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VIEWPOINT

The Critical Need for Pooled Data on Coronavirus Disease 2019 in African Children: An AFREhealth Call for Action Through Multicountry Research Collaboration

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Globally, there are prevailing knowledge gaps in the epidemiology, clinical manifestations, and outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among children and adolescents; and these gaps are especially wide in African countries. The availability of robust age-disaggregated data is a critical first step in improving knowledge on disease burden and manifestations of coronavirus disease 2019 (COVID-19) among children. Furthermore, it is essential to improve understanding of SARS-CoV-2 interactions with comorbidities and coinfections such as human immunodeficiency virus (HIV), tuberculosis, malaria,

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sickle cell disease, and malnutrition, which are highly prevalent among children in sub-Saharan Africa. The African Forum for Research and Education in Health (AFREhealth) COVID-19 Research Collaboration on Children and Adolescents is conducting studies across Western, Central, Eastern, and Southern Africa to address existing knowledge gaps. This consortium is expected to generate key evidence to inform clinical practice and public health policy-making for COVID-19 while concurrently addressing other major diseases affecting children in African countries.

Keywords. SARS-CoV-2; COVID-19; children; neonates; Africa.

GLOBAL EPIDEMIOLOGY OF CORONAVIRUS DISEASE 2019 AMONG CHILDREN

There continues to be a global upsurge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and associated novel coronavirus disease 2019 (COVID-19). As of 31 January 2021, the World Health Organization (WHO) reported more than 102 million confirmed cases and 2.2 million deaths globally [1]. The African region has recorded nearly 2.6 million cases and more than 62 000 deaths due to COVID-19 [1]. However, there is a significant knowledge gap with respect to COVID-19 epidemiology among children. To date, available data indicate that children and adolescents aged 0–19 years (hereafter referred to as "children") constitute a relatively small proportion of COVID-19 cases worldwide. Systematic reviews based on data largely from China, the United States, Spain, and other European and Asian countries report that children comprise 1% to 5% of all COVID-19 cases reported [2–4]. A recent meta-analysis of 107 datasets from 47 studies in 23 countries estimated a 3.4% SARS-CoV-2 general seroprevalence globally; prevalence in children was reported at 2.3% [5]. It is worth noting that the meta-analysis reported significantly high heterogeneity (I^2 = 99.4%) for the overall estimate, and the pediatric data were based on 11 datasets, with only 1 dataset from an African country, Kenya [5].

The WHO's COVID-19 global surveillance data from January 2020 through July 2020 indicated that most confirmed cases reported are in the 25- to 64-year age group, with only 3.7% reported among children aged <15 years [6]. However, 72% of cases in this database were reported from the Americas and Europe. Evidence from primarily high-income countries with higher proportions of older populations may not be valid for the younger populations in low- and middle-income countries (LMICs). The age distribution of cases partly reflects the population's age structure and the age-dependent probability of being tested. While data from high-income countries show that younger individuals are less likely to develop symptomatic disease than older adults, there are additional factors in Africa, such as the health effects of food insecurity and high prevalence of communicable diseases, that may counteract potential age-related protective factors for disease [7]. Of concern is that the WHO COVID-19 situation reports have not consistently included age-disaggregated data, and the WHO African region has not provided such data on their public website to date.

Given the limited data available to estimate pediatric COVID-19 burden, UNICEF reanalyzed country-level data from the Max Planck Institute for Demographic Research (MPIDR) on SARS-CoV-2 infection among children aged <20 years [8]. Since not all countries routinely report COVID-19 data by standard age group and sex, the MPIDR team redistributed unknown age group measures to standardized 5-year age groups using the 2019 World Population Prospects, with reference to the year 2020. Using available age-disaggregated data from 87 countries (which account for 54% of global SARS-CoV-2 infections), they estimated that as of November 2020, children accounted for 11% of reported COVID-19 cases [8]. The proportion of confirmed positive cases in children aged <20 years varied widely among countries, ranging from 1.1% to 30%. Of these cases, 68% were among patients aged 10–19 years, and 32% among the 0- to 9-year age group. In sub-Saharan Africa (SSA), the volume and detail of available pediatric COVID-19 data remain inadequate at both country and regional levels, and many knowledge gaps and research questions so far remain unanswered (Table 1, Figure 1).

CLINICAL MANIFESTATIONS AND OUTCOMES OF COVID-19 AMONG CHILDREN

There is an expanding pool of data on the manifestations and clinical outcomes of COVID-19 among children. To date, most of this data are from China, followed by the United States, Spain, the United Kingdom, and other European and Asian countries [2–4, 9, 10]. Overall, reported disease severity has been lower, and clinical outcomes (including case fatality rates) better among children compared with adults. A recent meta-analysis by Li et al included 96 studies involving more than 7000 children with confirmed COVID-19; the mean age of children across 49 studies with age-disaggregated data was 6.48 years (95% confidence interval, 5.20–7.75) [10]. The most common presenting symptoms were fever (47%) and cough (42%), while 23% of children had no symptoms at presentation. The prevalence of severe/critical disease was 7% among children aged <5 years and 3% for those aged ≥5 years, with an overall mortality rate of 1% [10]. Data shown here should be interpreted with caution, as the number and size of datasets used for the analyses varied across different pediatric age groups and by inclusion criteria.

There are few reports on COVID-19 in children from SSA. The largest cohort reported to date is from South Africa,

Table 1. Areas of Specific Interest and Concern and Research Questions for Pediatric Severe Acute Respiratory Syndrome Coronavirus 2–Coronavirus Disease 2019 Research in Africa

		Areas of Specific Interest and Concern	Key Research Questions
1	Epidemiology	• Country- and regional-level geographic differences in pediatric COVID-19 prevalence in Africa • Major differences in demographic profiles among countries with younger populations in SSA vs HIC • Role of children in SARS-CoV-2 transmission and SARS-CoV-2 viral loads in children • Very limited testing among children in Africa	• What is the burden of SARS-CoV-2 among children in African countries? • What are the dynamics of SARS-CoV-2 acquisition and transmission patterns among SSA children in the community and in schools?
2	Clinical manifestations and disease severity	• Asymptomatic and mild disease commonly reported among children in HIC [3, 4, 9, 10] • MIS-C in children is uncommon but can be severe, reported primarily in HIC [13–15] • Few reports from Africa; MIS-C reported only from South Africa to date [16, 17]	• What are the clinical features of SARS-CoV-2–COVID-19 in African children, and do they differ from those in HIC? • What factors, including acute and chronic disease comorbidities, are associated with severe disease among children in Africa? • Is MIS-C being seen or recognized in African children, and do characteristics and outcomes differ compared with children from HIC?
3	Communicable disease comorbidities	• High prevalence of human immunodeficiency virus, tuberculosis, malaria, respiratory infections among children in SSA vs HIC [29] • Limitations in SARS-CoV-2 testing and diagnostics for pneumonia make it difficult to differentiate from other infectious respiratory diseases [29]	• Are specific coinfections highly prevalent in SSA countries associated with more severe COVID-19 in children? [29] • Does SARS-CoV-2 infection result in poor outcomes of coinfection in African children with such coinfections? [29]

4	Noncommunicable disease comorbidities	• Obesity associated with disease severity in HIC; no data on malnutrition
		• High prevalence in SSA
		  ◦ SCD
		  ◦ Hypertension, cardiovascular disease
		  ◦ Diabetes
		  ◦ Asthma
		  ◦ Malignancies
		  ◦ Often undiagnosed mental health conditions
		• Poverty-related issues such as crowding, poor housing, household air pollution
			• How does nutritional status of children (malnutrition, obesity) affect risk of disease severity in SSA children? [29]
			• What is the impact of SCD on risk and outcomes of COVID-19 disease among children in SSA? [29]
			• How do cardiovascular, metabolic, and other comorbidities impact the risk and outcomes of COVID-19 in African children?
			• How do housing density, crowding, and household air pollution affect risk of SARS-CoV-2 infection in children in SSA?
			• What is the prevalence of depression and stigma experienced among children with COVID-19 or in the context of the COVID-19 pandemic in Africa?

5	Outcomes	• In HIC children, disease less severe than in adults, but limited SSA data suggest possible high rates of hospitalization/higher need for intensive care for younger children with COVID-19 (South Africa) [17] and possible increased mortality among adolescents (Democratic Republic of the Congo) [22] • Longer-term consequences (eg, cardiac, neurologic) post-recovery are being observed primarily among adults in HIC	• How do outcomes in African children with COVID-19 disease differ from outcomes in adults (and from children in HIC)? • What are the independent factors that may impact pediatric outcomes of COVID-19 in Africa? • What are the healthcare system–related vs individual factors that may impact outcome? • What are the long-term consequences of SARS-CoV-2–COVID-19 in African children?
6	Treatment and prevention (including vaccines)	• Intensive care/respiratory support may be less available in SSA • Limited availability of treatment drugs (eg, remdesivir, monoclonal antibody) in SSA vs HIC • Role of BCG in COVID-19 acquisition, prevention, and severity • Lack of randomized, controlled trial data and access to COVID-19 treatments and vaccines effective for children [29]	• What are key low-cost and effective intensive care interventions that improve outcome of children with severe COVID-19 in SSA? • Is BCG vaccination potentially protective against COVID-19? • What is COVID-19 vaccine efficacy and safety in children vs adults in Africa? • How do we prioritize vaccine access for children in Africa? [29]
7	Scope and quality of health system for management of COVID-19 children in Africa	• Access to SARS-CoV-2 polymerase chain reaction/antigen and antibody testing in SSA limited, particularly for children • Access to higher-level ancillary COVID-19 tests, eg, D-dimer, IL-6, IL-10, troponin, brain natriuretic peptide • Access to basic care (eg, oxygen) at primary, secondary, and tertiary hospital levels of care; lack of intensive care and mechanical ventilation facilities • Lower quality of care contributing to excess mortality	• What low-cost, highly sensitive molecular antigen and antibody tests can be made available for broader testing of children in SSA? • How could access to critical ancillary tests be expanded, especially for children with MIS-C or other severe COVID-19 manifestations? • How does differential access to and quality of healthcare impact clinical pediatric COVID-19 outcomes within (eg, urban vs rural) and across African countries? [28] • Is there excess COVID-19 mortality among SSA children vs HIC children, and is this associated with quality of healthcare? [35]

Abbreviations: BCG, Bacille Calmette-Guérin tuberculosis vaccine; COVID-19, coronavirus disease 2019; HIC, high-income country; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children and adolescents, temporally related to COVID-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCD, sickle cell disease; SSA, sub-Saharan Africa.

comprising 159 children aged <13 years with polymerase chain reaction-confirmed SARS-CoV-2 infection presenting to Tygerberg Hospital, Cape Town, between April 2020 and July 2020 [11]. Children in this South African cohort were relatively young (median age, 48 months), but this is likely due to data collection being limited to those aged <13 years. Of the 159 children, 81 (50.9%) were symptomatic, with cough (88.9%, 72 of 81) and fever (61.7%, 50 of 81) predominating symptomatology at presentation. A total of 51 children (32.1%) required hospital admission for symptomatic care. Lower respiratory tract infection (pneumonia) was the most common reason for admission (41.2%), particularly for children aged <3 months (68.8%). Multisystem inflammatory syndrome in children temporally related to COVID-19 (MIS-C) was diagnosed in 3 children. Intensive care admission was required for 11 of 51 children admitted (21.6%), out of which 4 required mechanical ventilation. Median length of hospital stay was 5 days, and despite severity, there were no deaths among children admitted to intensive care. There was 1 death in a 5-week-old human immunodeficiency virus (HIV)–exposed, uninfected infant, which was determined to be secondary to sepsis and not directly due to COVID-19.

MIS-C, also known as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS), is a newly recognized severe manifestation of SARS-CoV-2 infection that mimics Kawasaki disease and toxic shock syndrome [12]. The earliest reports of MIS-C/PIMS were from Italy in May 2020 [13] the United Kingdom [14] and the United States [15] in June 2020. MIS-C has rarely been described among the relatively large Chinese COVID-19 pediatric cohorts to date [10]; however, this may be due to many reports predating the recognition of this syndrome. MIS-C has begun to be reported from SSA, with the largest case series to date (N = 23) from South Africa; mean age was 6.6 years, 80% were Black, and all survived [16]. In a separate report, 4 South African children with confirmed SARS-CoV-2 infection were initially diagnosed with acute appendicitis; 3 had an appendectomy and were subsequently diagnosed with MIS-C, and 1 was managed nonsurgically with no MIS-C diagnosis [17]. In addition to the South African cohorts described [11, 16, 17], the mention of MIS-C is notably absent from the few small SSA studies reporting COVID-19 manifestations and/or outcomes among children, for example, from Ethiopia [18], Nigeria [19, 20], Ghana [21], the Democratic Republic of the Congo (DRC) [22], and Sierra Leone [23]. This may be due to the underrecognition of MIS-C and its potential to manifest among African children. In the United States and the United Kingdom, Black children have been reported to have significantly higher SARS-CoV-2 test positivity rates and higher rates of severe COVID-19/MIS-C than their non-Black counterparts [24–27]. Furthermore, in a well-characterized cohort of 766 hospitalized COVID-19 patients in DRC, in-hospital mortality among 34 children aged <20 years (11.4%) was unexpectedly high and second only to that of the ≥60-year age group (32.0%) [22] with no clear explanation. This DRC study's small pediatric sample size and the possible effects of unmeasured confounding factors, such as the quality and scope of pediatric intensive care, precluded concrete conclusions about excess COVID-19 mortality among children in this setting.

A recent systematic review of 443 studies and 145 national reports data by Kitano et al suggests that children in LMICs have poorer COVID-19 outcomes compared with those in higher-income countries [28]. They analyzed data from 3788 global pediatric COVID-19 deaths, 91.5% of which were reported from LMICs. In fact, 83.5% of reported pediatric cases were in LMICs. The COVID-19 case fatality rate was significantly higher among children in LMICs than in higher-income countries (0.24% vs 0.01%, respectively; $P < .001$), while intensive care unit admissions were significantly lower, and the highest case fatality rates were among infants aged <1 year. The authors additionally noted that many countries failed to report age-disaggregated outcome data for children; there was a lack of national-level data, particularly for children in Africa and the Middle East; and there was a paucity of intensive care unit admission data from LMICs [28]. It would be important to evaluate pediatric (including neonatal) COVID-19 outcomes in multicountry studies across Africa to augment our understanding of the prevalence of SARS-CoV-2 infection and degree and impact of severe disease in this population (Table 1, Figure 1).

COINFECTIONS AND COMORBIDITIES IN PEDIATRIC COVID-19

Where evaluated for, acute coinfections were commonly identified among children with COVID-19; a 29% coinfection rate was determined in the systematic review by Li et al [10]. *Mycoplasma* spp., followed by influenza A, influenza B, Epstein-Barr virus, adenovirus, and respiratory syncytial virus were the most predominant microorganisms [10]. In a South African cohort (N = 159), 2 (1.3%) children were living with HIV and 13 (8.2%) were HIV-exposed but uninfected. Other preexisting conditions included sickle cell disease (SCD), aplastic anemia, asthma, prematurity, and tuberculosis [11]. Of note, 7 children had a recent or current diagnosis of tuberculosis; 2 children were on antituberculosis treatment at presentation, and an additional 4 children received a new tuberculosis diagnosis during admission [11].

Infectious diseases such as HIV, tuberculosis, and malaria and noncommunicable diseases such as SCD and malnutrition are highly prevalent among children in SSA and can pose significant diagnosis and disease management challenges at individual and public health levels if coexisting with COVID-19 [29]. In a meta-analysis, Tsankov et al determined that children with underlying comorbidities, such as chronic respiratory

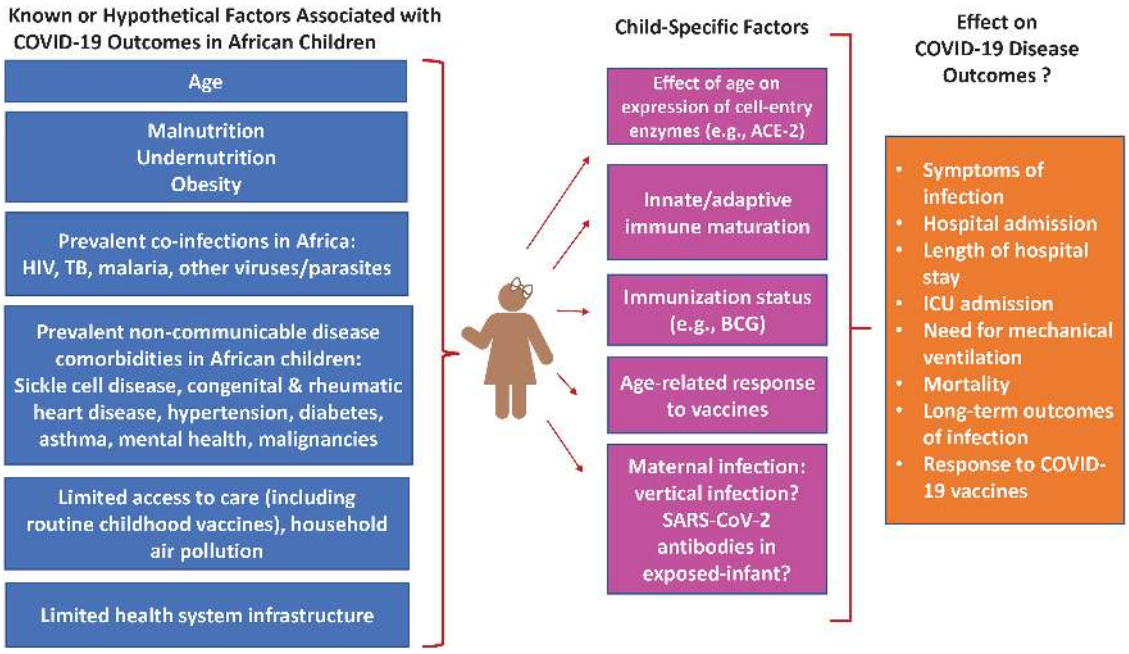

Figure 1. Known or hypothetical factors associated with coronavirus disease 2019 in adults and children and potential effects on health outcomes in African children. Abbreviations: ACE-2, angiotensin-converting enzyme 2; BCG, bacille Calmette-Guérin tuberculosis vaccine; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis.

disorders (including asthma), immune disorders (including "immunosuppression" but not HIV), cardiovascular disease, metabolic disorders (including diabetes), obesity, neurologic disorders, hematologic disorders (including SCD), and cancers, have significantly more severe COVID-19 manifestations and higher associated mortality [30]. More studies are needed to determine the impact of comorbidities common in the SSA region on pediatric COVID-19 outcomes [29] (Table 1, Figure 1).

ESTABLISHED PEDIATRIC COVID-19 RESEARCH CONSORTIA

In the wake of the COVID-19 pandemic, several countries and regions have established research consortia to generate evidence for policy and practice on prevention and treatment, including among children. The pediatric consortia have leveraged preexisting networks, for example, the Pediatric Tuberculosis Network European Trials Group [31], or have forged new alliances, for example, the CoviDOMINGO (COVID in South American Children) study group [32]. The Cape Town MIS-C Team has been established in South Africa, which has by far the highest number of COVID-19 cases in Africa [16], which is part of an ongoing drive to expand in-country MIS-C collaboration. Additionally, the South African COVID-19 in Children Research Network is coordinated by the South African Medical Research Council [33]. Within-country collaborations are needed to generate local evidence to shape national responses for children, while multicountry and intraregional collaborations will make it possible and easier to rigorously address additional research questions, particularly those with rare outcomes. Pooling data across countries has the advantages of enhancing statistical power and the ability to compare outcomes across sites or settings (increased internal validity), as well as generalizability of the findings to the continent (increased external validity). The African Forum for Research and Education in Health (AFREhealth) [34] has assembled a multicountry team of pediatric and infectious diseases clinicians and researchers to address the paucity of pediatric COVID-19 evidence in Africa, starting with SSA. Furthermore, AFREhealth has established a multicountry COVID-19 Research Collaboration group that has prioritized pregnant women and neonates for studies spanning Western, Central, Eastern, and Southern Africa [35]. These consortia will serve as a ready resource for further prospective and retrospective COVID-19 studies to drive the response at country, regional, and/or continental level.

THE PROBLEM OF WEAK HEALTH INFORMATION SYSTEMS IN AFRICAN COUNTRIES

One of the reasons AFREhealth's COVID-19 Research Collaboration on Children and Adolescents was necessary was the relative lack of public health data on pediatric COVID-19 at the SSA country and regional levels. Health information systems (HIS) are an essential building block of health systems and allow for rapid review of data for evidence-based decision-making and efficient use of resources. HIS challenges in

SSA were well described prior to the COVID-19 pandemic; an overreliance on household surveys and poor integration of other key data sources (eg, civil registration and health facility statistics, especially from the private sector) were noted [36]. To date, measures to strengthen HIS in SSA include the African Health Initiative's Population Health Implementation and Training Partnership, established in 2010 [37]. It focused on strengthening district health systems and improving health planning in 5 SSA countries. Currently, it is unclear whether and how the partnership is contributing to COVID-19 reporting and decision-making in the respective countries. The importance of national public health agencies and prior experience with outbreaks such as Ebola has been reported, in addition to how ineffective governance and chronically poor HIS have affected prior outbreaks and ongoing COVID-19 responses [38, 39].

Private facility data are often not included in national reports, and few countries have highly functioning HIS with transparent data-sharing for COVID-19. Unique issues for children include outright exclusion or poorly age-disaggregated data, both in public health and in research reports. Research consortia, especially those that are child-focused, can bridge some of these gaps by engaging investigators and/or including data from private clinics and smaller district (vs larger referral) facilities to present more representative findings; incorporating verbal or social autopsy studies to provide or support mortality data that may be unavailable or inadequate; and initiating large-scale primary or secondary data collection from health facilities, especially where (pediatric) data is not being collected, reported, or age-disaggregated by public health agencies.

CONCLUSIONS

Critical knowledge gaps remain about the epidemiology, clinical manifestations, and outcomes of SARS-CoV-2 infection in African children. Prevailing weak HIS further complicate data collection to address these gaps. While available data may be more robust and accessible in higher-income countries outside SSA, knowledge regarding COVID-19 among children is far from adequate, even in those settings. For many reasons, including population demographics, health system infrastructure, potentially genetics, and other disease epidemiology, it is difficult to draw comparisons between pediatric COVID-19 data from SSA and those from other geographic regions. However, it remains that more data are needed from all over the world. Initiatives such as AFREhealth's child-focused, multicountry research consortium and emerging in-country collaborations (eg, the South African pediatric COVID-19 and MIS-C networks) are important mechanisms for generating evidence and supplementing health information systems to guide public health policy and program decision-making for COVID-19 for children.

Notes

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