

Global Representation During a Global Pandemic

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The COVID-19 pandemic has highlighted the importance of international research collaborations to quickly understand and successfully combat emerging and reemerging infectious pathogens globally. As SARS-CoV-2, the causative agent of COVID-19, spread across the world, the number of collaborative international studies defining the impact of COVID-19 have increased rapidly. From these studies, we have gained valuable information regarding the spectrum of clinical disease and the underlying risk factors associated with SARS-CoV-2-induced morbidity and mortality. These data have been important to guide public health interventions globally. However, despite the extensive geographic reach of SARS-CoV-2, low- and middle-income countries (LMICs) and inclusion of subgroups such as children have often been underrepresented within research collaborations. Given the distinct health conditions and resource limitations observed in LMICs, particularly for children, data generated from high-income countries may not be universally valid. Thus, studies conducted in LMICs that focus on COVID-19 outcomes are essential to providing appropriate clinical care and prioritizing interventions of greatest benefit regionally.

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The study conducted by Nachega et al¹ as part of the African Forum for Research and Education in Health (AFRE-health) COVID-19 Research Collaboration on Children and Adolescents helps to fill the knowledge gap regarding COVID-19 among children in LMICs. This multicenter multicountry study described COVID-19 illness among hospitalized children in sub-Saharan Africa and was the first, to our knowledge, to collate clinical information from across the African region, providing important data on severity of disease and outcomes. The study evaluated clinical data from 469 children (aged 0-19 years) with confirmed SARS-CoV-2 infection between March and December 2020 in 25 health facilities across the Democratic Republic of the Congo, Ghana, Kenya, Nigeria, South Africa, and Uganda. The authors concluded that COVID-19 was associated with high morbidity and mortality among hospitalized children younger than 1 year and select noncommunicable disease comorbidities, suggesting the pandemic has been more consequential across sub-Saharan Africa than previously recognized. These findings illustrate the value of pan-African collaborations to generate awareness of region-specific COVID-19 outcomes.

It is well recognized that underlying comorbid conditions place individuals infected with SARS-CoV-2 at high risk of disease progression. Comorbid conditions, such as asthma, congenital disorders, diabetes, obesity, and preterm birth, have been identified in approximately 40% of children hospitalized with COVID-19 in the United Kingdom and the US and have been associated with almost all COVID-19-associated deaths among children.^{2,3} In contrast, Nachega et al¹ described slightly lower rates of comorbidities (24.5%) among children hospitalized with COVID-19 in sub-Saharan Africa, despite documentation of more severe disease at the time of hospitalization. This is an important point because a major narrative during the course of the COVID-19 pandemic has been that children without preexisting medical conditions are largely protected from progression to severe COVID-19 illness. Although age younger than 1 year and the presence of a comorbid condition, such as hypertension, chronic lung disease, or hematologic disorders, were associated with higher risk of mortality, the findings of the Nachega et al¹ study suggested that approximately 75% of hospitalized children were otherwise healthy before receiving a COVID-19 diagnosis. However, there were several undisclosed variables, including seasonality of diseases such as malaria and the presence of malnutrition, that may have had implications for the study outcomes. More in-depth analysis of underlying childhood health over an extended period will be required to assess the role of these variables in COVID-19 outcomes among children.

At the time of hospital presentation, 47.5% of the children enrolled in the Nachega et al¹ study had severe or critical disease based on World Health Organization disease severity staging.⁴ This finding is in contrast to those of other studies from high-income countries such as the US, in which only 11.3% of hospitalized children had severe disease, and 9.4% had very severe disease.⁵ The reason for the large proportion of severe cases at the time of hospital presentation in the Nachega et al¹ study remains unclear. It is likely that underascertainment of childhood COVID-19 cases in sub-Saharan Africa occurred owing to a broad range of factors, including lack of infrastructure, scarcity of resources, and fear of stigmatization. A recent World Health Organization report⁶ found that only 1 in 7 cases of COVID-19 were detected in Africa, making it impossible to identify the true burden and severity of disease in children. Without testing availability and acceptability, delay in COVID-19 diagnosis is inevitable. Moreover, delay in care has been associated with adverse clinical outcomes in countries such as Malawi.⁷

One of the most notable statistics from the Nachega et al¹ study was that hospitalized children with COVID-19 appeared to have substantially higher mortality than those in other regions globally, with overall mortality at 8.3% in sub-Saharan Africa vs 1% in the United Kingdom and 0% to 0.7% in the US.^{3,8} Countries in sub-Saharan Africa are not alone in their description of high mortality rates secondary to COVID-19

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among children. A large study from Brazil⁹ also reported high mortality (7.6%) among children hospitalized with COVID-19. Life-saving resources for severely ill patients are not universal across the region; even supportive care tools, such as oxygen supplementation, are not ubiquitous. For instance, in central Africa, only 20.0% of centers had reliable oxygen supply, 14.3% had tertiary care facilities, and 28.6% had mechanical ventilators on site.¹ Treatment interventions recommended by the World Health Organization,¹⁰ such as corticosteroid medications (updated in September 2020), interleukin 6 receptor blockers (updated in July 2021), and neutralizing monoclonal antibody therapies (updated in September 2021), which have been reported to reduce either disease severity or mortality, were not part of the treatment regimen. Thus, children living in the context of inadequate health care infrastructure with limited therapeutic options are more vulnerable than children from regions in which resources are widely available and used.

Although it is important to note the high in-hospital mortality rates and the underlying socioeconomic factors associated with health outcomes, interpretation of COVID-19-associated excess mortality is difficult without knowledge of baseline in-hospital mortality. The baseline in-hospital mortality rates for centers in the Nachega et al¹ study are unknown; however, the rates are likely to be in the range of 1% to 7%, depending on the facility, and they are associated with seasonality.^{11,12} The full consequences of COVID-19 for excess in-hospital mortality are difficult to ascertain but important for developing targeted COVID-19 interventions.

Based on available data, it is evident that children in sub-Saharan Africa are at substantial risk of adverse outcomes associated with COVID-19. Beyond the direct impact, many countries across Africa have also reported substantial indirect impacts of COVID-19 for health outcomes among children, in-

cluding reductions in childhood immunization uptake, disruptions in treatment for common infectious disease such as pneumonia, malaria, and diarrheal disease, and reductions in outpatient and emergency hospital visits, while simultaneously reporting increases in childhood malnutrition.¹³⁻¹⁵ Despite the disproportionate direct and indirect adverse outcomes observed among children in sub-Saharan Africa, resources have not been proportionately distributed to aid in COVID-19 pandemic control. Use of therapeutic and preventive interventions are imperative, yet these tools are lacking in sub-Saharan Africa. In comparison with many high-income countries, in which more than 60% of the population is fully vaccinated, only 15 countries in sub-Saharan Africa have more than 10% of their populations fully vaccinated against COVID-19.¹⁶ Furthermore, despite potentially higher rates of mortality among children in sub-Saharan Africa, only 6 countries (Guinea, Jordan, Malawi, Morocco, Namibia, South Africa, and Zimbabwe) recommend vaccination of children 12 years and older. Despite these recommendations, vaccines remain largely unavailable to children in many countries. The vaccine equity gap, which has disproportionate consequences for LMICs, remains a major factor associated with the COVID-19 pandemic worldwide.

Recent news of the omicron variant in November 2021, now creating new viral waves around the world, reflects the critical nature of a global disease control vision. This vision needs to include the important research being conducted across LMICs to understand the challenges and risks of COVID-19 in LMICs for all groups, including children. Collaborative research teams across Africa, such as AFREhealth, are poised to answer these important questions. It is only with contributions from all regions that we can move forward together to address COVID-19 inequity and have a true evidence-based global approach to COVID-19 pandemic control.

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