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Clinical Experience With Severe Acute Respiratory Syndrome Coronavirus 2–Related Illness in Children: Hospital Experience in Cape Town, South Africa

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(See the Editorial Commentary by Marais on pages e945-7.)

Background. Children seem relatively protected from serious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related disease, but little is known about children living in settings with high tuberculosis and human immunodeficiency virus (HIV) burden. This study reflects clinical data on South African children with SARS-CoV-2.

Methods. We collected clinical data of children aged <13 years with laboratory-confirmed SARS-CoV-2 presenting to Tygerberg Hospital, Cape Town, between 17 April and 24 July 2020.

Results. One hundred fifty-nine children (median age, 48.0 months [interquartile range {IQR}, 12.0–106.0 months]) were included. Hospitalized children (n = 62), with a median age of 13.5 months (IQR, 1.8–43.5 months) were younger than children not admitted (n = 97; median age, 81.0 months [IQR, 34.5–120.5 months]; $P < .01$.). Thirty-three of 159 (20.8%) children had preexisting medical conditions. Fifty-one of 62 (82.3%) hospitalized children were symptomatic; lower respiratory tract infection was diagnosed in 21 of 51 (41.2%) children, and in 11 of 16 (68.8%) children <3 months of age. Respiratory support was required in 25 of 51 (49.0%) children; 13 of these (52.0%) were <3 months of age. One child was HIV infected and 11 of 51 (21.2%) were HIV exposed but uninfected, and 7 of 51 (13.7%) children had a recent or new diagnosis of tuberculosis.

Conclusions. Children <1 year of age hospitalized with SARS-CoV-2 in Cape Town frequently required respiratory support. Access to oxygen may be limited in some low- and middle-income countries, which could potentially drive morbidity and mortality. HIV infection was uncommon but a relationship between HIV exposure, tuberculosis, and SARS-CoV-2 should be explored.

Keywords. COVID-19; children; respiratory virus infections; MIS-C; sub-Saharan Africa.

Accumulating data show that children and adolescents are relatively protected from severe coronavirus disease 2019 (COVID-19), and the majority are asymptomatic or have mild disease [1, 2]. When severe disease does occur in young children and adolescents, the case fatality rates remain low. To date, data on COVID-19 in children in low- and middle-income countries (LMICs) and sub-Saharan Africa in particular are sparse, and results from China, Europe, and North America may not be directly applicable [1–4].

Compared to well-resourced settings, the under-5 pneumonia mortality rate is significantly higher in sub-Saharan Africa [5, 6]. The reasons for this include a high prevalence of tuberculosis (TB), human immunodeficiency virus (HIV), other infectious diseases, and other poverty-related illnesses, in particular malnutrition [6, 7]. Risk factors associated with poor outcomes in pneumonia could potentially have an important impact on COVID-19 outcomes. Crowding and poor housing may increase the disease burden, and delayed access to care for the underprivileged population may lead to higher morbidity and mortality. COVID-19 may therefore impact children in sub-Saharan Africa differently [5, 8].

South Africa is the epicenter of the COVID-19 pandemic in sub-Saharan Africa over the last months, with Cape Town as the initial epicenter [9, 10, 11]. Of the first 116 adult patients with COVID-19 illness admitted to a hospital in Cape Town, 24 (21%) were HIV infected, 4 patients had TB at admission, and 9 had history of prior TB [12]. In 2018 there were approximately

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450 000 people living with HIV in the Western Cape, including about 13 000 children <15 years of age. In that same year there were an estimated 56 000 new TB cases, with around 40% of TB cases also coinfected with HIV [13]. Comparable analysis for children living in a setting with a high burden of TB and HIV is not available. We hypothesize that COVID-19 illness in children living in a setting with a high burden of TB and HIV might be more severe due to high prevalence of underlying infectious diseases and poor nutrition. This study reflects the clinical experience at the pediatric department of a major public hospital in Cape Town, South Africa.

MATERIALS AND METHODS

We present routine care data from an observational cohort of children aged 0–13 years with a laboratory-confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presenting to Tygerberg Hospital (TBH). We defined laboratory confirmation as a positive test for SARS-CoV-2 on real-time reverse-transcription polymerase chain reaction (rRT-PCR) on a respiratory sample. We excluded infants born diagnosed in the neonatal service and children diagnosed with multisystem inflammatory syndrome (MIS-C) who did not have a positive rRT-PCR. We included data from 17 April to 24 July 2020. At TBH, the first confirmed positive SARS-CoV-2 rRT-PCR in a child was on 17 April 2020 [14].

Setting

TBH is a hospital in Cape Town providing secondary and tertiary care. As infections increased and community spread accelerated, the case definitions and indication for testing were adjusted according to the local prevalence and testing capacity (Supplementary Figure 1). Pulse oximetry measurement of <94% or less is used as a cutoff for oxygen supplementation. At TBH, children receive noninvasive respiratory support (NIRS) via heated humidified high-flow nasal cannula oxygen (HFNO) via the Optiflow system or nasal continuous positive airway pressure (CPAP) via variable flow Fisher-Paykel simple CPAP system in designated pediatric ward high-care areas, as intensive care spaces are limited. N95 respirators, visors, and disposable gowns and gloves were used when managing these patients.

SARS-CoV-2 Molecular Testing

Total nucleic acid content was isolated using the Nuclisens Easymag system (bioMérieux, Marcy l'Etoile, France) and the NIMBUS automated extraction system (Seegene, Seoul, Republic of Korea). SARS-CoV-2 RT-PCR testing was performed with the Allplex 2019-nCoV assay (Seegene) at the Division of Medical Virology, Stellenbosch University, and the National Health Laboratory Service Tygerberg. This assay detects 3 genes (E, RdRP, and N) and an internal control in a multiplex PCR reaction. During short periods of reagent shortage, an in-house SARS-CoV-2 PCR was performed using the primers described by Corman and colleagues [15]. The manufacturers' cycle threshold (Ct) cutoff values for positive tests were used.

Data Collection and Definitions

Children with a positive SARS-COV-2 test were identified from the hospital record-keeping systems. We collected data from the routine screening documentation used at the testing areas as per the National Department of Health, the paper-based clinical records, and electronic clinical records, as well as records from the laboratory data system for hospitalized children. Images were reviewed on the picture archiving and communication system and chest radiographs (CXR) were evaluated by a pediatric pulmonologist.

Weight-for-age *z* scores (WAZ) were calculated using the World Health Organization child growth standards for children up to 10 years of age. For children older than 10 years, weight-for-age percentiles were determined with the Centers for Disease Control and Prevention calculator.

Data Analysis

Deidentified data were entered into a RedCap database and analyzed using SPSS software version 26 (IBM SPSS, Chicago, Illinois). Descriptive statistics were used to describe the characteristics of the children with laboratory-confirmed COVID-19 for both inpatients and outpatients and the different age groups. Pearson χ^2 test was used to compare the differences between inpatients and outpatients and the different age groups. The Yates continuity correction was used if the expected cell size was <5. Nonparametric tests were used to compare differences between the age groups and continuous/dichotomous variables (Kruskal-Wallis test/Mann-Whitney *U* test).

Ethical Considerations

The Human Research Ethics Committee (HREC N20/04/013_COVID) of the Faculty of Health Sciences, Stellenbosch University, South Africa, approved this study. The data were entered without patient identifiers using only routinely collected data. A waiver of consent for this process was obtained.

RESULTS

Between 17 April and 24 July 2020, 1126 SARS-CoV-2 PCR tests were performed on children aged 0–13 years, among whom 159 (14.1%) tested positive for SARS-CoV-2. A slight male predominance was noted in both the children needing hospitalization (n = 35/62 [56.5%]) and children who were not admitted (n = 53/97 [54.6%]) (Table 1). The median age of all children was 48.0 months (interquartile range [IQR], 12.0–106.0 months); hospitalized children were significantly younger with a median age of 13.5 months (IQR, 1.8–43.5 months) compared with children who were not admitted (median age, 81.0 months [IQR, 34.5–120.5 months]; $P < .01$.). Forty-one of

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Table 1. Characteristics of Inpatient and Outpatient Children With Positive Severe Acute Respiratory Syndrome Coronavirus 2 Molecular Test

Characteristic	No.	All (N = 159)	Outpatients (n = 97)	Inpatients (n = 62)	*P* Value
Sex, male	159	88 (55.3)	53 (54.6)	35 (56.5)	.87
Age, mo, median (IQR)	159	48.0 (12.0–106.0)	81.0 (34.5–120.5)	13.5 (1.8–43.5)	<.01
Age group	159				<.01
0–3 mo		23 (14.5)	4 (4.1)	19 (30.6)	
3–12 mo		18 (11.3)	7 (7.2)	11 (17.7)	
1–5 y		46 (28.9)	25 (25.8)	21 (33.9)	.01
>5 y		72 (45.3)	61 (62.9)	11 (17.7)	
Comorbidities					
Any comorbidities	159	33 (20.8)	4 (4.1)	29 (46.8)	NA
Prematurity		…	NR	8 (12.9)	
Hematology		2 (1.3)	0	2 (3.2)	
Oncology		6 (3.8)	1 (1.0)	5 (8.1)	
HIV infection		2 (1.3)	…	2 (3.6)	
Tuberculosis		2 (1.3)	…	2 (3.2)	
Cardiac		2 (1.3)	…	2 (3.2)	
Gastrointestinal		2 (1.3)	…	2 (3.2)	
Asthma		4 (2.5)	3 (3.1)	1 (1.6)	
Other		7 (4.4)	…	7 (11.3)	
HIV exposed	32	…	NR	13 (40.6)	NA
Symptoms					
Symptomatic	159	81 (50.9)	70 (72.2)	51 (82.3)	.20
Cough	159	72 (45.3)	58 (59.8)	22 (35.5)	.04
Fever/ history of fever	159	50 (32.1)	31 (32.0)	22 (35.5)	.73
Sore throat	88[a]	18/88 (20.5)	16/72 (22.2)	2/16 (12.5)	.03
Tight chest	159	27 (17.0)	7 (7.2)	20 (32.2)	<.01
Gastrointestinal symptoms					
Abdominal pain	16[a]	…	NR	10/16 (62.5)	
Diarrhea	159	22 (13.8)	10 (10.3)	12 (19.4)	.03
Vomiting	159	18 (11.3)	2 (2.1)	15 (24.1)	<.01
Anosmia or ageusia	88[a]	9/88 (10.2)	9/72 (12.5)	0	
Headache	88[a]	15/88 (17.0)	14/72 (19.4)	1/16 (6.3)	
Convulsions	159	5 (3.1)	0	5 (8.1)	
Rash[b]	159	6 (3.8)	0	6 (9.7)	

Data are presented as No. (%) unless otherwise indicated. Pearson χ^2 test was used to compare the differences between inpatients and outpatients. The Yates continuity correction was used if the expected cell size was <5.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NR, not recorded.

[a]Corrected for children able to report these symptoms, >3 years of age.
[b]Rashes included 1 petechial rash, 2 macular papular rashes, 1 erythematous rash, and 2 vesicular rashes.

the 159 (25.8%) children were <1 year of age including 30 of 62 (48.4%) of the admitted children.

Preexisting medical conditions were noted in 33 of 159 (20.8%) children: 4 of 97 (4.1%) of the outpatients and 29 of 62 (46.8%) of the admitted children. Of the hospitalized children, 5 (8.1%) had hematological-oncological conditions (1 sickle cell, 1 aplastic anemia), 11 (29.7%) were known to be HIV-exposed but uninfected (HEU), and 8 (5.0%) were known to be premature. Two of the 62 (3.6%) hospitalized children were HIV infected, 2 (1.9%) were recently diagnosed with pulmonary TB and on treatment at the time of SARS-CoV-2 testing, and 1 had recent history of tuberculous meningitis. Asthma and sickle cell anemia each were noted in 1 child each.

Children who did not require admission presented with cough and sore throat more frequently compared with hospitalized children (59.8% vs 35.5%, $P = .04$ and 22.2% vs 12.5%, $P = .03$, respectively). Gastrointestinal symptoms such as diarrhea and vomiting were more frequently reported in the hospitalized children compared with the nonadmitted children (19.4% vs 10.3%, $P = .03$ and 24.1% vs 2.1%, $P < .01$, respectively).

Weight-for-height and body mass index were not available, but as per weight-for-age, the hospitalized children were not malnourished or overweight; for children younger than 10 years, the median WAZ was –0.5 (IQR, –1.6 to 0.3) (Table 2). The weight-for-age percentiles in the older children ranged from the 59th to 76th percentiles.

Ten of the 62 (16.1%) hospitalized children were asymptomatic and were tested for SARS-CoV-2 for other reasons; these children were removed from the clinical analysis (Table 2). Males were predominant in all age groups, but specifically

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Table 2. Characteristics of Symptomatic Hospitalized Children With Positive Severe Acute Respiratory Syndrome Coronavirus 2 Molecular Test, by Age Group

Characteristic	All (N = 51)	All Ages	0–3 mo (n = 16)	>3–12 mo (n = 7)	>1–5 y (n = 18)	>5 y (n = 10)	*P* Value
Sex, male	51	28 (54.9)	10 (62.5)	4 (57.1)	8 (44.4)	6 (60.0)	.63
BCG vaccination history or scar	36	34 (94.4)	14 (87.5)	3 (42.9)	11 (61.1)	6 (60.0)	.53
WAZ, median (IQR)[a]	46	–0.5 (–1.6 to 0.3)	–0.7 (–1.7 to 0.5)	–2.1 (–6.0 to –0.3)	–0.3 (–0.5 to 0.3)	–0.3 (–1.9 to 0.8)	.16
HIV infection	46	1 (2.2)	1 (6.3)	0	0	0	
HEU	32	11 (34.4)	7 (43.8)	1 (14.3)	3 (16.6)	0	.05
Premature	51	7 (13.7)	2 (12.5)	3 (42.9)	1 (5.5)	1 (10.0)	
Hematology	51	1 (1.9)	0	0	1 (5.5)	0	
Oncology	51	2 (3.9)	0	0	1 (5.5)	1 (10.0)	
Clinical presentation							
Respiratory	51	24 (47.1)	11 (52.6)	5 (71.4)	6 (33.3)	2 (20.0)	
URTI		3 (5.9)	0	1 (14.3)	2 (11.1)	0	
LRTI		21 (41.2)	11 (69.8)	4 (57.1)	4 (22.2)	2 (20.0)	
Gastrointestinal		9 (17.6)	1 (10.5)	1 (14.3)	3 (16.6)	4 (40.0)	
Infectious		7 (13.7)	2 (10.5)	0	4 (22.2)	1 (10.0)	
Neurology		6 (11.8)	1 (5.3)	1 (14.3)	3 (16.6)	1 (10.0)	
Cardiovascular		3 (5.9)	1 (5.3)	0	1 (5.5)	1 (10.0)	
Other		2 (3.9)	0	0	1 (5.5)	1 (10.0)	
Hospital course							
Respiratory support	51	25 (49.0)	13 (81.3)	4 (57.1)	6 (33.3)	2 (20.0)	.02
Duration of respiratory support, d, median (min–max)	48	6.0 (1.0–21.0)	7.0 (2.0–21.0)	6.0 (1–13.0)	1.0 (1.0–21.0)	3.5 (1.0–6.0)	.10
NPO_2	51	24 (47.1)	13 (81.3)	3 (42.9)	6 (33.3)	2 (20.0)	.02
NIRS	51	14 (27.5)	7 (43.8)	3 (42.9)	3 (16.7)	1 (10.0)	.14
IPPV	51	5 (9.8)	2 (12.5)	0	2 (11.1)	1 (10.0)	
PICU admission	51	11 (23.5)	3 (18.8)	2 (28.6)	3 (16.7)	3 (30.0)	
Outcome							
LOS, d, median (IQR)	51	5.0 (2.0–9.0)	7.0 (4.0–16.0)	5.0 (1.5–9.5)	3.0 (1.0–5.5)	7.0 (1.5–8.5)	.06
Died	51	1 (2.0)	1 (6.3)	0	0	0	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: d, days; HEU, human immunodeficiency virus exposed but uninfected; HIV, human immunodeficiency virus; IPPV, intermittent positive pressure ventilation; IQR, interquartile range; LOS, length of stay; LRTI, lower respiratory tract infection; NIRS, noninvasive respiratory support; NPO_2, nasal prong oxygen; PICU, pediatric intensive care unit; URTI, upper respiratory tract infection; WAZ, weight-for-age *z* score.

[a]For children older than 10 years (n = 5), we used the Centers for Disease Control and Prevention weight-for-age calculation in percentiles (59.0, 65.8, 68.5, 74.9, 76.0); see text.

in children <3 months of age. Admission diagnosis made by the treating physician and lower respiratory tract infection (LRTI) were the most common COVID-19–related reasons for hospitalization, in 21 of 51 (41.2%) children. Children aged <12 months, and particularly <3 months, were most likely to be admitted with LRTI. Gastrointestinal symptoms were the most common clinical presentation in children >5 years of age, including abdominal pain, diarrhea, and vomiting. Six hospitalized children presented with seizures, which were focal in nature in 3 children. Lumbar punctures were done in all these children and did not suggest meningitis. One child presented with a stroke (right middle cerebral artery), and SARS-CoV-2 PCR was negative on the cerebrospinal fluid of this child. As previously reported [16], 4 children with a positive SARS-CoV-2 test were initially diagnosed with acute appendicitis; 3 had appendectomy and were diagnosed with MIS-C, and in the fourth child MIS-C was excluded clinically. Six of the admitted children had a rash at presentation; 1 child was suspected of measles, but antibody tests were negative in this child. One child had a rash compatible with MIS-C clinical picture.

Laboratory markers showed that C-reactive protein (CRP) and platelet counts were only slightly elevated (Supplementary Table 1). CRP was significantly higher in the oldest age group compared to the youngest children ($P = .04$)

Of 40 children with CXR, 38 (95.0%) had an acceptable-quality CXR (Supplementary Table 1). Of these, 7 (18.4%) had normal CXR, 16 (42.1%) had diffuse alveolar disease, 6 (15.7%) had perihilar infiltrate, 3 (7.9%) had a lobar pneumonia, and 3 (7.9%) had a bronchopneumonia. Twelve of 21 (57.1%) children with LRTI had diffuse alveolar disease on CXR. The proportion of children with LRTI and alveolar disease on CXR was highest in children <3 months of age (8/11 [72.7%]).

Oxygen supplementation was required in 25 of 51 (49.0%) children; 14 (27.5%) required NIRS (HFNO or CPAP) in the wards or in the pediatric intensive care unit (PICU). Both the need for respiratory support as well as the duration of support were highest in children younger than 3 months; in this group, 13 of 16 (81.3%)

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children required respiratory support. The duration of respiratory support was not significantly different between groups.

Intensive care admission was common; 11 of the 51 (21.6%) children, with median age 20 months (IQR, 3.0–62.0 months), needed PICU admission (Table 3). Pneumonia was the indication for admission in 5 children, of whom 4 required intubation. There were no deaths among those admitted to the PICU.

The median hospital length of stay was 5 days (IQR, 2.0–9.0 days). One child died, a 5-week-old HEU infant. He initially presented with only fever and presumed bacterial sepsis and was treated with antibiotics. The SARS-CoV-2 test was positive, but all cultures were negative and infectious markers were low. The baby was discharged after 6 days and presented again 2 days later with abdominal distention. He rapidly deteriorated and died on the same day, likely due to sepsis. The repeat SARS-CoV-2 test was negative.

Systemic steroids were given to 20 of 51 (39.2%) children who were admitted; including 9 of 11 (81.8%) children in the PICU. Thirteen of 51 (25.5%) children initially received steroids for non–COVID-19 indications, including asthma exacerbation, airway obstruction, and leukemia. In 4 of these children, the initial indication was a severe pneumonia with hypoxia; steroids were continued in view of subsequent COVID-19 pneumonia diagnosis. In 5 of 51 (9.8%) children, the initial indication for steroids was a COVID-19 pneumonia, and they were all younger than 3 months. Two children in the oldest age group were given steroids for MIS-C.

In 16 of 51 (30.8%) hospitalized children, a new, incidental, diagnosis was made. Eight children had new cardiovascular diagnoses, including congenital cardiac defects and cardiac arrhythmias. Four were newly diagnosed with TB [17], 1 newly diagnosed with acute myeloid leukemia (AML), and 2 children with clinical rickets confirmed on laboratory assessment. The child with newly diagnosed AML was later also diagnosed with MIS-C after initial chemotherapy; hemophagocytes were confirmed on bone marrow aspiration.

Seven of 51 children (13.7%) had an unscheduled readmission to hospital, including 2 children with worsening of LRTI.

DISCUSSION

We describe our clinical experiences with COVID-19 in South African children. We found that children <1 year of age are disproportionally represented in hospitalization, as 307 of 5168 (6.0%) positive pediatric cases reported in the Western Cape were <1 year of age, but almost 50% of the hospitalizations were in this age group (provincial data personal communication, up to end of July 2020). These children mainly present with severe respiratory illness requiring significant respiratory support. In contrast, Asia, North America, and Europe have shown a propensity of infants and young children to have mild symptoms without the need for respiratory support [2–4]; however, these studies reported that children <1 month of age were at high risk for requiring intensive care admission, especially if viral coinfections were detected. The COVID-19 pandemic in South Africa occurred during the respiratory season, but respiratory viruses were less prevalent during this season due to national lockdown, social distancing, and mask wearing. Overall admission numbers were down by one-third compared to the

Table 3. Summary of Children Who Were Polymerase Chain Reaction Positive for Severe Acute Respiratory Syndrome Coronavirus 2 Admitted to the Pediatric Intensive Care Unit, by Age Group

Admitted to PICU	All (N = 11)	Age <3 mo (n = 3 [27.3%])	Age 3–12 mo (n = 2 [18.2%])	Age >1–5 y (n = 3 [27.3%])	Age >5 y (n = 3 [27.3%])
PICU LOS, d, median (IQR)	4.0 (1.0–8.0)	5.0 (5.0–8.0)	4.5 (2.0–7.0)	4.0 (2.0–4.0)	1.0 (1.0–4.0)
Indication for admission–pneumonia	7 (58.3%)	2 (66.7%)	2 (100%)	3 (100%)	0
Cardiac arrhythmia	2 (16.7%)	1 (33.3%): SVT (1)	0	0	1 (33.3%): SVT with possible myocarditis (1)
Other	3 (25.0%)	0	0		2 (66.7%): Appendicitis/MIS-C (2)
Underlying/concurrent illness	7 (58.3%)	3 (100%): HIV (1) WPW syndrome (1) PDA (1)	2 (100%): Trisomy 21 with AVSD (1) Rickets (1)	2 (50%): Tuberculosis (PTB and TBM) (1) Asthma (1)	0
Respiratory viruses other than SARS-CoV-2[a]	5/6 (83.3%)	1/1 (100%): CMV	2/2 (100%): HRV/CMV (1) RSV (1)	2/3 (66.7%): HRV (1) HRV/CMV (1)	0
Invasive ventilation	4 (33.3%)	1 (33.3%)	0	2 (50.0%)	1 (33.3%)
Noninvasive ventilation	8 (66.7%)	3 (100%)	2 (100%)	2 (50.0%)	1 (33.3%)
Inotropic support	4 (33.3%)	2 (66.7%)	0	0	2 (66.7%)
Steroids	9 (75.0%)	2 (66.7%)	1 (50.0%)	4 (100.0%)	2 (66.7%)

Abbreviations: AVSD, atrioventricular septal defect; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HRV, human rhinovirus; IQR, interquartile range; LOS, length of stay; MIS-C, multisystem inflammatory syndrome in children; PDA, patent ductus arteriosus; PICU, pediatric intensive care unit; PTB, pulmonary tuberculosis; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SVT, supraventricular tachycardia; TBM, tuberculous meningitis; WPW, Wolf-Parkinson-White syndrome.

[a]A full respiratory panel was done in 6 of 12 children.

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same period last year (pediatric TBH statistics). The number of children requiring oxygen and NIRS in the young age group in this cohort is important as the need for oxygen may go unrecognized in LMICs, and access to oxygen may be limited, resulting in increased mortality [7, 8]. Our findings highlight the potential shortcoming and need for widespread implementation of oxygen and noninvasive respiratory support strategies throughout sub-Saharan Africa. We are not able to compare need for oxygen and NIRS in this group to those children with respiratory syncytial virus and other common viral LRTIs.

In 11 of the 62 hospitalized children, a positive SARS-CoV-2 test was positive without the child having symptoms. This is expected as SARS-CoV-2 infection can be seen in asymptomatic individuals [1]. We do not know the proportion of children who have asymptomatic infection, as our study was done in a hospital setting and detection of asymptomatic infections is dependent on testing strategy. In some cases, it is difficult to rule out causality of SARS-CoV-2 detection. Examples in this study include cardiac arrhythmia, focal seizures, or stroke. More data are needed to understand the full spectrum of SARS-CoV-2 disease in children.

Systemic steroids are commonly given in children presenting with a severe pneumonia with hypoxia owing to concern about possible *Pneumocystis jirovecii* pneumonia in our setting. This could potentially have ameliorated the outcomes, especially in the youngest children. We did observe that there is a proportion of children who require readmission to hospital, including some presenting with recurrent respiratory symptoms, and this will need to be followed up [18, 19].

While young children mainly presented with LRTIs, older children had a more varied clinical presentation. There is an increased awareness of gastrointestinal symptoms [16, 20] associated with a positive SARS-CoV-2 test and potentially MIS-C, which was also seen in our cohort [21]. Over the coming months, Africa will potentially see a relatively high number of MIS-C cases due to our racial demographic, and therefore awareness of this group of conditions is very important [21].

Though the numbers are small, unlike in adults [12], HIV infection did not seem to contribute to severe COVID-19 illness, but the proportion of HEU children among the admitted children was higher in the youngest children and the antenatal HIV prevalence in the province, which is estimated around 20% [13, 22]. This may indicate that HEU children may be more vulnerable to severe COVID-19 illness in the first year of life, which is in line with previous reports showing a higher risk for LRTIs in the first year of life in HEU children [22]. Seven children had a recent or current diagnosis of TB in our study; 1 child had a history of tuberculous meningitis, 2 children were on anti-TB treatment at presentation, and an additional 4 children received a new TB diagnosis during this admission. The role of respiratory viruses and specifically COVID-19 in childhood TB is unclear. Concurrent or sequential infections may alter the host response to new pathogens, affecting both innate immunity [23] or the development of acquired immunity [24] against *Mycobacterium tuberculosis* or SARS-CoV-2. More data are needed to determine the possible interaction between TB and SARS-CoV-2.

The majority of the children were vaccinated with BCG. Studies have speculated on the possible protective effect of BCG vaccination, which would be strongest in the first year after vaccination [25], but we saw that children <3 months of age had the most severe respiratory COVID-19 disease despite recent vaccination in almost 90% of these children. More research is needed to elucidate the role of BCG vaccination in children and adults with COVID-related illness.

In a quarter of the admitted children, a new underlying diagnosis was made. This could be partially explained by careful clinical review of each of these cases by an experienced pediatrician. In addition, we speculate that COVID-19 can unmask underlying illness, as SARS-CoV-2 infection in otherwise well children likely results in mild symptoms or asymptomatic carriage. In addition, this should be compared to other viral respiratory tract infections.

The higher CRP and a relative decrease in number of platelets were mostly noted in children >5 years of age. Higher CRP is linked to higher interleukin 6 levels and more severe disease in adults [26]. Older children might have a more pronounced inflammatory response, which is also seen in adults leading to a different clinical presentation, including MIS-C.

The limitations include the relatively small numbers of children and the lack of a control group that presents with other viral respiratory illnesses or concurrent respiratory virus infections, and including the need for oxygen in these different groups. From the children admitted in PICU, 5 of 6 children with pneumonia had a concurrent respiratory virus detected. Viral coinfections are seen in many respiratory illnesses and the clinical relevance is a point of discussion [2]. More data are needed to investigate the role of viral coinfections in children with a positive SARS-CoV-2 test.

Our study shows more severe COVID-19 respiratory illness in especially in the very young children in our setting, which underscores the need for widespread implementation of oxygen and noninvasive respiratory support strategies. The link between COVID-19 and TB and HIV exposure may need further investigation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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