
### Table 2. SARS-CoV-2 and HIV Published Reports

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Country</th>
<th>#</th>
<th>Age yr</th>
<th>ART</th>
<th>CD4/VL</th>
<th>Comorbidity</th>
<th>Sx</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baluku, J Med Virol</td>
<td>Uganda</td>
<td>1</td>
<td>34</td>
<td>Yes; NNRTI</td>
<td>965 / &lt;1000</td>
<td>No</td>
<td>No (later diarrhea)</td>
<td>mild; hospitalized 24 days</td>
</tr>
<tr>
<td>Patel, J Med Virol</td>
<td>US (FL)</td>
<td>1</td>
<td>58</td>
<td>Yes; PI</td>
<td>497 / NP</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild, hospitalized 5 days</td>
</tr>
<tr>
<td>Zhu, J Med Virol</td>
<td>China</td>
<td>1</td>
<td>61</td>
<td>New dx; start PI</td>
<td>56 / NP</td>
<td>Yes</td>
<td>Yes</td>
<td>Hospitalized 13 days</td>
</tr>
<tr>
<td>Benkovic, J Med Virol</td>
<td>US (NY)</td>
<td>4</td>
<td>56-65</td>
<td>Yes; InSTI 3, NNRTI</td>
<td>794-1412 / &lt;50 3/4</td>
<td>4/4</td>
<td>Yes</td>
<td>3 mild, 1 hospitalized (also flu A) 14 days</td>
</tr>
<tr>
<td>Gervasoni, CID</td>
<td>Italy</td>
<td>47</td>
<td>Mean 51</td>
<td>Yes; InSTI 42, PI 5</td>
<td>Mean 636, 3&lt;200 / &lt;20 44/47</td>
<td>30/47</td>
<td>46/47</td>
<td>34 mild;13 hospitalized, 2 deaths (both comorbidities)</td>
</tr>
<tr>
<td>Haddad, ID Cases</td>
<td>US (PA)</td>
<td>1</td>
<td>41</td>
<td>Yes; InSTI</td>
<td>605 / &lt;50</td>
<td>No</td>
<td>Yes</td>
<td>Encephalopathy/seizure, critical; recovered</td>
</tr>
<tr>
<td>Schoergenhofer, Ann Int Med</td>
<td>Austria</td>
<td>8</td>
<td>22-36</td>
<td>Yes; PI 4</td>
<td>NP</td>
<td>5/8</td>
<td>NP</td>
<td>8 Mild, hospitalized</td>
</tr>
<tr>
<td>Wu, J Med Virol</td>
<td>China</td>
<td>2</td>
<td>47, 60</td>
<td>Yes 1; NNRTI; No 1</td>
<td>NP</td>
<td>1/2 (1 new dx)</td>
<td>Yes</td>
<td>Severe pneumonia, recovered</td>
</tr>
<tr>
<td>Wang, Int J Infect Dis</td>
<td>China</td>
<td>1</td>
<td>37</td>
<td>Yes; ns</td>
<td>34 / NP</td>
<td>NP</td>
<td>Yes</td>
<td>Moderate, hospitalized</td>
</tr>
<tr>
<td>Harter, Infection</td>
<td>Germany</td>
<td>33</td>
<td>31-70</td>
<td>Yes; PI 4, InSTI 31</td>
<td>69-1750 / &lt;50 30/32</td>
<td>20/33</td>
<td>Yes</td>
<td>19 mild;14 hospitalized; 6 ICU; 3 died (old; CD4 69; multiple comorbidities)</td>
</tr>
<tr>
<td>Aydin, J Med Virol</td>
<td>Turkey</td>
<td>4</td>
<td>34-44</td>
<td>Yes 3; InSTI 2; No 1</td>
<td>396-1385/ &lt;50 3/4</td>
<td>1/4</td>
<td>Yes</td>
<td>1 death (multiple comorbidities)</td>
</tr>
<tr>
<td>Su, AIDS</td>
<td>China</td>
<td>1</td>
<td>32</td>
<td>Yes; NNRTI</td>
<td>430 / NP</td>
<td>No</td>
<td>Yes</td>
<td>Moderate; hospitalized</td>
</tr>
<tr>
<td>Blanco, Lancet</td>
<td>Spain</td>
<td>5</td>
<td>29-49</td>
<td>Yes 4; PI 2, InSTI 2; No 1</td>
<td>13 (new dx)-1140 / &lt;50 4/5</td>
<td>2/5; 1 new dx with PCP</td>
<td>Yes</td>
<td>3 mild; 2/5 ICU; 1 mechanical ventilation/ECMO</td>
</tr>
<tr>
<td>Chen, J Med Virol</td>
<td>China</td>
<td>1</td>
<td>24</td>
<td>Yes; NNRTI</td>
<td>NP</td>
<td>NP</td>
<td>Yes</td>
<td>Moderate, hospitalized, recovered</td>
</tr>
<tr>
<td>Zhao, CID</td>
<td>China</td>
<td>1</td>
<td>38</td>
<td>Yes; NNRTI</td>
<td>584/undetectable</td>
<td>NP</td>
<td>Yes</td>
<td>Hospitalized 4 days</td>
</tr>
<tr>
<td>Riva, Pharmacol Res</td>
<td>Italy</td>
<td>3</td>
<td>57-63</td>
<td>Yes; PI 2</td>
<td>441-743/ &lt;20 3/3</td>
<td>2/3</td>
<td>Yes</td>
<td>2 moderate, 1 severe - mechanical ventilation</td>
</tr>
<tr>
<td>Iordanou, J Med Virol</td>
<td>Cyprus</td>
<td>1</td>
<td>58</td>
<td>Yes; InSTI</td>
<td>1640 / &lt;50</td>
<td>No</td>
<td>Yes</td>
<td>Severe, ICU - mechanical ventilation; recovered</td>
</tr>
<tr>
<td>Kumur, Trans Infect Dis</td>
<td>US (IL)</td>
<td>1</td>
<td>50</td>
<td>Yes; InSTI</td>
<td>395 / &lt;20</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild, not hospitalized</td>
</tr>
<tr>
<td>Louisa, JAIDS</td>
<td>Singapore</td>
<td>1</td>
<td>37</td>
<td>Yes; NNRTI</td>
<td>201 / &lt;20</td>
<td>No</td>
<td>Yes</td>
<td>Mild, hospitalzed no treatment</td>
</tr>
<tr>
<td>Suwanwongse, J Med Virol</td>
<td>US (NY)</td>
<td>9</td>
<td>31-76</td>
<td>Yes; InSTI 6, PI 1 NNRTI 1; No 1</td>
<td>179-1827 / &lt;50 9/9</td>
<td>9/9</td>
<td>Yes</td>
<td>7/9 died: septic shock 3/ARDS 2/hypoxemia 2 (includes 1 on no ART/CD4 179)</td>
</tr>
<tr>
<td>Ridgway, AIDS Pt Care STDs</td>
<td>US (IL)</td>
<td>5</td>
<td>38-53</td>
<td>Yes; PI 1, InSTI 4</td>
<td>265-500 /&lt;50 5/5</td>
<td>4/5</td>
<td>Yes</td>
<td>Hospitalized 2-7 d, all recovered</td>
</tr>
<tr>
<td>Vizcarra, Lancet</td>
<td>Spain</td>
<td>51</td>
<td>31-75</td>
<td>Yes; PI 11, NNRTI 8, InSTI 41</td>
<td>CD4 &lt;200, 6/51/ &lt;50 50/51</td>
<td>32/51 (63%)</td>
<td>38 (75%) mild; 28 (55%) hospitalized; 6 (12%) ICU; 5 (10%) mechanical ventilation; hospitalization 6-17 d</td>
<td></td>
</tr>
</tbody>
</table>
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 termed multi-system inflammatory syndrome (MIS-C) temporally associated with SARS-CoV-2 infection in children, with 230 suspected cases reported in the United Kingdom and European Union by 15 May. 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 had 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. By early May cases were also reported in New York, with 102 cases and 3 deaths by May 12. Following a May 14 CDC health advisory with a case definition and request for reporting of cases. By May 26, MIS-C had been reported in 23 states. Multiple case series from the United States, Italy, United Kingdom and France including 371 children, as well as numerous case reports, have now been published regarding this syndrome and potential association with SARS-CoV-2 (Chiotos, Verdoni, Riphagen, Belhadjer, Toubiana, Miller, Belot, Grimaud, Pouletty, Ramcharan, Perez-Toledo, Wolfer, Cheung).

While many cases resemble Kawasaki Disease (KD), MIS-C has distinct features (Shulman). Children with MIS-C are older: in KD, 50% of children affected are <24 months and 80% <5 years, compared to mean age 8-10 years, including adolescents, with MIS-C. 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.

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.

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.

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

While children with MIS-C can be critically ill, case reports suggest in additional to supportive care, a good response can be seen with anti-inflammatory treatment including steroids, intravenous immunoglobulin and IL-1 and IL6 blockers such as anakinra and sarilumab or tocilizumab, respectively (Viner, Shulman).
It is hypothesized that there may be a widening spectrum of SARS-CoV-2-related disease in children (*Figure 9*). The majority of children will have asymptomatic or mild infection; a small proportion may develop a post-infection inflammatory condition with persistent fever and signs of inflammation; a small proportion of these developing post-infection Kawasaki Disease-like syndrome; and a smaller minority developing the paediatric inflammatory multisystem syndrome.

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

Although the current incidence of multi-system inflammatory syndrome (MIS-C) is still low, the potential association of MIS-C with SARS-CoV-2 infection has stimulated intensive research interest in Europe and the United States with several research studies underway (e.g., the Overcoming COVID-19 study in the US; DIAMONDS study in Europe; multi-country Best Available Therapy Study[BATS]). International discussions, led by the World Health Organization, are underway to facilitate standardized approaches to define and investigate the condition and its management and a global clinical data platform has been set up to facilitate reporting (WHO website references).

While the focus of this review is on the direct effects of SARS-CoV-2/COVID-19 on children and adolescents, a number of modeling studies have been conducted to look at the potential indirect impact of the pandemic on children, adolescents’ and maternal health. Three such models are briefly reviewed below mainly as examples only, and Annex 2 contains three tables briefly summarizing several other models evaluating indirect effects of COVID-19 on A) maternal, neonatal and child health; B) sexual reproductive health; and C) vaccine-preventable diseases.

The potential impact of country responses to the COVID-19 pandemic on maternal and child health services has been explored through modeling exercises. While models enable to predict and project health and social impacts of COVID-19, they suffer from the main limitation of being scenario-based only and depend on input data of weak or poor quality. Caution is needed in interpreting the results.

Roberton and colleagues at the Johns Hopkins Bloomberg School of Public Health modeled 3 scenarios (small, moderate and large service interruption) using the Lives Saved Tool, in which the coverage of essential maternal and child health interventions was reduced by 9.8 to 51.9% and the prevalence of wasting was increased by 10-50% in 118 low and middle-income countries (Roberton). Depending on the scenario, there was a possible increase of 9.8 to 44.7% in under age 5-child deaths per month and 8.3% to 38.6% increase in maternal deaths per month across 118 countries.

Stover and colleagues used a simulation model of HIV to analyze the effects of a 3- or 6-month disruption in health services as a result of COVID-19, including the impact on mother-to-child HIV transmission in Zimbabwe, Uganda, Mozambique, and Malawi (Stover). Current coverage of services to prevent mother-to-child HIV transmission (PMTCT) was high in most countries, with few new child infections. Any disruption in PMTCT services could lead to large increases in new child infections, from ~10% if disruption was only for new HIV-positive ANC patients needing to start treatment; to ~50% with a 3-month disruption for PMTCT services for all women; and 100% or more with a 6-month disruption to all PMTCT services.

Finally, the Imperial College COVID-19 Response Team modeled 5 intervention scenarios for COVID-19 (no action, mitigation, suppression-lift, unmanaged, and well-managed suppression) and potential effects of such interventions on service disruption, and the impact on excess deaths due to HIV, TB and malaria from 2020-2024 (Hogan). For HIV, up to 10% increase in HIV-related deaths were anticipated, primarily due to interruptions in antiretroviral treatment during periods of high/extreme health system demand. For TB, up to 20% increase in TB deaths were anticipated, primarily due to reductions in timely diagnosis and treatment of new TB cases from long periods of COVID-19 unmanaged/well-managed suppression interventions that limit activities. For malaria, up to 36% increase in malaria deaths were anticipated, primarily due to reduced prevention activities (e.g., distribution of insecticide treated nets) during all phases of the COVID-19 response.

All the models illustrate the critical importance of maintenance of maternal and child essential health services and HIV, TB and malaria-specific services as much as possible as a part of the
COVID-19 response to reduce the broader potential public health impact of COVID-19 mitigation or suppression interventions.

7. Summary

There is much remaining to be learned about SARS-CoV-2 in children, adolescents and young people. 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 especially in low- and middle-income countries. 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 will need evaluation. As the spectrum of disease in children becomes better elucidated, it will be important to understand geographic and racial/ethnic differences, particularly as the pandemic moves to low- and middle-income countries where co-morbidities and other vulnerabilities are more frequent among children.

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

• In contrast to the dominant 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. This is evidenced by the higher share of cases among children and young people in low- and middle-income countries which have youthful population structures (e.g. 23% in Paraguay compared to 1% in Spain), suggesting that demographic structures might contribute to the age distribution of reported cases. This fact alone should propel us to far greater vigilance in generating and monitoring age-disaggregated data on the pandemic in all countries.

• There is no single place to obtain country comparable age-related data. Global data are not readily available disaggregated by age, and available country data likewise lack age breakdown 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. If the transmission risk from children to other children and adults is small, the impact of school closing on mitigating SARS-CoV-2 infection and COVID-19 disease in the community will be minimal and therefore makes guidance for school re-opening less complex.

Predictors of disease progression and severe morbidity and mortality in children need to be determined, particularly as the pandemic moves to low- and middle-income countries, where poor nutritional and health conditions and other vulnerabilities are more frequent among children than in higher-income settings. 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).

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 SARS-CoV-2 have been reported among children, particularly among those with co-morbidities. Whether this is due to decreased biologic susceptibility to the virus (and whether this might vary by age), or lower exposure to the virus than adults given mitigation/suppression efforts is unclear and needs to be examined. More data are needed on the paediatric population before conclusions can be drawn about the direct effects of SARS-CoV-2 on children and adolescents.

Optimal treatment of the most severe manifestations of SARS-CoV-2 in children must be evaluated, with inclusion of children in clinical therapy and vaccine trials. Clinical trials of treatment for COVID-19 have excluded children to date, resulting in a recurring lost opportunity to generate data in a timely fashion to guide treatment of a new disease in children (and similarly in pregnant women) (Hwang, Whitehead). It will be particularly important to ensure inclusion of children and pregnant women in planned future SARS-CoV-2 clinical and vaccine trials.

To evaluate the potential for mother-to-child SARS-CoV-2 transmission, appropriate specimens (including amniotic fluid, placenta, neonatal blood and respiratory secretions) must be obtained with suitable timing, including birth specimens.

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.
8. 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.
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## Annex 1: List of Countries in the Analysis and COVID-19 Data Source

<table>
<thead>
<tr>
<th>Country</th>
<th>Code</th>
<th>Region</th>
<th>Income Level Classification</th>
<th>COVID-19 Data Source and Dashboard</th>
<th>Data Last Update</th>
</tr>
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<tbody>
<tr>
<td>Argentina</td>
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<tr>
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<td>BRA</td>
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<tr>
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<td>CAN</td>
<td>North America</td>
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<td>Europe and Central Asia</td>
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<td>Philippines</td>
<td>PHL</td>
<td>East Asia and Pacific</td>
<td>Low and middle income</td>
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**Regions:**
- East Asia and Pacific
- South Asia
- Sub-Saharan Africa
- Europe and Central Asia
- Caribbean
- Latin America and Caribbean
- Africa
- Europe and Central Asia
- South Asia
- Europe and Central Asia
- Low and middle income
- High income

**Income Type:**
- Low and middle income
- High income
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<th>Country</th>
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Annex 2: Summary of Modeling Indirect Impacts of COVID-19

A. Modelling impact of COVID-19 on Maternal Neonatal Child Adolescent Health (MNCAH)

<table>
<thead>
<tr>
<th>Area</th>
<th>Questions</th>
<th>Main findings</th>
<th>Models</th>
<th>Countries</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health</td>
<td>• To assess COVID-19 secondary impacts on children’s lives</td>
<td>30 million children lives at stake 26 million at greater risk for infection if 30% reduction in DPT3. 5 million additional children suffering from malnutrition based on increase of 40% from current numbers. Additional 100,00 children will die of malaria an increase of 50% from current levels</td>
<td>Applied evidence from Ebola outbreak for the % reductions or increases, methods unclear for mortality estimates, time period unclear</td>
<td>24 countries SSA experiencing humanitarian crisis</td>
<td>World Vision</td>
</tr>
<tr>
<td>MNCH</td>
<td>• Excess maternal and U5 mortality from weak systems (lower provision) &amp; lower utilization of 72 RMNCH services  • 3 scenarios x 3 disruption durations</td>
<td>Excess mortality (selection of results):  • Reductions in coverage of around 15% for 6 months would result in 253,500 additional child deaths and 12,190 additional maternal deaths,  • Reductions of around 45% for 6 months would result in 1,157,000 additional child deaths and 56,700 additional maternal deaths</td>
<td>Lived Saved Tool, 6 month and 12-month disruptions, three levels of disruption</td>
<td>118 LMIC</td>
<td>John Hopkins University</td>
</tr>
<tr>
<td>MN</td>
<td>• Disrupted maternal healthcare during COVID-19 how will it impact maternal, stillbirth and newborn deaths</td>
<td>31,980 additional maternal deaths, 395,440 additional newborn deaths, and 338,760 additional stillbirths</td>
<td>Applied evidence from Ebola outbreak for the % reductions or increases and used LiST 12 months</td>
<td>HP+</td>
<td>India, Indonesia, Nigeria, and Pakistan</td>
</tr>
<tr>
<td>HIV, TB, Malaria and malnutrition in children under 5 years</td>
<td>• To assess cause-specific impacts (HIV, TB, Malaria, and malnutrition) applying reductions based on 2014 to cause specific mortality rates extrapolated to 2020 deaths to estimate excess mortality by country  • 8.6% for malnutrition in children</td>
<td></td>
<td>Applied evidence from 14 African countries Ebola outbreak for the % reductions or increases</td>
<td>33 countries Africa Projections to 2022</td>
<td>Cooper/Smith</td>
</tr>
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### B. Modelling impact of COVID-19 on Sexual Reproductive Health

<table>
<thead>
<tr>
<th>Area</th>
<th>Questions</th>
<th>Main findings</th>
<th>Model Assumptions</th>
<th>Countries</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual and Reproductive Health</td>
<td>• To estimates of the Potential Impact of the COVID-19 Pandemic on Sexual and Reproductive Health in Low- and Middle-Income Countries</td>
<td>10% decline in use of short- and long-acting reversible contraceptives would result in 48,558,000 additional women with an unmet need for modern contraceptives and thus 15,401,000 additional unintended pregnancies. 10% decline in service coverage of essential pregnancy related and newborn care would result in 1,745,000 additional women experiencing major obstetric complications without care and thus 28,000 additional maternal deaths. 2,593,000 additional newborns experiencing major complications without care and thus 168,000 additional newborn deaths. 10% shift in abortions from safe to unsafe would result in 3,325,000 additional unsafe abortions and thus 1,000 additional maternal deaths.</td>
<td>Using data from the 2019 Adding It Up study of sexual and reproductive health care provision, by estimating the effect of health services on cause-specific maternal and newborn deaths, using the LiST tool.</td>
<td>132 mostly LMICs in Africa, Asia, Eastern and Southern Europe, and Latin America and the Caribbean, in one year</td>
<td>Guttmacher Institute, New York. UK Aid BMGF, Dutch Ministry of Foreign Affairs and CIF/Caribbean</td>
</tr>
<tr>
<td></td>
<td>• To estimate impact on family planning in low- and middle-income countries</td>
<td>Some 47 million women in 114 LMIC unable to use modern contraceptives if the average lockdown continues for 6 months.  For every 3 months the lockdown continues, up to 2 million additional women may be unable to use modern contraceptives. Additional 7 million unintended pregnancies are expected to occur lockdown for 6 months.</td>
<td>Sensitivity analysis on the previously published estimates: 6-month disruption. Based on Ebola outbreak disruptions applied to estimates of current modern contraceptive users. (Estimates of additional unintended pregnancies based on an average rate of 0.3 unintended pregnancies averted per user.)</td>
<td>114 LMIC 6-month lockdown</td>
<td>Avenir Health, Johns Hopkins University (USA) and Victoria University (Australia), UNFPA</td>
</tr>
<tr>
<td>Family Planning</td>
<td>• To estimate impact on family planning in low- and middle-income countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Genital Mutilation</td>
<td>• To estimate impact on FGM for subset of countries with high FGM rates</td>
<td>COVID-19 could have far-reaching impacts on the effort to end female genital mutilation. Due to COVID-19 disruptions, we anticipate a 1/3 reduction in the progress towards ending FGM by 2030. Due to pandemic-related disruptions in prevention programmes, 2 million FGM cases could occur over the next decade that would otherwise have been averted.</td>
<td>Sensitivity analysis on the previously published estimates: Assume postpone the deployment of programmes to eliminate FGM.</td>
<td>Hig prevalence FGM countries (~30) 6-month lockdown</td>
<td>Avenir Health and UNFPA</td>
</tr>
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</table>
C. Modelling impact of COVID-19 on Vaccine Preventable Diseases

<table>
<thead>
<tr>
<th>Area</th>
<th>Questions</th>
<th>Main findings</th>
<th>Model Assumptions</th>
<th>Countries</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunization</td>
<td>• To weigh the health benefits of continued routine infant immunisation delivery in Africa</td>
<td>For one excess Covid-19 death attributable to an infection acquired during a child vaccination visit, there would be 128 (34 - 1,247) future deaths in children prevented from the time of vaccination to 5 years of age by sustaining the routine childhood vaccination programmes. If only the risk to the vaccinated child is considered, the benefit-risk ratio increases to 52,000 (3,000 - 46,487,000). Measles and pertussis containing vaccines each contribute about one-third of the vaccine preventable mortality in these estimates.</td>
<td>6-month disruption</td>
<td>SSA</td>
<td>LSHTM Centre for Mathematical Modelling of Infectious Disease Covid-19 Working Group:</td>
</tr>
<tr>
<td>VPDs &amp; polio</td>
<td>• VPD mortality from paused SIAs, low RI</td>
<td>RI benefits outweigh the risks of Covid spread during RI visits &gt;100:1 (link). Every 6 months, RI prevents 800k future US deaths in Africa, largely measles and pertussis (limited herd immunity due to high thresholds). High risk of measles outbreaks posed by cancelling some SIAs (eg – Ethiopia).</td>
<td>6-month disruptions of SIAS</td>
<td>All LMICs; countries with SIAs paused</td>
<td>VIMC, IDM, ICL, LSHTM, KidRisk</td>
</tr>
<tr>
<td>Immunization</td>
<td>• SIA disruptions and Measles</td>
<td>Range of measles cases 200,000 to 2 million, 3,000 to 58,000 deaths</td>
<td>Details pending</td>
<td>Ethiopia</td>
<td>LSTHM, IDM, PSU</td>
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</tbody>
</table>