

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 | July 2020

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

July 2020

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

Abstract: The initial impression that paediatric SARS-CoV-2 infection is uncommon and generally mild has been replaced by a more nuanced understanding of infectious manifestations in children and adolescents across low-, middle-, and high-income countries and by demographic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, co-morbidities, transmission, income-level, demographics, testing, data, disaggregated.

Acknowledgements

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

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

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

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.
- Alarming, 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.

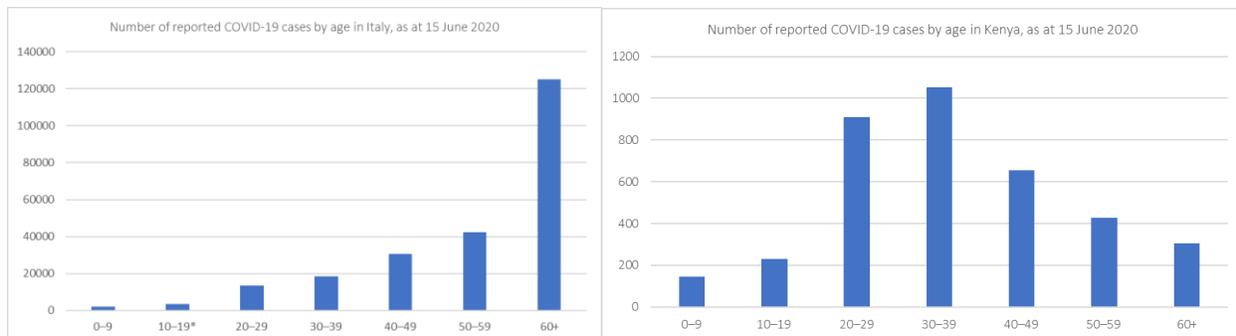
...although there appears to be wide variation among countries

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.

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



Note: *Age range is 10-18 years

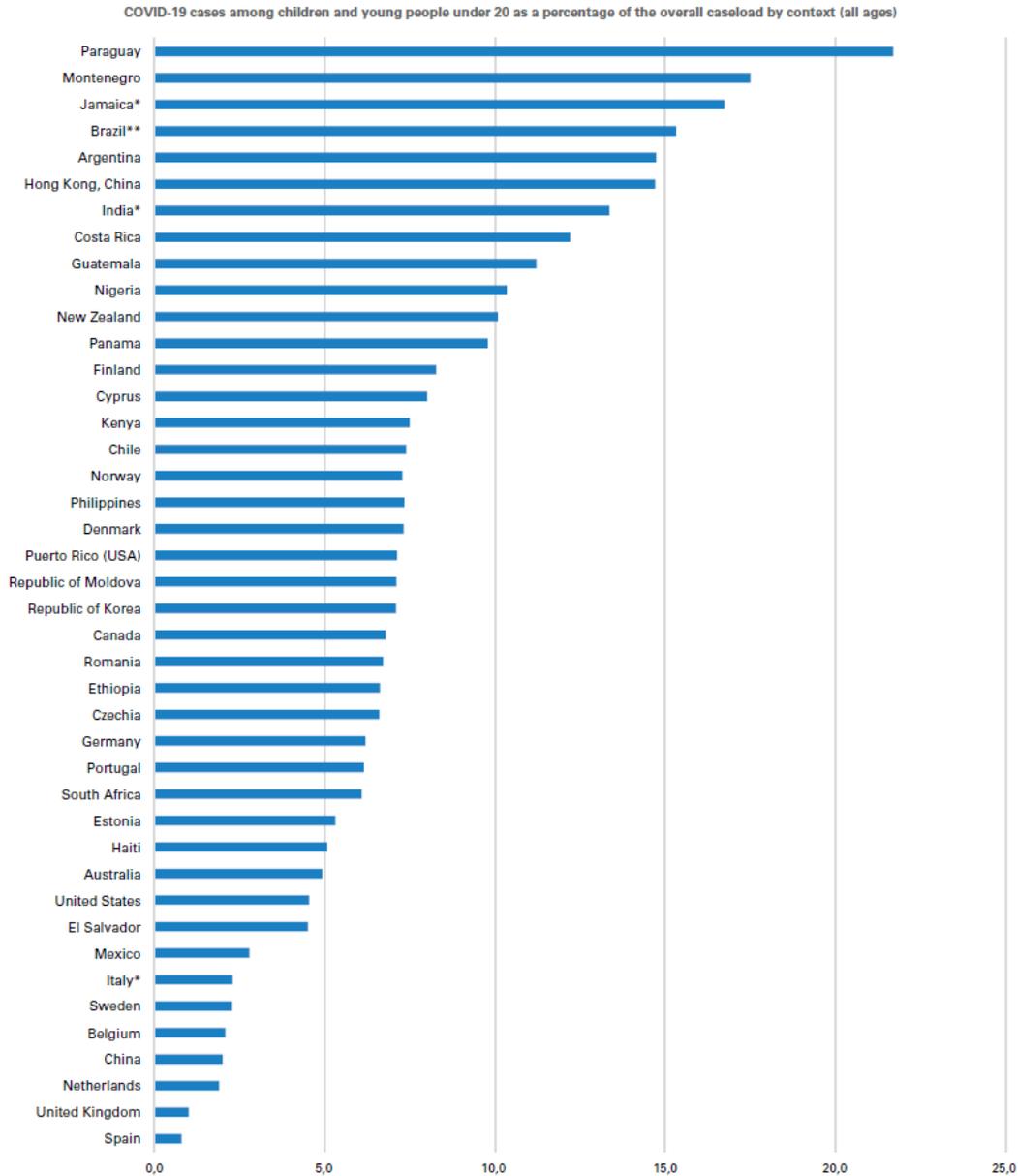
Source: Statista, 'Distribution of Coronavirus Cases in Italy as of June 22, 2020, by Age Group. Available at: <www.statista.com/statistics/1103023/coronavirus-cases-distribution-by-age-group-italy>, accessed 15 June 2020

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

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

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

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



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

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

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

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

It is difficult to determine proportional age breakdown of COVID-19 cases within the 0 to

19-year age range for children and adolescents. Data are limited, and the existing databases and reports often use different age categories (e.g., 1-5 years and 6-10 years versus 1-4 years and 5-9 years). National granular age disaggregated data on laboratory-confirmed

COVID-19 pediatric cases have been published from the United States and China (CDC COVID19, Dong Y) (Table 1). COVID-19 disease has been diagnosed across the full breadth of age categories - from the neonatal period through adolescence - with over 50 per cent

occurring in the adolescent age group in these reports. National age-disaggregated data are, therefore, crucial to enable countries to determine the age-appropriate health resources needed to care for infected children.

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

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

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

² Dong Y et al. Pediatrics. 2020 Mar 16

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

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

The definition of what constitutes a “case” has varied between studies and also in national surveillance and monitoring systems: individuals with symptomatic COVID-19 disease; individuals with a positive SARS-CoV-2 real-time polymerase chain reaction (rtPCR) test in respiratory or other samples, indicating current infection; or individuals positive for SARS-CoV-2 IgM and/or IgG antibody, indicating past infection. Additionally, there are multiple SARS-CoV-2 rtPCR and antibody tests, with varying sensitivity (Whitman, Lieberman), and 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 Gangel, 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 coinfecting with other respiratory viruses (picornavirus and influenza A), attended three schools while mildly symptomatic but did not transmit the SARS-CoV-2, although there was a high proportion of picornavirus and influenza infection among school contacts (Danis K). In 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 re-opening 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

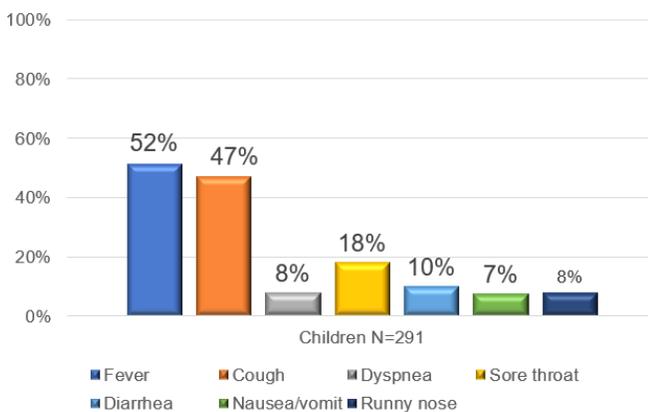
observed in 16 per cent of COVID-19 patients (Guan).

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.

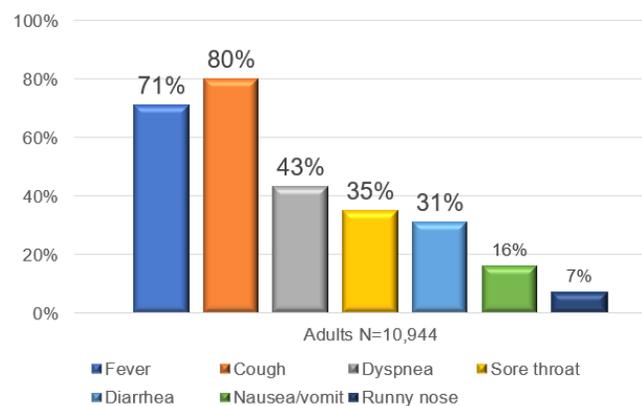
Figure 3: Symptoms of SARS-CoV-2 in children and adolescents compared with adults

Disease Symptoms in 1,780 Children and Adolescents 0-18 Years with SARS-CoV-2 Infection



Systematic Review - Liguoro I et al. Eur J Pediatr. 2020 May 18

Disease Symptoms in 10,944 Adults 18-64 Years in US with SARS-CoV-2 Infection



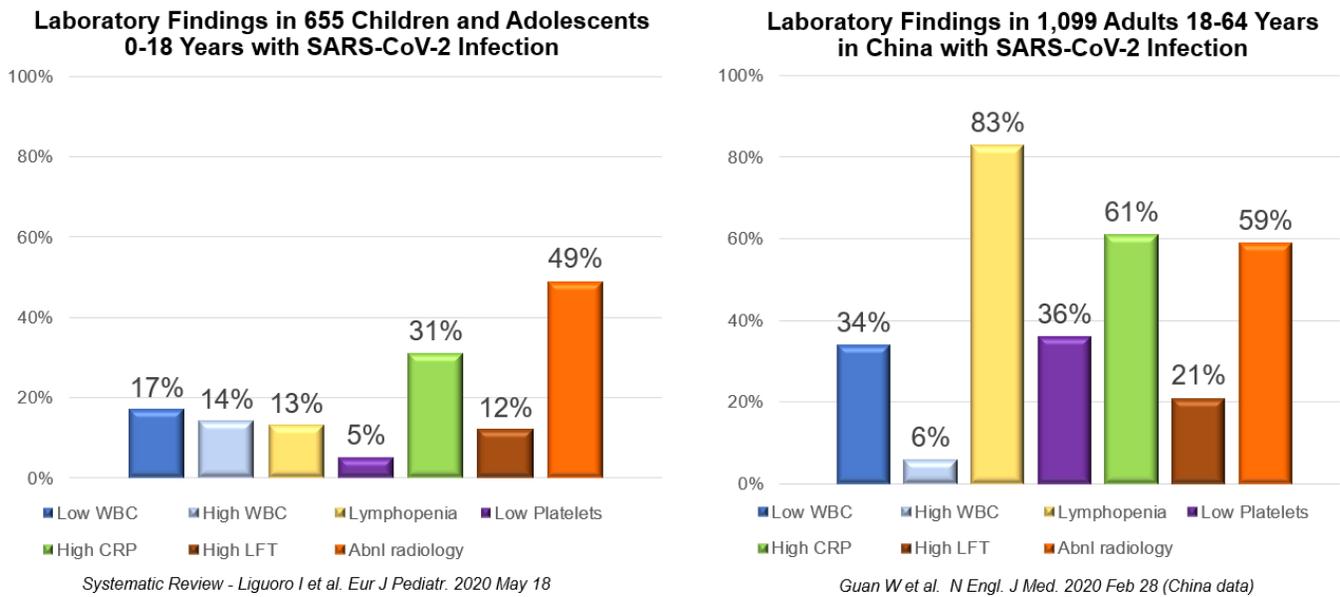
CDC COVID-19 Response Team. MMWR 2020 Apr 6;69 (US data)

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

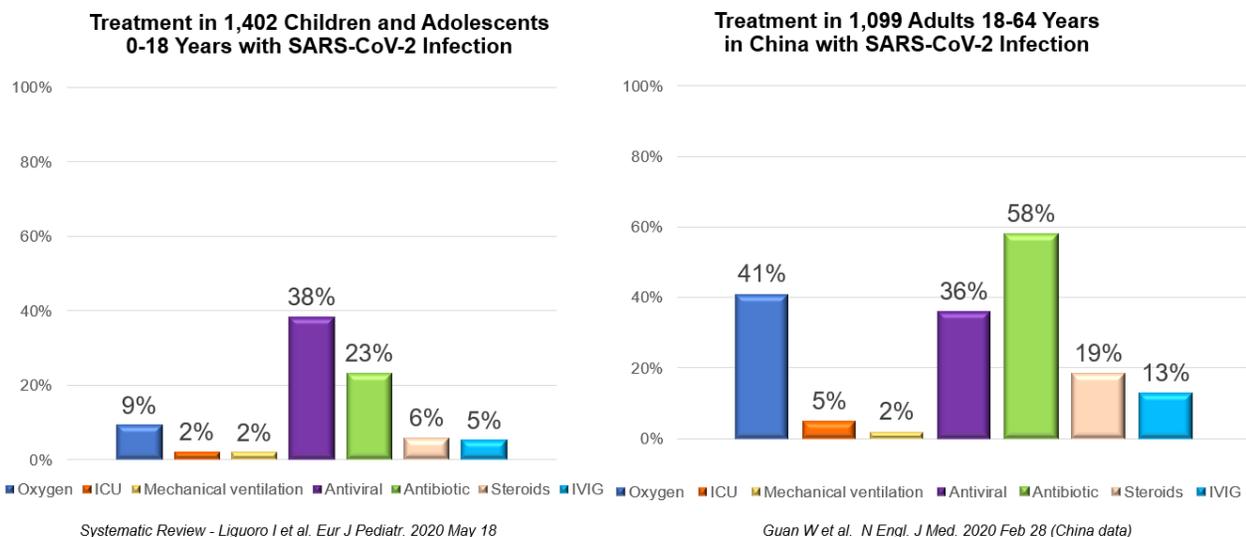


Treatment

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



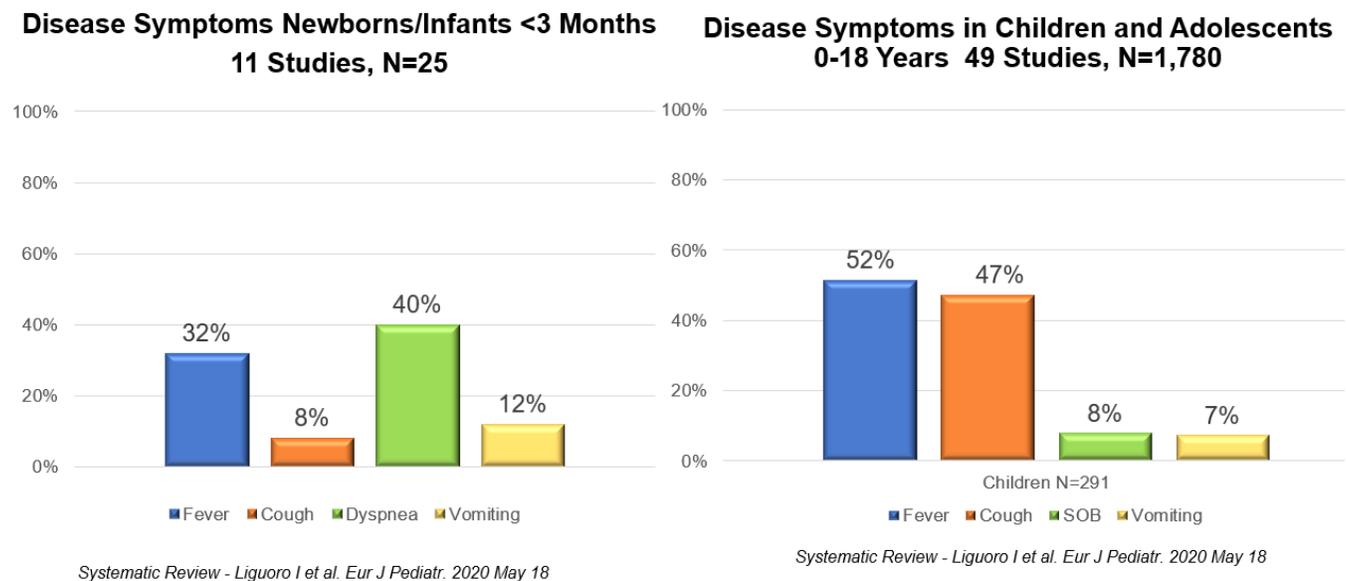
Newborns/infants age <3 months compared with all children and adolescents

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.

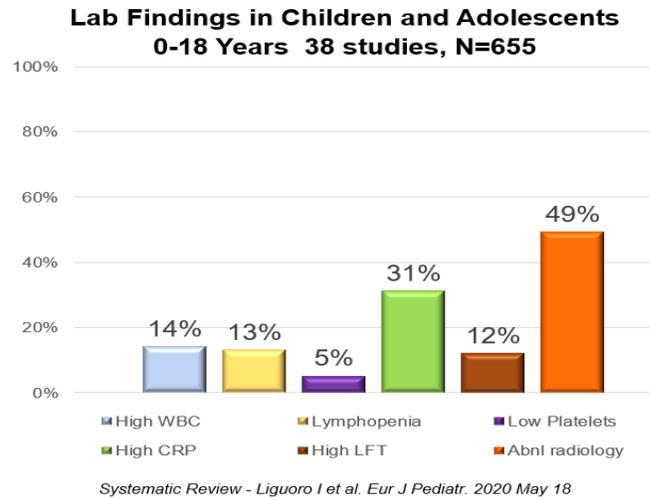
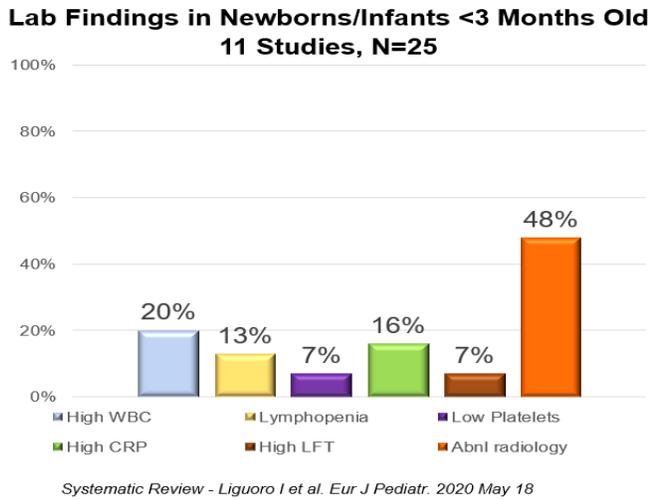
Figure 6: Symptoms of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents



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.

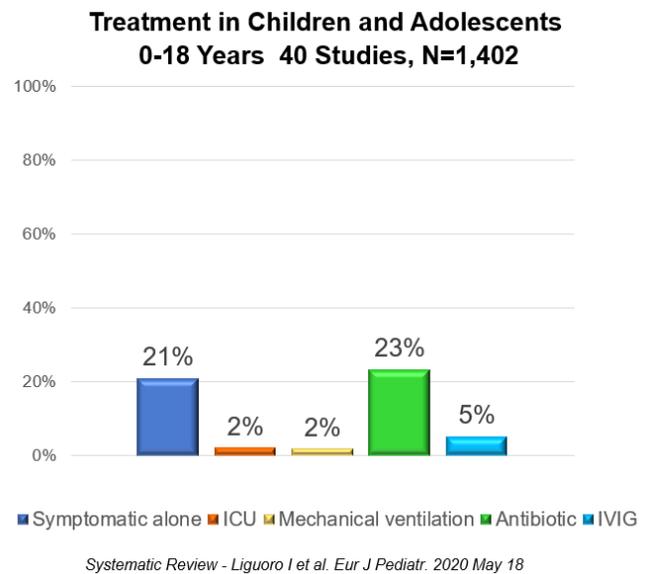
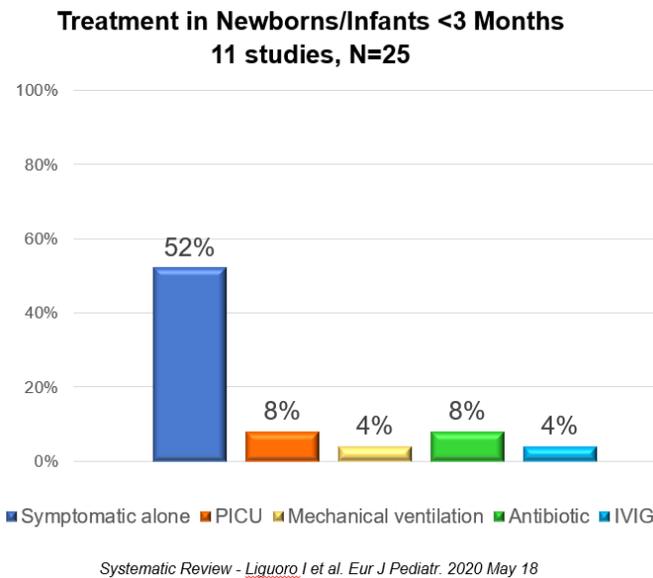
Figure 7: Laboratory and radiologic findings of SARS-CoV-2 in newborns/infants <3 months compared with all children and adolescents



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



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 (Shekerdeman). 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

Author/Journal	Country	#	Age yr	ART	CD4/VL	Comorbidity	Sx	Outcome
Baluku, J Med Virol	Uganda	1	34	Yes; NNRTI	965 / <1000	No	No (later diarrhea)	mild; hospitalized 24 days
Patel, J Med Virol	US (FL)	1	58	Yes; PI	497 / NP	Yes	Yes	Mild, hospitalized 5 days
Zhu, J Med Virol	China	1	61	New dx; start PI	56 / NP	Yes	Yes	Hospitalized 13 days
Benkovic, J Med Virol	US (NY)	4	56-65	Yes; InSTI 3, NNRTI 1	794-1412 / <50 3/4	4/4	Yes	3 mild, 1 hospitalized (also flu A) 14 days
Gervasoni, CID	Italy	47	Mean 51	Yes; InSTI 42, PI 5	Mean 636, 3<200 / <20 44/47	30/47	46/47	34 mild;13 hospitalized, 2 deaths (both comorbidities)
Haddad, ID Cases	US (PA)	1	41	Yes; InSTI	605 / <50	No	Yes	Encephalopathy/seizure, critical; recovered
Schoergenhofer, Ann Int Med	Austria	8	22-36	Yes; PI 4	NP	5/8	NP	8 Mild, hospitalized
Wu, J Med Virol	China	2	47, 60	Yes 1; NNRTI; No 1	NP	1/2 (1 new dx)	Yes	Severe pneumonia, recovered
Wang, Int J Infect Dis	China	1	37	Yes; ns	34 / NP	NP	Yes	Moderate, hospitalized
Harter, Infection	Germany	33	31-70	Yes; PI 4, InSTI 31	69-1750 / <50 30/32	20/33	Yes	19 mild;14 hospitalized; 6 ICU; 3 died (old; CD4 69; multiple comorbidities)
Aydin, J Med Virol	Turkey	4	34-44	Yes 3; InSTI 2; No 1	396-1385/ <50 3/4	1/4	Yes	1 death (multiple comorbidities)
Su, AIDS	China	1	32	Yes; NNRTI	430 / NP	No	Yes	Moderate; hospitalized
Blanco, Lancet	Spain	5	29-49	Yes 4; PI 2, InSTI 2; No 1	13 (new dx)-1140 / <50 4/5	2/5; 1 new dx with PCP	Yes	3 mild; 2/5 ICU; 1 mechanical ventilation/ECMO
Chen, J Med Virol	China	1	24	Yes; NNRTI	NP	NP	Yes	Moderate, hospitalized, recovered
Zhao, CID	China	1	38	Yes; NNRTI	584/undetectable	NP	Yes	Hospitalized 4 days
Riva, Pharmacol Res	Italy	3	57-63	Yes; PI 2	441-743/ <20 3/3	2/3	Yes	2 moderate, 1 severe - mechanical ventilation
Iordanou, J Med Virol	Cyprus	1	58	Yes; InSTI	1640 / <50	No	Yes	Severe, ICU - mechanical ventilation; recovered
Kumur, Trans Infect Dis	US (IL)	1	50	Yes; InSTI	395 / <20	Yes	Yes	Mild, not hospitalized
Louisa, JAIDS	Singapore	1	37	Yes; NNRTI	201 / <50	No	Yes	Mild, hospitalized no treatment
Suwanwongse, J Med Virol	US (NY)	9	31-76	Yes; InSTI 6, PI 1 NNRTI 1; No 1	179-1827 / <50 9/9	9/9	Yes	7/9 died: septic shock 3/ARDS 2/hypoxemia 2 (includes 1 on no ART/CD4 179)
Ridgway, AIDS Pt Care STDs	US (IL)	5	38-53	Yes; PI 1, InSTI 4	265-500 /<50 5/5	4/5	Yes	Hospitalized 2-7 d, all recovered
Vizcarra, Lancet	Spain	51	31-75	Yes; PI 11, NNRTI 8, InSTI 41	CD4 <200, 6/51/ <50 50/51	32/51 (63%)		38 (75%) mild; 28 (55%) hospitalized; 6 (12%) ICU; 5 (10%) mechanical ventilation; hospitalization 6-17 d

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

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

In mid-late April 2020, reports from Western Europe identified a new febrile paediatric entity 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.

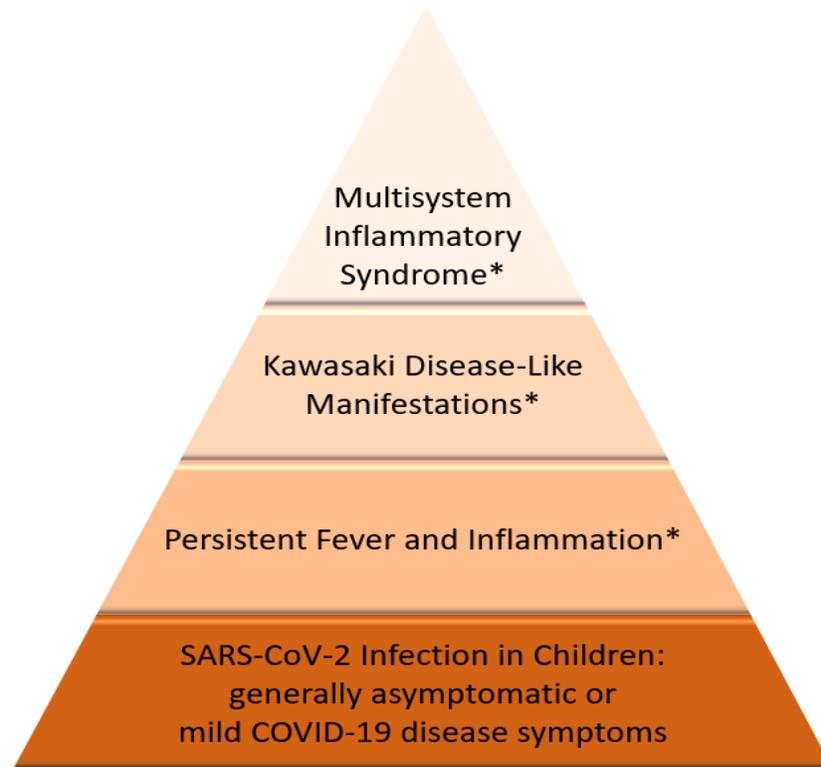
The clinical picture of MIS-C has been thought to resemble that of the later phase of severe adult COVID-19 that is felt to be secondary to an exaggerated host immune system response to infection characterized by cytokine storm, hyperinflammation, multi-organ damage including severe myocarditis and acute 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 addition 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



*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 (WHO website references).

6. Potential Indirect Impact of the COVID-19 Response on Maternal and Child Health: Brief review of selected modelling exercises

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 SAR-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.

REFERENCES

- 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
- 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
- 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.
- 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.
- 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.
- CDC COVID-19 Response Team. Coronavirus disease 2019 in children – United States, February 12-April 2, 2020. *Morbidity and Mortality Weekly Report*. 2020 Apr 6 early release;60.
- 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.
- 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)
- 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
- 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.
- 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.
- 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;pii:060.
- 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..
- Mao L-J, Xu J, Xu Z-H et al. A child with household transmitted COVID-19. *BMC Infect Dis*. 2020;20:329.
- Posfay-Barbe KM, Wagner N, Gauthey M et al. COVID-19 in children and dynamics of infection in families. *Pediatrics*. 2020 May 26:e20201576.
- 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.

- Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen China: a retrospective cohort study. *Lancet Infect Dis.* 2020 Apr 27;S1473-3099(20)30287-5.
- Zhang W, Cheng W, Luo L et al. Secondary transmission of coronavirus disease from pre-symptomatic persons, China. *Emerg Infect Dis.* 2020;26 (8).
- Wu J, Huang Y, Tu C et al. Household transmission of SARS-CoV-2, Zhuhai, China, 2020. *Clin Infect Dis.* 2020 May 12 (epub).
- Zhang J, Litvinova M, Liang Y et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science* 2020 April 29;eabb8001.
- Li W, Zhang B, Lu J et al. The characteristics of household transmission of COVID-19. *Clin Infect Dis.* 2020 Apr 17 (epub).
- Cheng H-Y, Jian S-W, Liu D-P, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Int Med.* 2020 May 1:e202020.
- Wang Z, Ma W, Zheng X et al. Household transmission of SARS-CoV-2. *J Infect.* 2020 April 14 (epub).
- Jing QL, Liu MJ, Yuan J et al. Household secondary attack rate of COVID-19 and associated determinants. *MedRxiv preprint server.* 2020. Doi: 10.1001/2020.04.11.20056010.
- Mizumoto K, Kagaya K, Zarebski A et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill.* 2020;25 (10).
- New South Wales Government. COVID-19 in schools – the experience in North South Wales. Sydney Australia, 2020. URL: http://ncirs.org.au/sites/default/files/2020-04/NCIRS%20NSW%20Schools%20COVID_Summary_FINAL%20public_26%20April%202020.pdf
- Viner RM, Mytton OT, Bonell C et al. Susceptibility to SARS-CoV-2 infection amongst children and adolescents compared with adults: a systematic review and meta-analysis. *MedRxiv.* 2020 May 20 (<https://doi.org/10.1101/2020.05.20.20108126>)
- Stringhini S, Wisniak A, Piumatti G et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva Switzerland (SEROCoV-POP): a population-based study. *Lancet* 2020 June 11 (epub).
- United Kingdom Office for National Statistics. Coronavirus (COVID-19) infection survey, June 2020. URL: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveypilot/5june2020#measuring-the-data> (accessed June 18 2020)
- Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA.* 2020 May 20 (epub).
- 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 (epub).
- Patel AB, Verma A. Nasal ACE2 levels and COVID-19 in children. *JAMA.* 2020 May 20 (epub).

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.

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.

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.

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)

Huff HV, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. *Clin Infect Dis*. 2020

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).

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.

Danis K, Epaulard O, Benet T et al. Cluster of coronavirus disease 2019 (COVID019) in the French Alps, 2020. *Clin Infect Dis*. 2020 Apr 11 (epub).

North South Wales Government. COVID-19 in schools – the experience in North South Wales. Sydney Australia, 2020. URL: http://ncirs.org.au/sites/default/files/2020-04/NCIRS%20NSW%20Schools%20COVID_Summary_FINAL%20public_26%20April%202020.pdf

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.

URL: <https://www.npr.org/sections/coronavirus-live-updates/2020/06/03/868507524/israel-orders-schools-to-close-when-covid-19-cases-are-discovered>

URL: <https://www.independent.co.uk/news/world/europe/coronavirus-france-school-cases-reopen-lockdown-a9520386.html>

URL: <https://www.cnn.com/2020/05/29/asia/south-korea-coronavirus-shuts-down-again-intl/index.html>).

Huang L, Zhang X, Zhang X et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside of Wuhan and characteristics of young patients with COVID-19: a prospective contact tracing study. *J Infect*. 2020;8:-:e1-13.

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).

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).

- Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of COVID-19? *Brit Med J*. 2020;369:m1548.
- 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).
- 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.
- Hooper MW, Napoles AM, Perez-Stable EJ. COVID-19 and racial/ethnic disparities. *JAMA* May 11
- 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.
- 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).
- 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).
- 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 (epub).
- 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.
- Kim SY, Park SJ, Cho SY et al. Viral RNA in blood as an indicator of severe outcomes in Middle East Respiratory Syndrome coronavirus infection. *Emerg Infect Dis*. 2016;22:1813-6.
- Ling Y, Xu S-B, Lin Y-X et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J*. 2020;133:1039-43.
- 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.
- Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323:1843-4.
- 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.
- Young BE, Ong SWx, Kalimuddin S et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. 2020;323:1488-94.
- Chen W et al. *Emerg Microb Infect*. 2020;9:469-73.
- 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.

- 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.
- 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.
- University of Birmingham. COVID-19 in Pregnancy (PregCOV-19LSR).URL <https://www.birmingham.ac.uk/research/who-collaborating-centre/pregcov/about/prevalence.aspx> (accessed June 16 2020).
- 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 Scan*. 2020;99:565-8.
- Blumberg DA, Underwood MA, Hedriana HL, Lakshminrusimha S. Vertical transmission of SARS-CoV-2: what is the optimal definition? *Am J Perinatol*. 2020 Jun 5 (epub). doi: 10.1055/s-0040-1712457
- Li M, Xu M, Zhan W, Han T, Zhang G, Lu Y. Report of the first cases of mother and infant infections with 2019 novel coronavirus in Xinyang City Henan Province. *Chin J Infect Dis*. 2020;38 online pre-publishing.
- Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK: a national cohort study using the UK Obstetric Surveillance System (UKOSS). 2020 preprint (<https://www.npeu.ox.ac.uk/downloads/files/ukoss/annual-reports/UKOSS%20COVID-19%20Paper%20pre-print%20draft%2011-05-20.pdf>)
- Carosso A, Cosma S, Borella F, et al. Pre-labor anorectal swab for SARS-CoV-2 in COVID-19 pregnant patients: is it time to think about it? *Eur J Obstet Gynecol Repro Biol*. 2020 Apr 14;S0301-3115(20_30202-5..
- Buonsenso D, Costa S, Sanguinetti M, et al. Neonatal Late Onset Infection with Severe Acute Respiratory Syndrome Coronavirus 2. *Am J Perinatol*. 2020 May 2 (epub).
- Penfield CA, Brubaker SG, Limaye MA, et al. Detection of SARS-COV-2 in Placental and Fetal membrane Samples. *Am J Obstet Gynecol MFM* 2020 May 8: 100133.
- Algarroba GN, Rekawek P, Vahanian SA, et al. Visualization of SARS-CoV-2 virus invading the human placenta using electron microscopy. *Am J Obstet Gynecol* 2020 May 13 (epub).
- Baud D, Greub G, Favre G, et al. Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection. *JAMA*. 2020 Apr 30:e207233..
- Dong L, Tian J, He S, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. *JAMA*. 2020;323:184608.
- Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA* 2020.
- Wu Y, Liu C, Dong L, et al. Coronavirus disease 2019 among pregnant Chinese women: case series data on safety of vaginal birth and breastfeeding. *BJOG*. 2020 May 5.
- Lackey KA, Pace RM, Williams JE et al. SARS-CoV-2 and human milk: what is the evidence? *MedRxiv*. 2020 Apr 7. doi:10.1101/2020.04.07.20056812.

Widders A, Broom A, Broom J. SARS-CoV-2: the viral shedding versus infectivity dilemma. *Infection, Disease and Health*. 2020 May 20 (epub). doi:10.1016/j.idh.2020.05.002

Liguoro I, Pilotto C, Bonanni M, et al. SARS-CoV-2 infection in children and newborns: a systematic review. *Eur J Pediatr*. 2020 May 18:1-18.

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.

Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-20.

Trad ATA, Ibirogbra 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).

Bandi S, Nevid MZ, Mahdavinia M. African American children are at higher risk for COVID-19 infection. *Pediatr Allergy Immunol*. 2020 May 29 (epub).

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)

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.

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.

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.

Turner D, Huang Y, Martin-de-Carpi J et al. Corona virus disease 2019 and paediatric inflammatory bowel diseases: global experience and provisional guidance (March 2020) from the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2020;70:727-33.

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).

Green WD, Beck MA. Obesity altered T cell metabolism and the response to infection. *Curr Opin Immunol*. 2017;46:1-7.

Sun D, Li H, Lu X-X, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020 Mar 19:1-9.

Hrusak O, Kalina T, Wolf J et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anti-cancer treatment. *Euro J Cancer*. 2020;132:11-16.

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.

- 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.
- Lee LYW, Cazier JB, Starkey T et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020 May 28 (epub).
- Baluku JB, Mwebaza S, Ingabire G, Nsereko C, Muwanga M. HIV and SARS-CoV-2 co-infection: a case report from Uganda. *J Med Virol*. 2020 May 21 (epub).
- Patel RH, Pella PM. COVID-19 in a patient with HIV infection. *J Med Virol*. 2020 May 22 (epub).
- Zhu F, Cao Y, Xu S, Zhou M. Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China. *J Med Virol*. 2020 Mar 11:10.1002/jmv.25732.
- Benkovic S, Kim M, Sin E. 4 cases: HIV and SARS-CoV-2 co-infection in patients from Long Island, New York. *J Med Virol*. 2020 May 19 (epub).
- Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. *Clin Infect Dis*. 2020 May 14 (epub).
- Haddad S, Tayyar R, Risch L et al. Encephalopathy and seizure activity in a COVID-19 well-controlled HIV patient. *Infect Dis Cases*. 2020 May 16:e00814.
- Schoergenhofer C, Jilma B, Stimpfl T et al. Pharmacokinetics of lopinavir-ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). *Ann Int Med*. 2020 May 12 (epub).
- Wu Q, Chen T, Zhang H. Recovery from COVID-19 in two patients with coexisted HIV infection. *J Med Virol*. 2020 May 13 (epub).
- Wang M, Luo L, Bu L, Xia H. One case of coronavirus disease 2019 (COVID-19) in a patient coinfecting by HIV with a low CD4 T-cell count. *Int J Infect Dis*. 2020;96:148-50
- Harter G, Spinner CD, Roeder J et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection*. 2020 May 11:1-6.
- Aydin OA, Karaosmanoglu HK, Yasar KK. HIV/SARS-CoV-2 coinfecting patients in Istanbul Turkey. *J Med Virol*. 2020 Apr 29 (epub).
- Su J, Shen X, Ni Q et al. Infection of severe acute respiratory syndrome coronavirus 2 in a patient with acquired immune deficiency. *AIDS*. 2020 Apr 17 (epub).
- Blanco JL, Ambrosioni J, Garcia F et al. COVID-19 in patients with HIV: clinical case series. *Lancet HIV*. 2020;7:e314-6.
- Chen J, Cheng X, Wang R, Zeng X. Computerized tomography imaging of an HIV-infected patient with coronavirus disease 2019 (COVID-19). *J Med Virol*. 2020 Apr 14 (epub).
- Zhao J, Liao X, Wang H et al. Early virus clearance and delayed antibody response in a case of COVID-19 with a history of coinfection with HIV-1 and HCV. *Clin Infect Dis*. 2020 Apr 9 (epub).
- Riva A, Conti F, Bernacchia D et al. Darunavir dose not prevent SARS-CoV-2 infection in HIV patients. *Pharmacol Res*. 2020;157:104826.

Iordanou S, Koukios D, Matsentidou C-T et al. Severe SARS-CoV-2 pneumonia in a 58-year old patient with HIV: a clinical case report from Republic of Cyprus. *J Med Virol*. 2020 May 25 (epub).

Kumar RN, Tanna SD, Shetty AA, Stosor V. COVID-19 in an HIV-positive kidney transplant recipient. *Transplant Infect Dis*. 2020 May 26:e13338.

Louisa SJ, Serene WXL, Gollamudi S. A case of HIV and SARS-CoV-2 coinfection in Singapore. *JAIDS*. 2020 May 11 (epub).

Suwanwongse K, Shabarek N et al. Clinical features and outcomes of HIV/SARS-CoV-2 coinfecting patients in Bronx, New York City. *J Med Virol*. 2020 May 28 (epub).

Ridgway JP, Farley B, Benoit J-L et al. A case series of five people living with HIV hospitalized with COVID-19 in Chicago, Illinois. *AIDS Patient Care STDs*. 2020 May 29 (epub).

Vizcarra P, Perez-Elias MJ, Quereda C et al. Description of COVID-19 in HIV-infected individuals: a single-center, prospective cohort. *Lancet HIV*. 2020 May 28 (epub).

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

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/>

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. *Morbidity and Mortality Weekly Report*. 2020 March 31;69 (early release)

Shekerdemian 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).

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).

Whittaker E, Bamford A, Kenny J et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020 June 8 (epub)

Chiotos K, Bassiri H, Behrens EM et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. *J Pediatr Infect Dis Soc*. 2020 May 28 (epub).

Verdoni L, Mazza A, Gervasoni A et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020 May 13 (epub).

Riphagen S, Gomez X, Gonzalez-Martinez, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during the COVID-10 pandemic. *Lancet*. 2020 May;395:1607-8.

Belhadjer Z, Meot M, Bajolle F et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020 May 17 (epub).

Toubiana J, Poirault C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. *Brit Med J*. 2020;369:m2094.

Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. *Gastroenterol*. 2020 May 7. doi: 10.1052/j.gastro.2020.05.079.

Belot A, Antona D, Renoulleau S et al. SARS-CoV-2-related paediatric inflammatory multi-system syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. 2020;25 (22):pii2001010.

Grimaud M, Starck J, Levy M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care*. 2020;10:69.

Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020 (epub) doi:10.1136/annrheumdis-2020-217960.

Ramcharan T, Nolan O, Lai CY, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2: cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. *Pediatr Cardiol*. 2020 Jun. doi:10.1007/s00246-020-02391-2.

Perez-Toledo M, Faustini SE, Jossi SE et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with paediatric inflammatory multisystem syndrome. *MedRxiv*. 2020 Jun 5. doi:10.1101/2020.06.05.20123117.

Wolfer A, Mannarino S, Giacomet V, Camporesi A, Zuccotti G. Acute myocardial injury: a novel clinical pattern in children with COVID-19. *Lancet Child Adolesc Health*. 2020 Jun 1 (epub).

Cheung EW, Zachariah P, Gorelik M et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020 Jun 8 (epub).

Shulman ST. Pediatric COVID-associated multi-system inflammatory syndrome (PMIS). *J Pediatr Infect Dis Soc*. 2020 May 22 (epub).

Diamanti AP, Rosado MM, Pilo 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).

Viner RM, Whittaker E. Kawasaki-like disease: emerging complications during the COVID-19 pandemic. *Lancet*. 2020 May 13 (epub).

<https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>

https://www.who.int/maternal_child_adolescent/research/covid-19/en/

Roberton T, Carter ED, Chou VB et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low and middle-income countries: a modeling study. *Lancet Glob Health*. 2020 May 12 (epub).

Stover J, Chagoma N, Taramusi I, Teng Y, Glaubius R, Mahiane G. Estimation of the potential impact of COVID-19 responses on the HIV epidemic: analysis using the Goals Model. *MedRxiv preprint*. 2020 May 8.

Hogan AB, Jewell B, Sherrand-Smith E et al. Report 19: the potential impact of the COVID-19 epidemic on HIV, TB, and malaria in low and middle income countries. Imperial College COVID-19 Response Team. May 1 2020 (<https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-19-hiv-tb-malaria/>).

Hwang TJ, Randolph AG, Bourgeois FT. Inclusion of children in clinical trials of treatment for coronavirus disease 2019 (COVID-19). *JAMA*. 2020 May 7 (epub).

Whitehead CL, Walker SP. Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. *Lancet*. 2020 May 13 (epub).

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

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

Hong Kong	HKG	East Asia and Pacific	High income	dat%2018%20me%202020%20an..pdf https://www.chp.gov.hk/files/pdf/local_situation_covid19_en.pdf	14/06/2020
India	IND	South Asia	Low and middle income	https://www.statista.com/statistics/1110522/india-number-of-coronavirus-cases-by-age-group/	26/04/2020
Italy	ITA	Europe and Central Asia	High income	https://www.statista.com/statistics/1103023/coronavirus-cases-distribution-by-age-group-italy/	9/06/2020
Jamaica	JAM	Latin America and Caribbean	Low and middle income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Jamaica#Statistics	12/06/2020
Kenya	KEN	Sub-Saharan Africa	Low and middle income	https://www.health.go.ke/wp-content/uploads/2020/06/Kenya-SITREP-090-15-Jun-2020.pdf	15/06/2020
Mexico	MEX	Latin America and Caribbean	Low and middle income	https://coronavirus.gob.mx/datos/	14/06/2020
Moldova	MDA	Europe and Central Asia	Low and middle income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Moldova	13/06/2020
Montenegro	MNE	Europe and Central Asia	Low and middle income	https://www.coronainfocg.me/	14/06/2020
Netherlands	NLD	Europe and Central Asia	High income	https://www.rivm.nl/documenten/epidemiologische-situatie-covid-19-in-nederland-19-mei-2020	14/06/2020
New Zealand	NZL	East Asia and Pacific	High income	https://www.statista.com/statistics/1108939/new-zealand-number-of-coronavirus-cases-by-age-group/	2/06/2020
Nigeria	NGA	Sub-Saharan Africa	Low and middle income	https://ncdc.gov.ng/diseases/sitreps/?cat=14&name=An%20update%20of%20COVID-19%20outbreak%20in%20Nigeria	13/06/2020
Norway	NOR	Europe and Central Asia	High income	https://www.statista.com/statistics/1103986/number-of-coronavirus-covid-19-cases-in-norway-by-age-groups/	10/06/2020
Panama	PAN	Latin America and Caribbean	High income	http://minsa.gob.pa/coronavirus-covid19	14/06/2020
Paraguay	PRY	Latin America and Caribbean	Low and middle income	https://www.mspbs.gov.py/reporte-covid19.html	14/06/2020
Philippines	PHL	East Asia and Pacific	Low and middle income	https://ncovtracker.doh.gov.ph/	14/06/2020
Portugal	PRT	Europe and Central Asia	High income	https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Portugal	14/06/2020
Puerto Rico	PRI	Latin America and Caribbean	High income	https://bioseguridad.maps.arcgis.com/apps/opsdashboard/index.html#/d7308c1abb4747e584329adf1215125e	14/06/2020
Republic of Korea	KOR	East Asia and Pacific	High income	https://www.statista.com/statistics/1102730/south-korea-coronavirus-cases-by-age/	8/06/2020
Romania	ROU	Europe and Central Asia	Low and middle income	https://www.statista.com/statistics/1104592/romania-covid-19-infections-by-age-group/	14/06/2020
South Africa	ZAF	Sub-Saharan Africa	Low and middle income	https://www.nicd.ac.za/wp-content/uploads/2020/05/COVID19-Daily-Report-National-18-May-2020_public.pdf	18/05/2020
Spain	ESP	Europe and Central Asia	High income	https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_68_COVID-19.pdf	06/04/2020
Sweden	SWE	Europe and Central Asia	High income	https://fohm.maps.arcgis.com/apps/opsd	14/06/2020

		Asia		ashboard/index.html#/68d4537bf2714e63b646c37f152f1392	
United Kingdom	GBR	Europe and Central Asia	High income	https://www.statista.com/statistics/1115083/coronavirus-cases-in-england-by-age-and-gender/	14/06/2020
United States	USA	North America	High income	https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html	14/06/2020

Annex 2: Summary of Modeling Indirect Impacts of COVID-19

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

Area	Questions	Main findings	Models	Countries	Group
Child Health	<ul style="list-style-type: none"> To assess COVID-19 secondary impacts on children's lives 	<p>30 million children lives at stake</p> <p>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.</p> <p>Additional 100,00 children will die of malaria an increase of 50% from current levels</p>	Applied evidence from Ebola outbreak for the % reductions or increases, methods unclear for mortality estimates, time period unclear	24 countries SSA experiencing humanitarian crisis	World Vision
MNCH	<ul style="list-style-type: none"> Excess maternal and U5 mortality from weak systems (lower provision) & lower utilization of 72 RMNCH services 3 scenarios x 3 disruption durations 	<p>Excess mortality (selection of results):</p> <ul style="list-style-type: none"> 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 	Lived Saved Tool, 6 month and 12-month disruptions, three levels of disruption	118 LMIC	John Hopkins University
MN	<ul style="list-style-type: none"> Disrupted maternal healthcare during COVID-19 how will it impact maternal, stillbirth and newborn deaths 	31,980 additional maternal deaths, 395,440 additional newborn deaths, and 338,760 additional stillbirths	Applied evidence from Ebola outbreak for the % reductions or increases and used LiST 12 months	HP+	India, Indonesia, Nigeria, and Pakistan
HIV, TB, Malaria and malnutrition in children under 5 years	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 8.6% for malnutrition in children 	Applied evidence from 14 African countries Ebola outbreak for the % reductions or increases	33 countries Africa Projections to 2022	Cooper/Smith

B. Modelling impact of COVID-19 on Sexual Reproductive Health

Area	Questions	Main findings	Model Assumptions	Countries	Group
Sexual and Reproductive Health	<ul style="list-style-type: none"> To estimates of the Potential Impact of the COVID-19 Pandemic on Sexual and Reproductive Health In Low- and Middle-Income Countries 	<p>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</p> <p>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. 2,591,000 additional newborns experiencing major complications without care and thus 168,000 additional newborn deaths</p> <p>10% shift in abortions from safe to unsafe would result in 3,325,000 additional unsafe abortions and thus 1,000 additional maternal deaths</p>	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	132 mostly LMICs in Africa, Asia, Eastern and Southern Europe, and Latin America and the Caribbean, in one year	Gutmacher Institute, New York. UK Aid BMGF, Dutch Ministry of Foreign Affairs and CIFFribbean
Family Planning	<ul style="list-style-type: none"> To estimate impact on family planning in low- and middle-income countries 	<p>Some 47 million women in 114 LMIC unable to use modern contraceptives if the average lockdown continues for 6 months</p> <ul style="list-style-type: none"> 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 	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	114 LMIC 6-month lockdown	Avenir Health, Johns Hopkins University (USA) and Victoria University (Australia), UNFPA
Female Genital Mutilation	<ul style="list-style-type: none"> To estimate impact on FGM for subset of countries with high FGM rates 	<p>COVID-19 could have far-reaching impacts on the effort to end female genital mutilation</p> <p>Due to COVID-19 disruptions, we anticipate a 1/3 reduction in the progress towards ending FGM by 2030</p> <p>Due to pandemic-related disruptions in prevention programmes, 2 million FGM cases could occur over the next decade that would otherwise have been averted</p>	Sensitivity analysis on the previously published estimates: Assume postpone the deployment of programmes to eliminate FGM	High prevalence FGM countries (~30) 6-month lockdown	Avenir Health and UNFPA

Gender Based Violence	<ul style="list-style-type: none"> To estimate impact on Gender Based Violence globally 	<p>COVID-19 pandemic is likely to cause a one-third reduction in progress towards ending gender-based violence by 2030</p> <p>If the lockdown continues for 6 months, 31 million additional gender-based violence cases can be expected</p>	<p>Sensitivity analysis on the previously published estimates:</p> <ul style="list-style-type: none"> Reducing prevention and protection efforts, social services and care Increasing the incidence of violence 	<p>193 United Nations member states</p> <p>6-month lockdown</p>	<p>Avenir Health and UNFPA</p>
-----------------------	--	---	---	---	--------------------------------

C. Modelling impact of COVID-19 on Vaccine Preventable Diseases

Area	Questions	Main findings	Model Assumptions	Countries	Group
Immunization	<ul style="list-style-type: none"> To weigh the health benefits of continued routine infant immunisation delivery in Africa against the risk of acquiring coronavirus infections through visiting vaccination services. 	<p>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</p>	6-month disruption	54 SSA	<p>LSHTM Centre for Mathematical Modelling of Infectious Disease Covid-19 Working Group:</p>
VPDs & polio	<ul style="list-style-type: none"> VPD mortality from paused SIAs, low RI Risk of Polio spread (WPV1 and cVDPV2) Trade-off: RI benefit vs COVID spread risk 	<p>RI benefits outweigh the risks of Covid spread during RI visits >100:1 (link). Every 6 months, RI prevents 800k future U5 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).</p>	6-month disruptions of SIAs	All LMICs; countries with SIAs paused	<p>VIMC, IDM, ICL, LSHTM, KidRisk</p>
Immunization	<ul style="list-style-type: none"> SIA disruptions and Measles 	<p>Range of measles cases 200,000 to 2 million, 3,000 to 58,000 deaths</p>	Details pending	Ethiopia	<p>LSTHM, IDM, PSU</p>