



# Pediatric coronavirus disease 2019 in Africa

Marieke M. van der Zalm<sup>a</sup>, Daniele Dona<sup>b</sup> and Helena Rabie<sup>c</sup>

## Purpose of review

Three years into the coronavirus disease 2019 (COVID-19) pandemic, data on pediatric COVID-19 from African settings is limited. Understanding the impact of the pandemic in this setting with a high burden of communicable and noncommunicable diseases is critical to implementing effective interventions in public health programs.

## Recent findings

More severe COVID-19 has been reported in African settings, with especially infants and children with underlying comorbidities at highest risk for more severe disease. Data on the role of tuberculosis and HIV remain sparse. Compared to better resourced settings more children with multisystem inflammatory disease (MIS-C) are younger than 5 years and there is higher morbidity in all settings and increased mortality in some settings. Several reports suggest decreasing prevalence and severity of MIS-C disease with subsequent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variant waves. Whether this decrease continues remains to be determined. Thus far, data on long-COVID in African settings is lacking and urgently needed considering the severity of the disease seen in the African population.

## Summary

Considering the differences seen in the severity of disease and short-term outcomes, there is an urgent need to establish long-term outcomes in children with COVID-19 and MIS-C in African children, including lung health assessment.

## Keywords

Africa, coronavirus disease 2019, pediatrics, severe acute respiratory syndrome coronavirus-2

## INTRODUCTION

As of the 1 January 2023, more than 664 million cases and 6.7 million deaths associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are reported globally, of which more than 57 million cases and 43 000 deaths are estimated among children and adolescents aged 0–19 years [1]. Of all World Health Organization (WHO) Regions, Africa contributes 1.4% of all reported confirmed cases, which is the lowest of all regions. There are many speculations about why Africa has been relatively spared, including underreporting, limited testing/ capacity and that children younger than 18 constitute almost 50% of people living in Africa [2,3]. Despite the high proportion of children and adolescents living in Africa and the unprecedented volume of coronavirus disease 2019 (COVID-19) research done over the past three years, data on the epidemiology, clinical features and outcomes of African children and adolescents remain sparse [4]. This review will discuss recent literature on COVID-19 in children and adolescents living in Africa, including multisystem inflammatory syndrome (MIS-C) and long-COVID.

## ACUTE CORONAVIRUS DISEASE 2019

Available literature from the last 3 years consistently shows that children and adolescents are relatively protected from severe COVID-19 disease, with the vast majority having either asymptomatic or mild disease [5,6]. When severe disease does occur in

<sup>a</sup>Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa, <sup>b</sup>Division of Paediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy and <sup>c</sup>Paediatric Infectious Diseases, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa

Correspondence to Marieke M. van der Zalm, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa. Tel: +27 21 9389764; e-mail: mariekevdzalm@sun.ac.za

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## KEY POINTS

- More severe coronavirus disease 2019 has been reported in African settings, especially in infants and children with underlying comorbidities compared to higher-resource settings.
- African children with multisystem inflammatory disease (MIS-C) are generally younger than 5 years and there is a higher morbidity and in some settings an increased mortality reported.
- Several reports suggest decreasing prevalence and severity of MIS-C disease with subsequent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variant waves.
- Long-term outcome data is needed in African children, both for acute SARS-CoV-2 illness and MIS-C.

young children and adolescents, case fatality rates generally remain low. However, the majority of this data comes from high-resource settings. A systematic review of global literature on severe pediatric COVID-19 illness by Kitano *et al.* [7<sup>■</sup>] report that the overall case fatality rate was significantly higher in low-and middle-income countries (LMICs) (0.24%) than in high-income countries (HICs) (0.01%). Reports from African settings subsequently confirmed this finding [8<sup>■</sup>]. This may be explained by the fact that coincident infections with tuberculosis, other respiratory viruses, and HIV may synergistically impact outcomes. Although data is limited on the role of tuberculosis and HIV, adult data shows that these are risk factors for more severe COVID-19 disease [9,10,11]. The high prevalence of concurrent communicable diseases, such as tuberculosis and HIV and noncommunicable diseases, including malnutrition, are expected to play a role in the differences.

Most publications on clinical experiences from African settings describe either case series or small cohorts of mostly asymptomatic children found through contact tracing [12–16]. Table 1 summarizes clinical data of four hospital-based studies in Africa, of which three are from Sub-Saharan Africa and one from North Africa (Tunisia) [8<sup>■</sup>,17<sup>■</sup>,18<sup>■</sup>,19<sup>■</sup>]. The Tunisian study only includes children admitted to the pediatric intensive care unit (PICU). The first South African study was done during the ancestral wave [18<sup>■</sup>], and the second was done during the first Omicron wave [17<sup>■</sup>]. The vast majority of children with SARS-CoV-2 illness requiring hospitalization were under five years of age, with a large proportion of children being infants. The two South African studies reported incidental SARS-CoV-2 detection of 16 and 36%. Underlying comorbidities were seen in

about half of the children, with 3–4% living with HIV or tuberculosis.

Fever, respiratory and gastrointestinal symptoms were most common. Seizures were reported in both South African studies but were more frequently reported during the Omicron wave. Laboratory findings were similar between studies and showed an increased C-reactive protein (CRP), high white blood cell count and raised platelets. During the ancestral wave in South Africa, children more often required oxygen therapy, mechanical ventilation and PICU admission. The mortality ranged from 2 to 7.9% in the non-PICU studies. Overall the clinical data from African studies show a high proportion of especially young children being affected by more severe COVID-19 disease, requiring oxygen and respiratory support. In addition, the mortality rates were higher compared to other high-resource settings [7<sup>■</sup>]. Infants and children with underlying comorbidities are at highest risk for more severe disease and poor outcomes. To date, limited data is available on the role of tuberculosis and HIV on disease severity. Adult studies have shown that both active tuberculosis and a past history of tuberculosis are associated with more severe disease and death [10]. For HIV, results are conflicting; a recent analysis by du Bruyn *et al.* showed that the immune response to SARS-CoV-2 is adversely affected by co-existent HIV-1 and tuberculosis [9]. More data is needed on the role of tuberculosis and HIV on the severity of the disease in children with COVID-19. Furthermore, considering the high proportion of young children affected who require respiratory support long-term lung health consequences need to be considered.

## MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In April 2020, the first reports of MIS-C emerged in the United Kingdom as a serious pediatric manifestation of SARS-CoV-2 [20]. Since then, there have been multiple reports of MIS-C in other parts of the world; however, despite MIS-C being more common in black children worldwide, there is limited published data on MIS-C in Africa. The incidence of MIS-C is uncertain, as it has been difficult to accurately estimate the number of children exposed to SARS-CoV-2 globally, especially when different testing strategies are used. In general, it is considered a relatively rare complication of COVID-19 in children, occurring in <1 percentage of children with confirmed SARS-CoV-2 infection. Several reports suggest decreasing prevalence and severity of MIS-C with subsequent SARS-CoV-2 variant waves likely explained by increasing seroprevalence and vaccination [21<sup>■</sup>,22<sup>■</sup>].

**Table 1.** Summary of findings of published clinical hospital cohorts in Africa

	vd Zalm <i>et al.</i> [18 <sup>a</sup> ]	Nachega <i>et al.</i> [8 <sup>b,c</sup> ]	Cloete <i>et al.</i> [17 <sup>d</sup> ]	Borgi <i>et al.</i> [19]
Design	Prospective single-center observational study of SARS-CoV-2 PCR positive children	Multicenter retrospective record study of SARS-CoV-2 PCR positive children	Prospective multicenter observational study of SARS-CoV-2 positive children	Retrospective record study of SARS-CoV-2 PCR positive children in PICU
Number included, N	62	469	183 COVID positive hospital admissions	20
Setting	Hospital, single center	Hospital, multiple center	Hospital, multiple center (n = 38)	PICU, single center
Country of study	South Africa, Cape Town	25 healthcare facilities in 6 different Sub-Saharan countries <sup>a</sup>	South Africa, Tshwane district	Tunisia
Inclusion start date	17 April 2020	1 March 2020	31 October 2021	23 June 2021
Inclusion end date	24 July 2020	31 December 2020	11 December 2021	16 August 2021
Period covered, months	3	10	1.5	2
Age children included	0–13 years	0–19 years	0–13 years detailed clinical data	0–15 years
Age, years	4.0 (0.2–3.6)	5.9 (1.7–11.1)	4.2 ± 4.1	47 days (6.5–77)
• <1	48.4		35%	
• 1 to 5	33.9		28%	
• 5–9	17.7 <sup>c</sup>		25%	
• 10 to ≤ 13			12%	
Male, %	56.5%	52.4%	56%	46%
Black African ethnicity	Not reported	>90%	89%	Not reported
SARS-CoV-2 test positive		Not reported		Not applicable
• Incidental	16.1%		36%	
• Contributory	Na		20%	
• Causative	82.3%		44%	
Comorbidities	46.8%	Not reported	51%	None
TB	3.6%	4.1%	Not specified	
HIV exposure	40.6%	Not reported	5%	
HIV infection	3.2%	3.2%	4%	
Clinical symptoms		Not reported		
• Fever	35.5%		46%	95%
• Cough	35.5%		40%	25%
• Diarrhea	19.4%		20%	40%
• Shortness of breath or difficulty breathing	32.2%		22%	Not reported
• Seizures	8.1%		20%	Not reported
• Skin rash	9.7%		3%	Not reported
Laboratory findings	Only reported in COVID illness	Not reported		
• CRP, normal range <10 mg/L	13.5 (2.0–43.8)		40.3 (0–502.0)	12.5 (3.5–54.7)
• White blood cell count, normal range 3.90–10.20 × 10 <sup>9</sup> /L	12.5 (9.5–20.8)		10.5 (0.1–29.0)	
• Platelets, normal range 180–440 × 10 <sup>9</sup> /L	406 (227–544)		318.0 (38.0–795.0)	272 (239–360)
PICU admission (%)	23.5%	15.0%	5%	100%
Ventilated (%)	9.8%	7.8%	5%	85%
Oxygen therapy (%)	49.0%	34.6%	20%	30%
Duration of hospitalization, days	5.0 (2.0–9.0)	9.0 (5–16) <sup>d</sup>	2 (1–3)	10 days (5–19) <sup>e</sup>
Mortality, %	2.0%	7.9%	3% <sup>b</sup>	20%

CRP, C-reactive protein; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TB, tuberculosis.

<sup>a</sup>Part of data vd Zalm *et al.*

<sup>b</sup>Considered due to complex underlying copathology.

<sup>c</sup>For children >5 years (groups combined).

<sup>d</sup>For children recovered (not died).

<sup>e</sup>In PICU.

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The case definitions used by the United States Centers for Disease Control and Prevention (CDC) and the WHO vary slightly but the CDC case definition requires the child to have severe symptoms requiring hospitalization [23]. Both case definitions include fever, elevated inflammatory markers, at least two signs of multisystem involvement, evidence of SARS-CoV-2 infection or exposure, and exclusion of other potential causes. These case definitions are likely to change as high seroprevalence of SARS-CoV-2 will not allow for differentiation between children.

Five cohort studies describe 251 children with MIS-C from four countries, South Africa, Nigeria, Kenya and Egypt, with most data coming from South Africa (Table 2) [21<sup>■</sup>,24<sup>■</sup>–27<sup>■</sup>]. The median age of children across the studies was 4.0–7.5 years as opposed to 9 years in the USA [28]. In the USA, 24.5% of children were <5 years old age. Two cohorts reported the number of children <5 years, 59% and 39.3% in Durban and Nigerian, respectively. A decline in the age of children diagnosed with MIS-C was seen over time, with the youngest children presenting during the Omicron wave. A male majority was noted in four of the studies. The clinical presentation of MIS-C was generally similar in African children compared to other reports with rash, abdominal pain, conjunctivitis, tachycardia and hypotension being common. Altered levels of consciousness were reported in 34% of children from Durban, South Africa and coma in 44.4% of Egyptian children, which was associated with shock.

Similarly, CRP, ferritin, hemoglobin, neutrophil count, cardiac markers and coagulation markers are markedly deranged in African children with MIS-C.

Cardiac abnormalities, particularly ventricular dysfunction, were common, but echocardiography was not performed in all children. Hospital stay was longer than the reported five days from the USA, with the shortest median stay from Cape Town (7 days) and the longest, 18 days from Egypt. Children from Durban and Egypt had high mortality, 20.6 and 33.3%, respectively. In both studies, children that died had higher serum ferritin, and liver enzymes were higher in Egyptian children. Data from high-resource countries have estimated mortality of 2% and overall good long-term outcomes [29,30].

No prospective treatment data is available for MIS-C, and it is unclear whether intravenous immune globulins (IVIGs) work better alone or in conjunction with glucocorticoids. In addition, IVIG is expensive, and availability is limited in many African regions. Therapy in African studies did not always include IVIGs, with remarkably low use in the report from Kenya [26<sup>■</sup>]. The best available treatment study did not show the superiority of

IVIGs alone compared to glucocorticoids alone [31]. Prospective randomized treatment studies designed for LMICs are urgently needed. The Nigerian study showed normal echocardiogram and electrocardiogram findings in all patients assessed at six months follow-up; however, only 28.5% of children were assessed [25<sup>■</sup>]. None of the other African studies reported long-term outcomes.

## LONG-CORONAVIRUS DISEASE IN CHILDREN

Although during the first part of the pandemic, the attention of public authorities and scientific committees was focused on the acute phase of SARS-CoV-2 infection. In the last year, after the massive vaccination campaign and the emergence of clinically milder variants, the evaluation and characterization of the emerging long-COVID condition have become more critical. Long-COVID is a heterogeneous multisystemic condition with signs and symptoms that persist, develop, or fluctuate after SARS-CoV-2 infection [32,33<sup>■</sup>]. In October 2021, the WHO proposed a clinical definition for post-COVID-19 through a Delphi consensus that requires symptoms lasting at least two months, cannot be explained by an alternative diagnosis, affects everyday functions, and occurs three months from the onset of COVID-19 [34]. Differently the National Institutes of Health (NIH) also define long-COVID as postacute symptoms with a different time frame of four weeks [35]. In February 2022, the National Institute for Health and Care Excellence (NICE) published a guideline defining long-COVID as signs and symptoms that continue or develop after acute COVID-19—dividing by time in ongoing symptomatic (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) [36]. The definition encompasses a broad range of symptoms, including anatomical complications of COVID-19 (pulmonary fibrosis, myocardial dysfunction), mental health conditions, and more subjective, non-specific symptoms such as postviral chronic fatigue syndrome [37].

To our knowledge, no reports have been published on long-COVID in African countries. Most published research on long-COVID comes from adult literature, with limited data on pediatric populations. Estimates of the prevalence of long-COVID vary, partly because these definitions encompass a broad range of symptoms, including anatomical complications of COVID-19 (pulmonary fibrosis, myocardial dysfunction), mental health conditions, and more subjective, nonspecific symptoms such as postviral chronic fatigue syndrome. The importance of lower respiratory tract infections on child lung health is increasingly acknowledged, but little is still

**Table 2.** Summary of findings of published MIS-C cohorts in Africa

	South Africa, Cape Town [21 <sup>***</sup> ]	South Africa, Durban [24 <sup>***</sup> ]	Nigeria [25 <sup>***</sup> ]	Kenya [26 <sup>***</sup> ]	Egypt [27 <sup>***</sup> ]
Number included, N	129	29	28	20	45
Inclusion start date	1 May 2020	1 June 2020	10 July 2020	1 August 2020	February 2021
Inclusion end date	31 March 2022	30 April 2021	30 July 2021	31 August 2021	31 January 2022
Period covered, months	22	10	12	12	11
Age children included	0–13 years	0–13 years	0–13 years	0–18 years	0–16 years
Age, years	6.85 (3.39–9.28)	4.6 ± 3.8 [1]	7.5 (2.3–9.4)	4.0 (1.7–7.4)	4.0 (1.3–10.0)
Male, %	53.5%	45.0%	64.5%	70.0%	53.3%
Black African ethnicity	51.2%	86%	Not explicitly reported	85.5%	Not explicitly reported
SARS-CoV-2 PCR positive (%)	13.3%	55%	39.3%	20% (1/5 tested)	62.2%
Comorbidities	21.5%	28%	Not reported	25%	0%
Clinical symptoms					
• Fever	100%	100%	100%	90%	100%
• Mucocutaneous	83.7%	65%	89.3%	65.0%	17.8%
• Gastrointestinal	59.7%	59%	75%	Not reported	31.1%
• Respiratory	Not reported	41%	60.7%	Not reported	64.4%
• Neurological	28.7%	34%	32.1%	Not reported	48.9%
• Renal	29.5%	41%	32.1%	15.0%	11.1%
ECHO performed	100%	69%	100%	30%	100%
ECHO abnormal	70.9%	50%	46.4%	85%	37.7%
• Coronary artery abnormality	7.8%	0	46.4%	33.3%	2.2%
• Ventricle dysfunction	Median ejection fraction 59% (IQR, 47–65) <sup>a</sup>	Not reported	39.3%	66.7%	33.3%, not specified
Laboratory findings					
• CRP, normal range <10 mg/l	213 (127–302)	181 (106–233)	142 (87.8)	68.2 (19.9–143.0)	45 (15–93)
• Ferritin, normal range 7–84 ng/l	552 (287–1020)	631 (226–1593)	Only 2 patients tested	Not reported	500 (327–599)
• White blood cell count, normal range 3.90–10.20 × 10 <sup>9</sup> /l	16.5 (12.0–23.5)	12 (9.1–21.3)	25.2 (5.9–55.0)	9.8 (8.1–13.2)	73 (67–77)
• Neutrophil count, normal range 1.7–5.0 × 10 <sup>9</sup> /l	11.7 (7.4–17.9)	Not reported	Not reported	5.3 (3.9–8.4)	6.7 (4.2–9.1)
• Neutrophil ratio	Not reported	Not reported	77.5% neutrophils	Not reported	Not reported
• Lymphocytes, normal range 1.90–4.30 × 10 <sup>9</sup> /l	1.3 (0.8–2.6)	1.4 (1.1–2.1)	25.2 (range 5.9–55.0)	3.3 (1.8–5.18)	1.8 (1.3–2.7)
• Platelets, normal range 180–440 × 10 <sup>9</sup> /l	193 (144–296)	133 (78–312)	581 (range of 218–1200)	325.5 (236.0–426.0)	230 (141–413)
• Hemoglobin, normal range 11.2–14.5 g/dl (6–12 years)	Not reported	Not reported	Not reported	11.5 (9.6–12.2)	10.3 ± 1.8 [1]
• Anemia as per national reference ranges	Not reported	Not reported	17/28 (60.7%) HB <10 g/dl	Not reported	Not reported
Treated with IVIG (%)	Not reported	72.0%	60.7%	10.0%	100%
Ventilated (%)	Not reported	34.0%	3.5%	5.0%	51.1%
Inotrope support (%)	33.3%	52.0%	17.8%	5.0%	57.8%
Duration of hospitalization, days	7 (6–10)	11 (7–19)	11.1 ± 5.7 [1]	Not reported	18 (11–23)
Mortality, %	0.8%	20.6%	0	0	33.3%

Data are presented as median values with interquartile range (IQR), or proportions with percentage, unless stated otherwise in the Table [mean with standard deviation (SD)].

CRP, C-reactive protein; IVIG, intravenous immunoglobulins; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

<sup>a</sup>Where multiple symptoms and features in the same system was mentioned the most prevalent is referenced.

known about the impact of early-in-life SARS-CoV-2 infection on long-term lung health in children, especially in children with other underlying illnesses affecting the lungs.

In a recent retrospective cohort study of electronic health records of 659 286 children <21 years

of age (59 893 with a SARS-CoV-2 infection), the incidence of ≥1 symptom or syndrome/condition or use of medication between COVID- positive and COVID- negative groups was 3.7% [95% confidence interval (CI) 3.2–4.2], suggesting a minor difference between postviral illness in children that had

COVID-19 and other respiratory infections [38<sup>11</sup>,39<sup>12</sup>]. These findings underline the importance of appropriate control groups (including children with other infections) and, simultaneously, the challenge of distinguishing persistent symptoms due to the pandemic restrictions or COVID-19.

Whether symptoms reported as part of long-COVID are specific to SARS-CoV-2, potentially part of postviral illnesses or are related to the pandemic is unclear. Therefore, the CDC analyzed an extensive medical claims database assessing nine potential post-COVID signs and symptoms and 15 potential post-COVID conditions among 781 419 United States children and adolescents <18 years of age with documented COVID-19 compared with 2 344 257 children without the infection. Symptoms and conditions reported slightly more likely in the COVID-19 group were rare or uncommon such as acute pulmonary embolism, myocarditis and cardiomyopathy, venous thromboembolic event, acute and unspecified renal failure, and type 1 diabetes [40<sup>13</sup>]. Conversely, symptoms and conditions that were less likely in children with COVID-19 included respiratory signs and symptoms, mental health symptoms and conditions, neurological conditions, muscle disorders, and sleeping disorders. Furthermore, a large retrospective cohort study that evaluated neurologic and psychiatric trajectories in COVID-19 patients of any age-matched patients affected by other respiratory infections showed that the increased incidence of mood and anxiety disorders in COVID-19 patients (adults and children) was transient, with no difference with the group of non-COVID respiratory illnesses. However, in the six months after the SARS-CoV-2 infection, children had an increased risk of cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root, and plexus disorders, psychotic disorders, and seizures compared with children any other respiratory infection [41<sup>14</sup>]. Taken together, the data suggest that long-COVID and long-non-COVID illness is similar with different clinical features compared to adults. However, even if rare, the possible consequences can profoundly impact children's quality of life.

Understanding the predisposing factors for this condition represents another critical point. The main risk factors associated with long-COVID in the pediatric population have been identified include older age, female gender, comorbidities (including mostly body mass index  $\geq$ 85th percentile for age and sex and allergic diseases), the number of symptoms at presentation and organs involved [42<sup>15</sup>,43<sup>16</sup>]. However, further research is needed to determine the prevalence and identify

risk factors for long-COVID in African children and adolescents.

The pathogenesis of long-COVID is unknown. So far, different mechanisms have been proposed, including SARS-CoV-2's direct and indirect effects. The hypotheses of the virus's direct effect include a possible viral latency, persistent immune system activation and inflammation with microvascular or endothelial damage [44–46]. As suggested by Lopez-Leon *et al.* [47<sup>17</sup>], since many of the most common long-COVID symptoms are also associated with dysautonomia, it has been hypothesized that these direct infection effects could lead to the dysfunction of the sympathetic and/or parasympathetic autonomic nervous system. The hypothesis for the indirect effects of the pandemic is linked to posttraumatic stress and social isolation [33<sup>18</sup>]. Clarifying this point will help to understand the difference between long-COVID and other postviral syndromes and will allow for developing targeted intervention, prevention and management guidelines. Understanding how pediatric vaccinations and the emergence of new variants will influence the prevalence and the burden of post-COVID sequelae is pivotal. Recent studies in adults suggest that vaccines are associated with reducing the risk of long-COVID in adults [48]. However, only a few studies on children reported the percentage of vaccinations [47<sup>17</sup>]. Since COVID-19 remains predominantly an asymptomatic or mild infection in the pediatric population understanding the incidence and burden of sequelae is essential to balance risks and benefits for decisions on COVID-19 vaccines for children, especially in more vulnerable groups [37,49<sup>19</sup>,50]. This is especially important in Africa as vaccine uptake is low, and not all vaccines have been approved for use in young children by African regulating authorities.

## CONCLUSION

Overall, the presentation and outcomes of acute SARS-CoV-2 and MIS-C differ in African children, with higher morbidity and mortality rates than in other high-resource settings. In general, access to diagnostic tests, specific drugs, and intensive care is limited in most African countries due to high costs and the availability of resources. This, in combination with a high prevalence of underlying comorbidities and concurrent endemic infections, might explain worse outcomes. Considering the differences seen in the severity of the disease and short-term outcomes, there is an urgent need to establish long-term outcomes in children with COVID-19 and MIS-C in African children, including lung health assessment.

Despite the increasing literature about long-COVID in children, there is still a significant gap in knowledge in Africa, which accounts for a large proportion of pediatric COVID-19 cases globally. More resources and funding are needed in Africa and other LMICs, to fill this important gap. The limited healthcare system resources, high prevalence of infectious diseases, and malnutrition limit the application of interventions already developed in HICs [51]. Future research perspectives on long-term outcomes must consider a standardized approach, scalable in different socio-economic settings and populations, to compare the effect of these sequelae in different populations and the outcomes of different interventions.

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### Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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This global systematic review includes data of 216 countries. Among the 3,788 global pediatric COVID-19 deaths, 91.5% of deaths were reported from low- and middle-income countries (LMIC), while 83.5% of pediatric population from all included countries were from LMIC. The overall case fatality rate was significantly higher in LMICs (0.24%) than in high-income countries (0.01%).

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