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Abbreviations

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
ART	antiretroviral therapy
AVPU	alert, verbal, pain, unresponsive (conscious level)
bpm	breaths per minute
CI	confidence interval
CRF	case report form
ECMO	extracorporeal membrane oxygenation
HIC	high-income countries
HIV	human immunodeficiency virus
ICU	intensive care unit
ISARIC	International Severe Acute Respiratory and emerging Infection Consortium
LMIC	low- and middle-income countries
NICD	National Institute of Communicable Diseases (South Africa)
SpO_2	peripheral oxygenation saturation
VOC	variant of concern
WHO	World Health Organization

1. Introduction

1.1 Background

Reports of COVID-19 outcomes in children and infants across different regions have been inconsistent. Epidemiological studies have consistently demonstrated that children comprise only around 1–5% of all COVID-19 cases *(1)*. Although all ages and profiles could be affected by COVID-19, studies have demonstrated milder symptoms or no symptoms, and fewer hospitalizations and deaths in infected children (under 20 years) as compared with infected adults *(2-4)*.

A prospective cohort study of 66 neonates infected with COVID-19 in the United Kingdom found that 42% were hospitalized with severe disease and 33% required respiratory support *(3)*. However, only one death was reported, and it was not related to COVID-19. A national cohort study of 898 infants in Saudi Arabia (402 hospitalized with COVID-19) showed that the early neonatal group (0–6 days) had the highest hospitalization rate 80% (72/90), followed by late neonatal (7–27 days) at 57.5% (107/186) and post-neonatal (28–90 days) at 35.9% (223/622) *(5)*. The overall mortality rate was 1.6%, with a higher rate of death among infants in the early neonatal period 4.4% (4/90). On the other hand, a retrospective cohort study of 324 children aged 0–17 years from 17 paediatric hospitals (15 in Canada, one in Costa Rica and one in the Islamic Republic of Iran) showed that 36% of infants (0–11 months) and 64% of older children (1–17 years) were hospitalized for COVID-19. Infants had a shorter length of hospital stay and reduced odds of progressing to severe or critical disease compared with older children *(6)*. The study also reported that all six deaths occurred in children aged 14 months to 9 years with underlying conditions.

Health resource disparity is associated with paediatric COVID-19 mortality. In one study, mortality among children from low- and middle-income countries (LMIC) was 4.0% (n=9041) and that in high-income countries (HIC) was 3.3% (n=3819) *(7)*. Multivariate analysis demonstrated that LMIC (HR = 4.73; 95% CI: 3.16–7.10) as a country income group were significantly associated with increased mortality risk compared with HIC.

The different findings across studies are thought to include factors such as the neonatal period being the highest risk of any disease in the human life course, underlying conditions, testing capacity and underreporting of mild or asymptomatic cases.

Therefore, it would be important to pool data from geographically varied settings to inform on the reasons for such heterogeneity in the existing literature on the burden of COVID-19 among children to make meaningful and consistent deductions. Data have been contributed by Member States, partners and the network of investigators to the WHO Global Clinical Platform for COVID-19 *(8)*. These data were used to investigate the clinical outcome and characteristics of COVID-19, and the associated risk factors among children hospitalized with COVID-19 to inform improvements in public health interventions.

1.2 Objectives

This report describes clinical characteristics and outcomes among children hospitalized with COVID-19. The specific objectives of the analysis were to:

- determine the risk factors for severe disease at hospital presentation with COVID-19 and in-hospital mortality:
  - in children hospitalized with COVID-19;
  - between children and adults to evaluate differences in outcome;
  - between children living with HIV and HIV-negative children; and
  - between children infected by different variants of concern (VOC).

2. Methods

2.1 Data collection tools

Ministries of health, research networks, health facilities and other clinical and epidemiological platforms were invited to contribute anonymized clinical data to the WHO Global Clinical Platform *(8)*.

Data were harmonized to the standardized, multi-language CRF and data dictionary which describe a set of variables to be collected at hospital admission (within 24 hours of admission), on intensive care unit (ICU) admission or transfer, and at hospital discharge or death *(9)*. Variables included demographics, vital signs, underlying conditions, clinical features, laboratory testing, therapeutics, complications during hospitalization and clinical outcomes (discharge, death, transfer to another facility, or remaining hospitalized at the time of data entry). For pregnant people, additional data were collected within 22 days of a live or still birth.

To ensure data quality and consistency across various sources, the data harmonization process was conducted or assisted by the clinical platform team, which provided training to contributors on data entry and standardized data collection procedures. The two largest sources of data were the International Severe Acute Respiratory and emerging Infection (ISARIC) and the National Institute of Communicable Diseases (NICD), South Africa. Data submitted by ISARIC were collected as part of the ISARIC-WHO Clinical Characterization Protocol on CRFs aligned with the WHO platform, available in several languages on the ISARIC website (www.isaric.org). Some sites created locally adapted versions based on the WHO-ISARIC template. Detailed methods of the data collection and curation on the ISARIC platform are available elsewhere *(10)*. Data from NICD were collected through the national DATCOV platform and incorporated through collaborative data harmonization *(11)*.

2.2 Study design and population

All patients admitted to a health care facility with laboratory-confirmed or clinically suspected COVID-19 were eligible for inclusion. Data were extracted from the WHO Global Clinical Platform. For the purposes of this report, the population was classified as paediatric population (under 20 years old) or adult population (20–45 years old). Data collection was retrospective, prospective or both.

Cases were defined as severe or critical, according to a modified definition from the WHO *Clinical management of COVID-19 (12)* if they met one or more of the following: SpO_2 of less than 90%; respiratory rate of more than 30 breaths per minute (bpm) in adults and children over 5 years old, 60 bpm or more in children under 2 months old, 50 or more in children 2–11 months old, and 40 bpm or more in children 1–5 years old; received extracorporeal membrane oxygenation (ECMO); admitted to an ICU; received an inotrope or vasopressor; received oxygen therapy, and either invasive or non-invasive ventilation; systolic blood pressure of less than 70 mmHg in children less than 3 years, of less than 75 mmHg in children 3–5 years and of less than 90 mmHg in children 6 years and above; seizures, confusion or stroke; level of consciousness measured using AVPU scale (P and U components) and Glasgow coma score of less than 8. Cases not meeting any of the above conditions were described as mild or moderate.

The statistical analysis plan is available online *(13)*.

2.3 Statistical analysis

Demographic and clinical characteristics were summarized using appropriate measures of central tendency and dispersion, according to the distribution of each variable along with 95% confidence intervals (CI). For each analysis the denominator represents data that are available. The statistical significance level was set at 0.05.

The two clinical outcomes of interest were in-hospital mortality (deceased versus discharged) and clinical severity (mild or moderate versus severe or critical).

Time-to-event analysis was performed using proportional hazards regression modelling to estimate the hazard of independent risk factors for in-hospital mortality. Survival time was right-censored at 14 days (28 days) for those hospitalized or discharged prior to day 14 (day 28). Risk factors for severe COVID-19 disease at hospital admission were sought by logistic regression. Both models (the proportional hazards model and the logistic regression model) were adjusted for clustering at the country level.

Age for the paediatric population (0–27 days, 28 days–1 year old, 1–4 years old, 5–9 years old, 10–14 years old and 15–19 years old) and adults (20–45 years old) and sex were included in all models *a priori*, irrespective of bivariate analysis, for their clinical importance. Severity at hospital admission was considered in the survival analysis model when it was thought to be on the causal pathway for mortality. Other covariates were considered for inclusion in the model when not highly correlated with other variables using a correlation matrix threshold of > 0.8 and associated with the outcome in the bivariate assessment with $P < 0.10$.

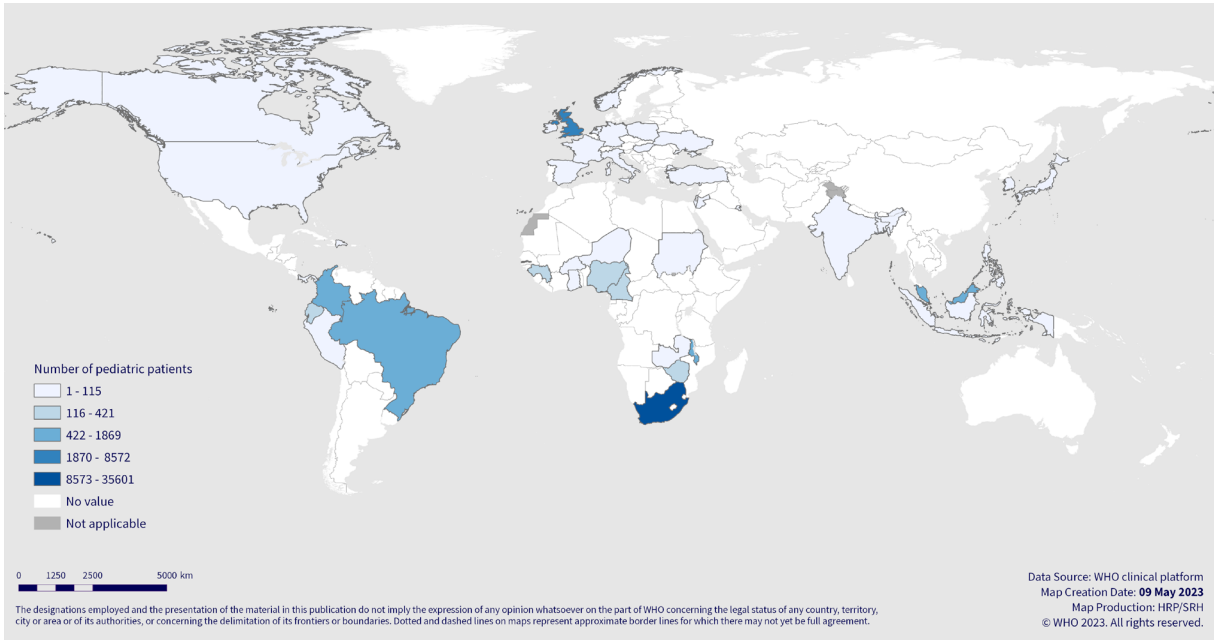
Information on virus sequencing was scarce, therefore we used as a proxy for VOC the patient hospital admission date and country-specific reports on the progression of virus mutations. A variant was considered predominant in the country if it affected more than 90% of the population using GISAID genetic sequencing data (https://gisaid.org) *(14)*. For this analysis data were restricted to variants predominant in most of the 45 countries that contributed data to this report *(15)*.

As a sensitivity analyses, data from high contributing countries will be excluded to assess the stability of estimates. Further data sources and supplementary information are included in the annexes. All analyses were conducted in R version 4.2.2 *(16)*.

3. Results

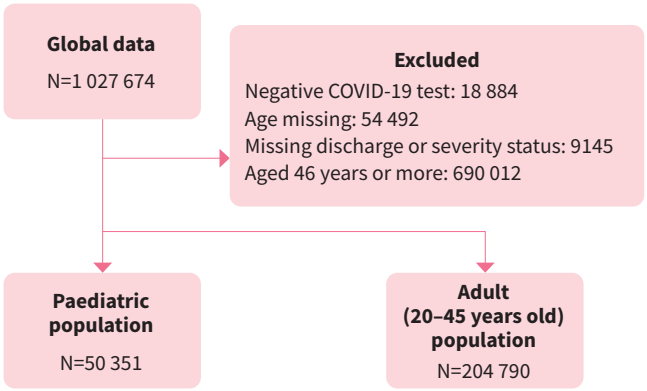
For this report, we conducted analyses on anonymized data from 45 countries, detailing 50 351 children and adolescents aged less than 20 years, with severity and discharge status available. The data were submitted to the WHO Global Clinical Platform for COVID-19 between January 2020 and December 2022. This dataset includes patients admitted to the hospital between January 2020 and November 2022 (see **Figs 1** and **2**).

Fig. 1. Countries contributing clinical data on children aged less than 20 years old to the WHO Global Clinical Platform



Data were available from: Bangladesh, Brazil, Burkina Faso, Cameroon, Canada, Colombia, Democratic Republic of the Congo, Dominican Republic, Ecuador, France, Gambia, Germany, Greece, Guinea, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Jordan, Kuwait, Malawi, Malaysia, Netherlands (Kingdom of the), Niger, Nigeria, Norway, Panama, Peru, Philippines, Poland, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Sudan, Türkiye, Ukraine, United Kingdom, United States of America, Zambia, Zimbabwe.

Fig. 2. Flow of participants through the analysis



Data from the adult population (20–45 years old) were extracted from the platform for patients admitted during the same period as for the paediatric population using the same criteria for a total of 204 790 adult patients to evaluate differences in outcome between children and adults (see **Fig. 2**).

3.1 Demographic characteristics, hospitalization and outcome

For the paediatric population, we found that there were more males than females across most age groups. Specifically, of those less than 1 month old, 53% (N=733) were male. This was also the case for 56% (N=5387) of those aged 1–11 months, 56% (N=6081) of those aged 1–4 years, 56% (N=3549) of those aged 5–9 years and 51% (N=3795) for those aged 10–14 years. However, amongst cases age 15–19 years, only 38% (5611) were male (see **Fig. 3** and **Table S2** for more details).

Fig. 3. **Age distribution of children hospitalized with COVID-19**

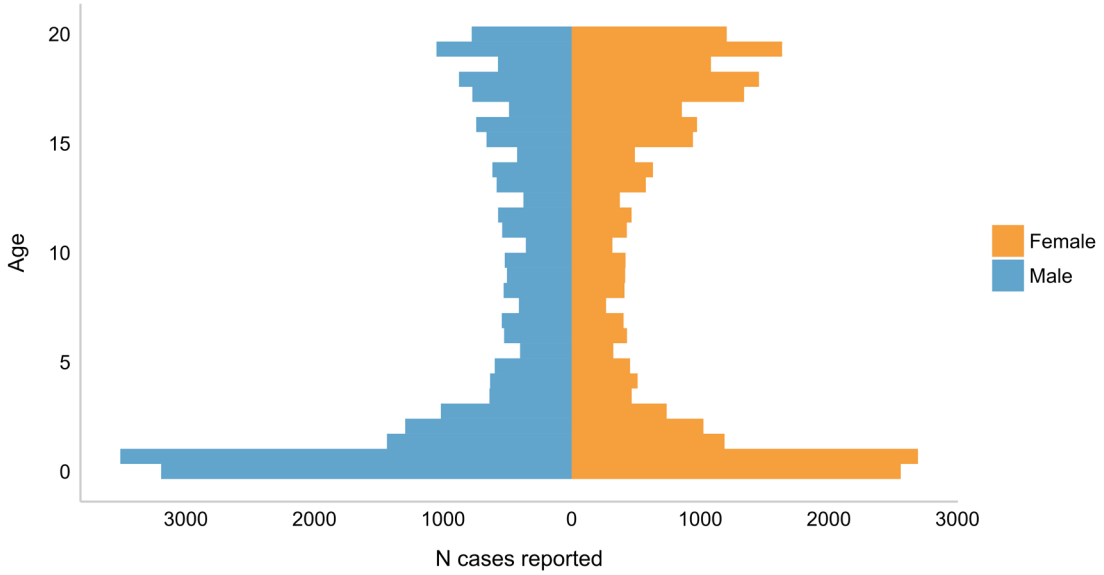
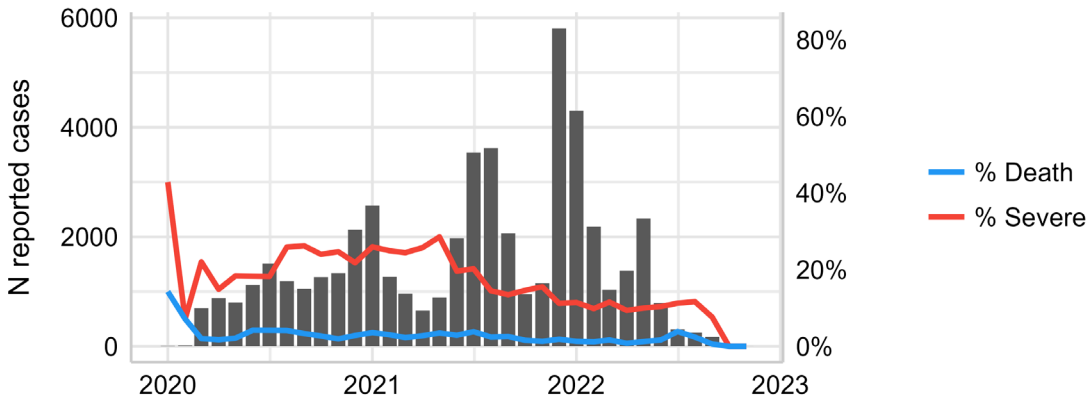


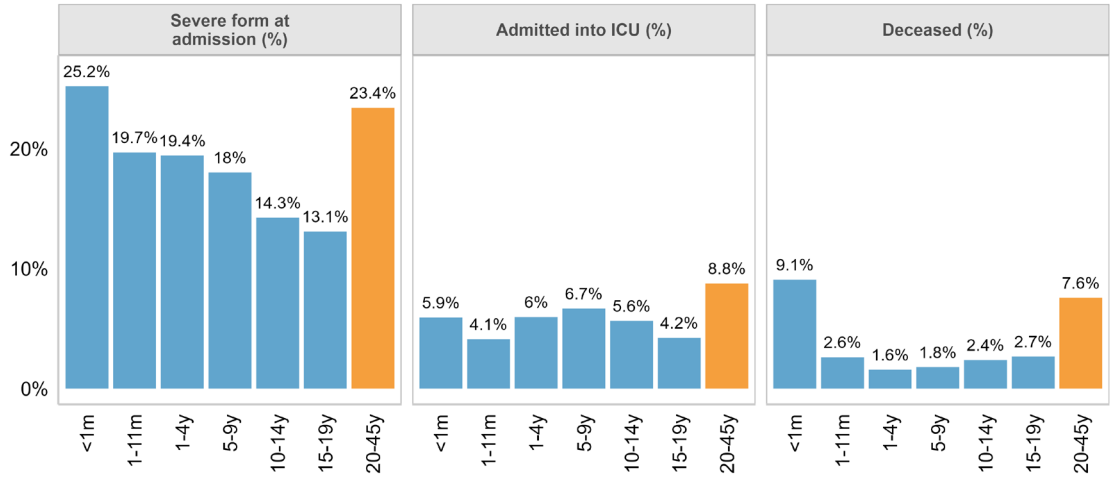
Fig. 4 illustrates the dynamics of children hospitalized with COVID-19, as recorded in the WHO database over 3 years. Four pronounced spikes in hospitalization are apparent: late 2020, mid-2021, late 2021 and mid-2022, with the initial pair coinciding with higher severity rates that lessened during the latter two waves. A declining trend can be observed in the in-hospital mortality rates over this period.

Fig. 4. **Evolution of the number of cases hospitalized during the pandemic from January 2020 to November 2022**



Note: The figure shows the number of cases, the percentage of severe cases, the percentage of deaths during hospitalization, and the progression of these over time.

Fig. 5. **Comparison of COVID-19 illness severity, ICU admission and in-hospital mortality between paediatric patients (blue) and adults (orange)**



3.2 COVID-19 severity and mortality among hospitalized children – relationship with age

Disease severity decreased with increasing age (see **Table 1**). All age groups of children older than 1 month had significantly lower odds of severe disease compared with adults aged 20–45 years, even after adjusting for sex and the presence of underlying conditions like HIV, chronic cardiac disease (not hypertension), diabetes, hypertension and pulmonary disease (inclusive of asthma) (see **Fig. 6a** and **Table S3**). Among paediatric patients, infants presented the highest risk of severe disease with risk compared with adults aged 20–45 years (aOR = 0.98; CI: 0.80–1.20).

Table 1. **Description of severe/critical disease, ICU admission and, in hospital mortality among children**

	Overall N=50 351[a]	<1 month N=1400[a]	1–11 months N=9586[a]	1–4 years N=10 823[a]	5–9 years N=6318[a]	10–14 years N=7503[a]	15–19 years N=14 721[a]	*P*[b]
Severe/critical disease	8482 (17%)	353 (25%)	1888 (20%)	2103 (19%)	1139 (18%)	1070 (14%)	1929 (13%)	< 0.001
ICU admission	1517 (5.1%)	55 (5.9%)	218 (4.1%)	312 (6.0%)	233 (6.7%)	269 (5.6%)	430 (4.2%)	< 0.001
Unknown	20 479	471	4294	5596	2822	2739	4557	
Death	1232 (2.4%)	127 (9.1%)	250 (2.6%)	170 (1.6%)	113 (1.8%)	179 (2.4%)	393 (2.7%)	< 0.001

Notes: [a] n (%); [b] Pearson's Chi-squared test.

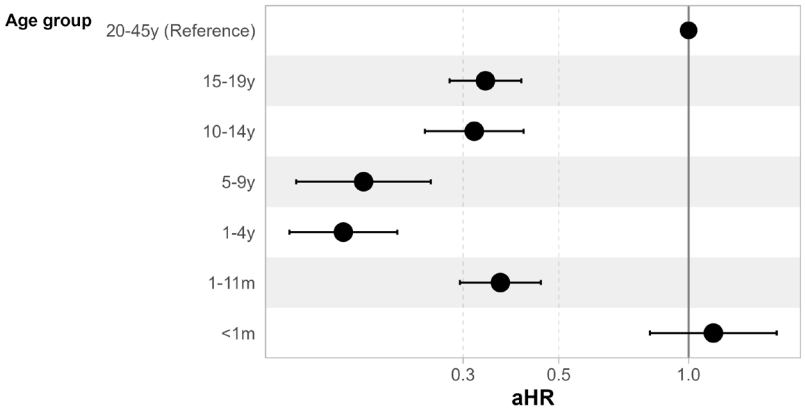
When considering in-hospital mortality within 14 days, children hospitalized with COVID-19 demonstrated a significantly lower adjusted hazard compared with adults after adjusting for sex and the presence of underlying conditions like HIV, chronic cardiac disease, diabetes, hypertension, pulmonary disease (inclusive of asthma), chronic kidney disease and malignant neoplasm (see **Fig. 6b** and **Table S4**). Within paediatric groups, infants had the highest mortality risk, which was comparable with that of adults aged 20–45 years (aHR = 1.14; CI: 0.81–1.60).

A sensitivity analysis including disease severity at admission as a covariate in the Cox proportional hazards mortality model did not change the shape of the association nor the magnitude of the estimated effects (see **Table S5**). The magnitude of the estimated hazard did not significantly differ when data censoring was extended from 14 to 28 days (see **Table S6**).

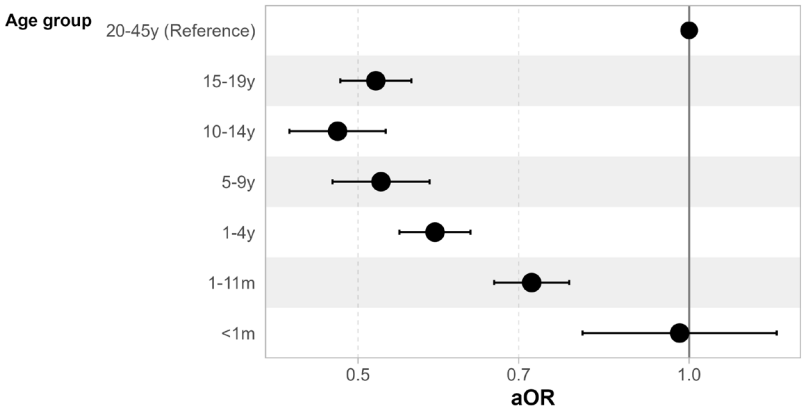
Sensitivity analyses were also performed to compare results with and without the inclusion of data from South Africa that represented 35 601 of 50 351 (71%) of the patients included in our analyses (see **Table S1**). Results of the analysis excluding this data demonstrated a modified shape of association between age and odds of severe disease: all age groups below 10 years old were observed to have higher odds than adults (see **Table S7**). Regarding in-hospital mortality, when excluding South African data, the shape of the association with age remained similar to that observed when analysing the whole dataset. That is, higher hazard ratios were found in younger children, but the difference between children and adults was less pronounced (aHR overall closer to 1, ranging from 0.37; CI: 0.17, 0.77 for children aged from 5–9 years to 0.77; CI: 0.47, 1.25 for young infants) (see **Table S8**).

Fig. 6. Differences in disease severity and in-hospital mortality for hospitalized children with COVID-19 by age group

6a: Severe disease



6b: In-hospital mortality



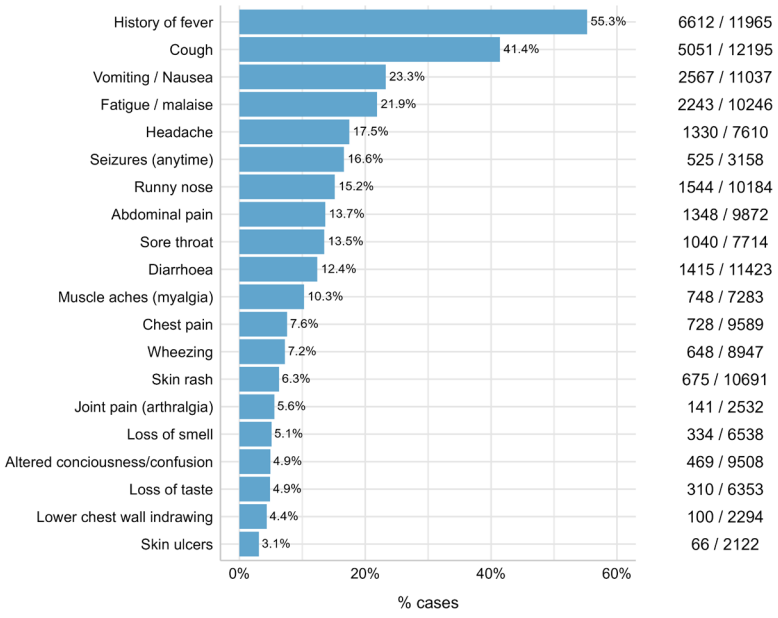
Note: 6a Adjusted odds ratio (aOR) of severe disease; and 6b adjusted hazard ratio (aHR) for in-hospital mortality after adjusting for gender and presence of underlying conditions. 20–45 years is the reference category. Note: logarithmic scale. Circles indicate adjusted ratios and error bars indicate 95% CI for predictors of multivariate mixed effects of logistic regression model.

3.3 Symptoms

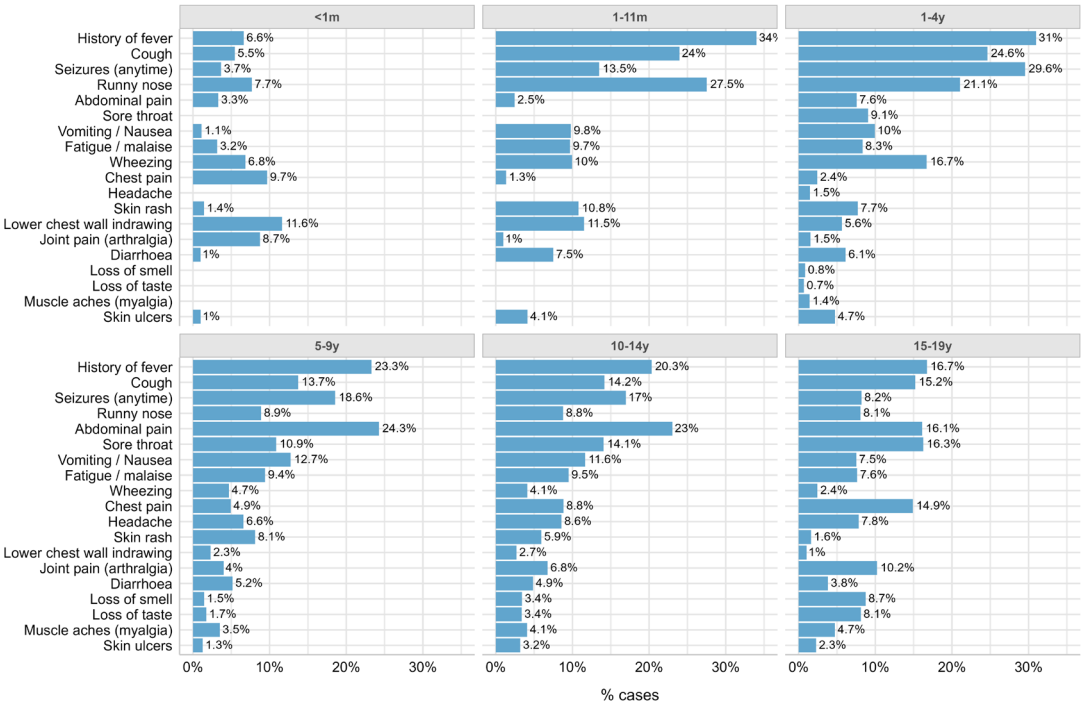
In the paediatric population history of fever was the most frequently reported symptom; observed in 55.3% (6612/11 965) of cases. Among the top 20 symptoms present at hospital presentation, four were respiratory in origin: cough 41.4% (5051/12 195), rhinorrhoea 15.2% (1544/10 184), chest pain 7.6% (728/9589) and wheeze 7.2% (648/8947) (see **Table S9**). However, when stratified by age group, this symptom was more common in children 1–11 months and 1–4 years. In contrast, among those aged 5–9 years and 10–14 years, abdominal pain was more common (see **Fig. 7b** and **Table S9**).

Fig. 7. Frequency of symptoms present in children with COVID-19 at hospital admission

7a: Overall



7b: Stratified by age



Note: Excludes symptoms with < 2% occurrence.

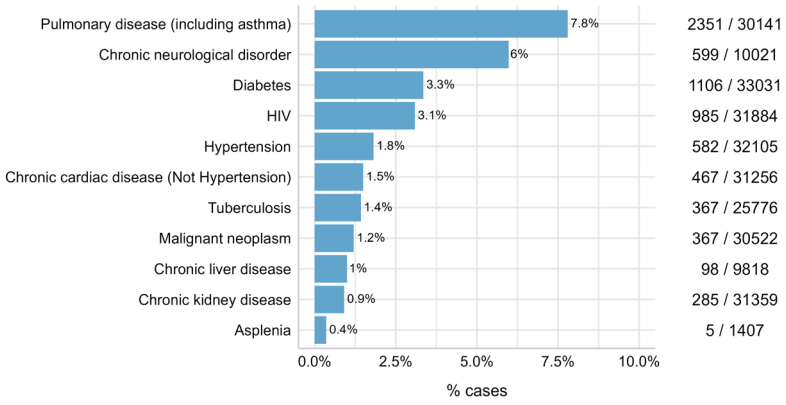
3.4 Underlying conditions

In the paediatric population, underlying conditions are summarized in **Fig. 8** and **Table S10**. Pulmonary disease, including asthma, was the most reported condition at 7.8% (2351/30 141), followed by chronic neurological disorders (6%), diabetes (3.3%) and HIV (3.1%).

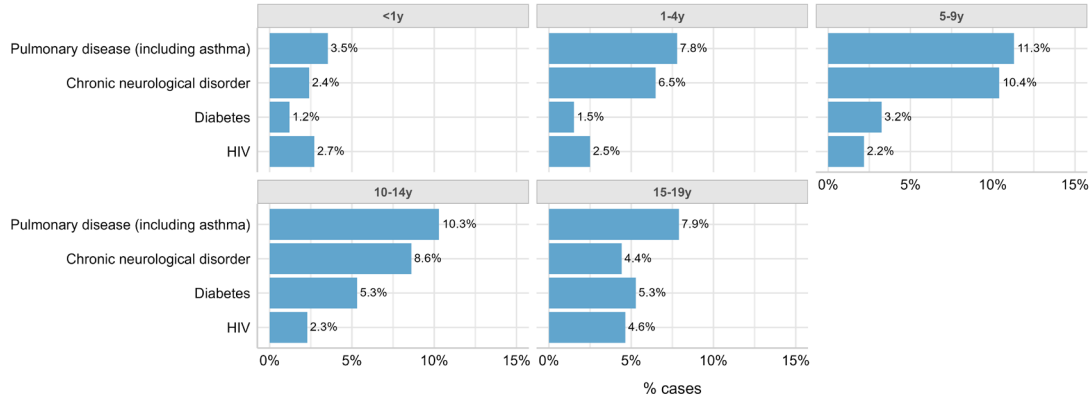
Pulmonary disease was the most predominant underlying condition across all age groups. It was recorded in 3.5% of patients aged < 1 year, 7.8% of those aged 1–4 years, 11.3% of those aged 5–9 years, 10.3% of those aged 10–14 years, and 7.9% of those aged 15–19 (see **Fig. 8b**).

Fig. 8. Frequency of underlying conditions reported among hospitalized children with COVID-19

8a: Paediatric population overall



8b: Paediatric population stratified by age group



In our analysis of the paediatric population, after adjusting for age and sex, we found that the presence of underlying conditions such as HIV (aOR = 2.04; 95% CI: 1.62, 2.57; $P < 0.001$), chronic cardiac disease (aOR = 1.68; 95% CI: 1.32, 2.13; $P < 0.001$), diabetes (aOR = 1.31; 95% CI: 1.07, 1.60; $P = 0.009$), hypertension (aOR = 1.75; 95% CI: 1.36, 2.26; $P < 0.001$) and pulmonary disease (aOR = 1.27; 95% CI: 1.11, 1.45; $P < 0.001$) increased the risk of presenting with severe or critical disease at hospital admission (see **Fig. 9a** and **Table S11**).

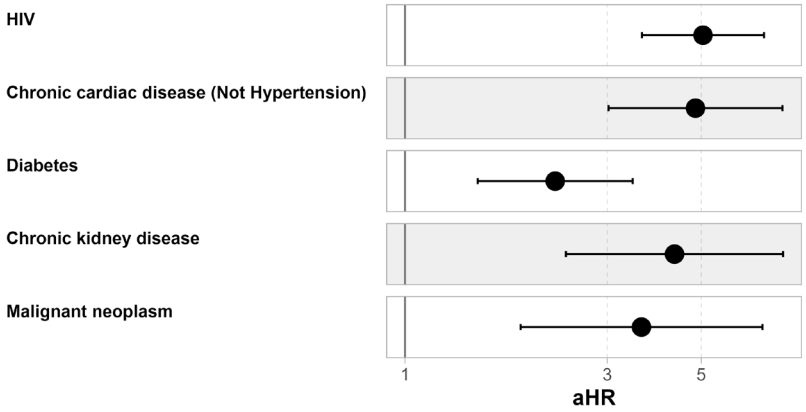
The presence of one or two underlying conditions (aOR = 1.41; CI: 1.30, 1.52; $P < 0.001$) and the presence of three or more underlying conditions (aOR = 1.79; 1.32, 2.42; $P < 0.001$) were associated with increased risk of presentation with severe disease at hospital admission (see **Fig. 10a** and **Table S13**).

Similarly, the risk of 14 days in-hospital mortality was increased in children with HIV (aHR = 5.05; 95% CI: 3.62, 7.03; $P < 0.001$), chronic cardiac disease (aHR = 4.85; 95% CI: 3.02, 7.77; $P < 0.001$), diabetes (aHR = 2.26, 95% CI: 1.48, 3.44; $P < 0.001$), chronic kidney disease (aHR = 4.32; 95% CI: 2.40, 7.80; $P < 0.001$) and malignant neoplasm (aHR = 3.61; 95% CI: 1.87, 6.97; $P < 0.001$) (see **Fig. 9b** and **Table S12**).

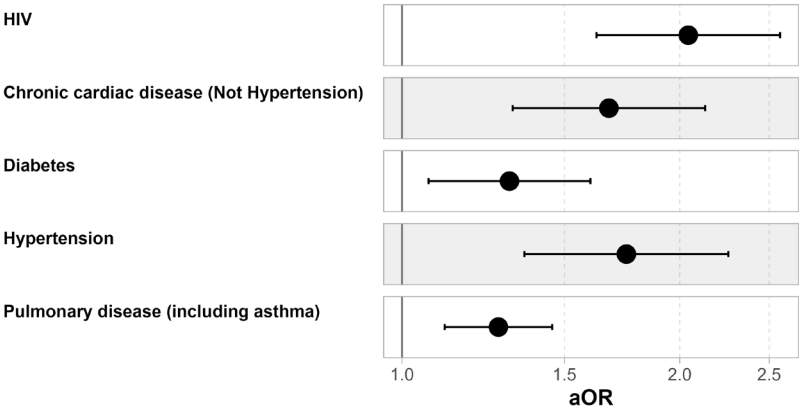
The presence of one or two underlying conditions (aHR = 2.85; 95% CI: 2.39, 3.39; *P* < 0.001) and three or more underlying conditions (aHR = 8.49; 95% CI: 5.48, 13.1; *P* < 0.001) was associated with a higher risk of in-hospital mortality among in the paediatric population (see **Fig. 10b** and **Table S14**).

Fig. 9. Differences in severe disease and in-hospital mortality of hospitalized children with COVID-19 by underlying condition

9a: Severe disease at hospital admission



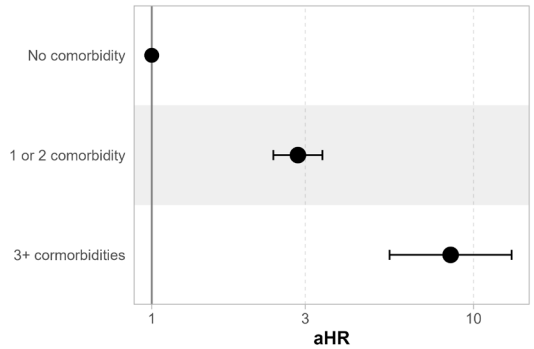
9b: In-hospital mortality



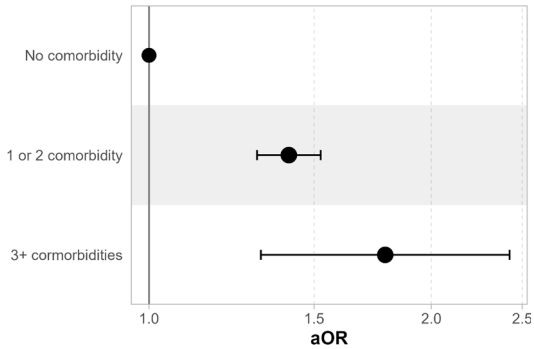
Note: aOR/aHR= adjusted odds/hazard ratio (using a model incorporating age and sex).

Fig. 10. Differences in severe disease and mortality amongst hospitalized children with COVID-19 by comorbidity burden

10a: Severe disease at hospital admission



10b: In-hospital mortality



Note: aOR/aHR= adjusted odds/hazard ratio (using a model incorporating age and sex).

Similar results to our initial analysis, in the paediatric population, of 14-day in-hospital mortality were observed when data censoring was extended to 28 days. These findings are detailed in **Table S15**.

We also reassessed the association of severe disease presentation and presence of underlying conditions when excluding South African data from this analysis. Associations were observed with HIV, hypertension, pulmonary disease (including asthma), malignant neoplasm and chronic neurological disorder. This differed from our primary analysis which also identified chronic cardiac disease (not hypertension) and diabetes as associated with severity at hospital admission but did not find associations with malignant neoplasm and chronic neurological disorder (see **Table S16**).

When evaluating the 14-day in-hospital mortality, underlying conditions were associated with a higher risk, including HIV, chronic cardiac disease, diabetes, chronic kidney disease, malignant neoplasm, pulmonary disease (including asthma) and chronic neurological disorder. When compared with our primary analysis, pulmonary disease (including asthma) and chronic neurological disorder were additional associations found when South African data was excluded, whereas chronic kidney disease was common factor in both analyses (see **Table S17**).

Focusing on South African data, our analysis showed that patients with active tuberculosis were not at higher risk of presenting with severe or critical COVID-19 disease at hospital admission (see Table S18). However, tuberculosis was significantly associated with a higher risk of 14 days in-hospital mortality (aHR = 2.83; 1.67; 4.77, p<0.001) (see **Table S19**).

3.5 Children living with HIV compared to HIV-negative children

Among 50 351 children hospitalized with COVID-19, 63% (N=31 884) had known HIV status (mostly from South Africa), of which, 3% (N=985/31 884) were living with HIV. Females represented 54% (528/981) of children living with HIV hospitalized with COVID-19 (see **Table 2**). Among children living with HIV 3.4% (25/736) were admitted to ICU whilst this proportion was 6.7% (1040/15 533) for HIV negative. Regarding HIV treatment, 82% (415/504) of children living with HIV were on antiretroviral therapy (ART). In-hospital death occurred in 10% (100/985) of children living with HIV compared with 1.7% (519/30 899) of those who were HIV negative.

Table 2. Core demographic characteristics and outcome for hospitalized children with COVID-19, by HIV status

		HIV status		
Characteristic		Positive, N=985[a]	Negative, N=30 899[a]	*P*
Severe		342 (35%)	4957 (16%)	< 0.0001
Death		100 (10%)	519 (1.7%)	< 0.0001
ICU admission		25 (3.4%)	1040 (6.7%)	< 0.0001
	Unknown	249	15 366	
Region	African	844 (86%)	22 366 (72%)	
	Americas	130 (13%)	2264 (7.3%)	
	South-East Asia	1 (0.1%)	96 (0.3%)	
	European	8 (0.8%)	5142 (17%)	
	Eastern Mediterranean	0 (0%)	155 (0.5%)	
	Western Pacific	2 (0.2%)	876 (2.8%)	
Age group	< 1 month	34 (3.5%)	669 (2.2%)	< 0.001
	1–11 months	140 (14%)	5575 (18%)	
	1–4 years	182 (18%)	7105 (23%)	
	5–9 years	90 (9.1%)	4038 (13%)	
	10–14 years	110 (11%)	4705 (15%)	
	15–19 years	429 (44%)	8807 (29%)	
Sex	Male	453 (46%)	15 624 (51%)	< 0.006
	Female	528 (54%)	15 239 (49%)	
	Unknown	4	36	
ART		415 (82%)	(not applicable)	
	Unknown	481	(not applicable)	

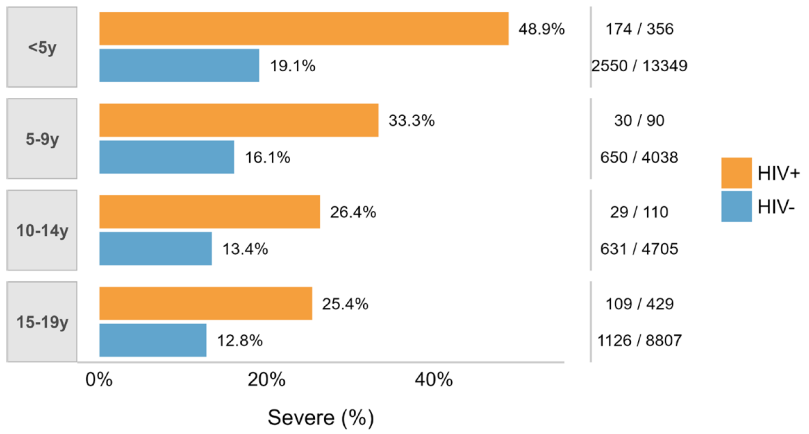
Note: [a] n (%).

In both children living with HIV and HIV-negative children, the prevalence of severe or critical disease at hospital admission decreased with increasing age. However, the proportion of severe cases was relatively higher in children living with HIV when compared with HIV-negative children. Among children living with HIV, the highest prevalence of severe disease was found in neonates (55.9%, 19/34), and the lowest in those aged 15–19 years (25.4 %, 109/429) as shown in **Fig. 11**. After adjusting for sex, age and underlying conditions, children living with HIV were found to have an overall increased odds of presenting with severe or critical disease at hospital admission (aOR = 1.70; 95% CI: 1.39, 2.07; *P* < 0.001) (see **Table S20**).

When considering 14-day in-hospital mortality, higher mortality rates were observed for children living with HIV when compared with HIV-negative children across all age groups (see **Fig. 11)**. Kaplan-Meier curves, as shown in **Fig. 12**, provide a visual representation of the survival probability across different age groups by HIV status, suggesting higher mortality rates for children living with HIV. Further analysis adjusting for age, sex and underlying conditions confirmed this observation. As indicated in **Table S21**, children living with HIV were found to have an overall increased risk of 14-day in-hospital mortality (aHR = 7.12; 95% CI: 5.32, 9.52; *P* < 0.001) compared with HIV-negative children.

Fig. 11. Rates of disease severity and in-hospital mortality amongst children living with HIV hospitalized with COVID 19, by age group

11a: Severe or critical disease at hospital admission



11b: In-hospital mortality

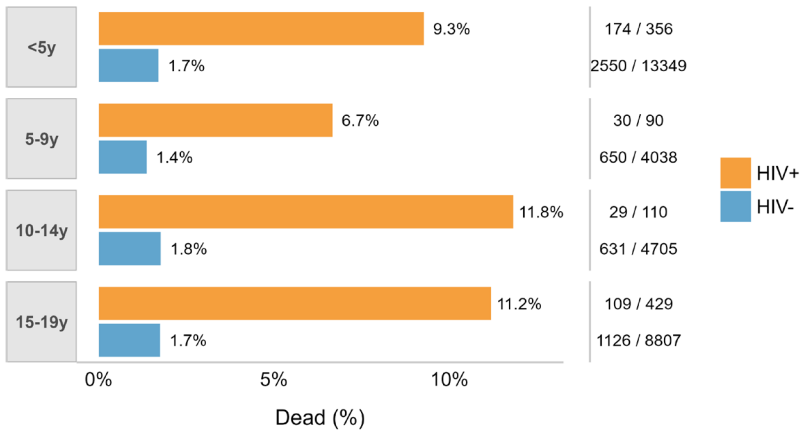
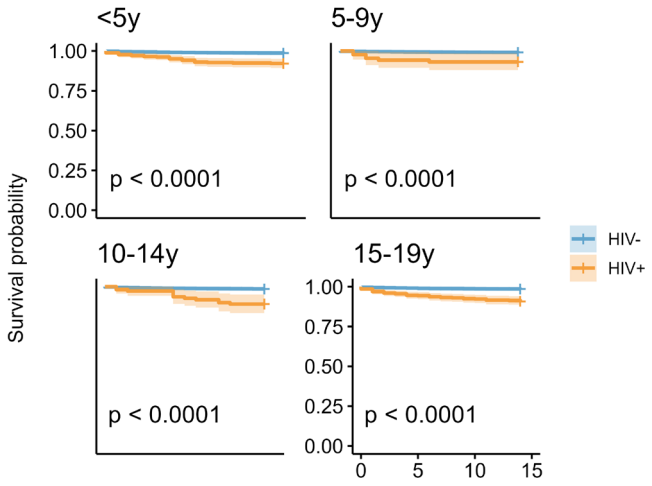


Fig. 12. **In-hospital survival amongst children living with HIV hospitalized with COVID-19, stratified by age group**



Notes: Kaplan-Meier survival curves. p = proportional hazards comparison by group.

The magnitude of the association between HIV and in-hospital mortality remained similar to that of the 14-day in-hospital mortality model when data censoring was extended from 14 to 28 days (see **Table S22**).

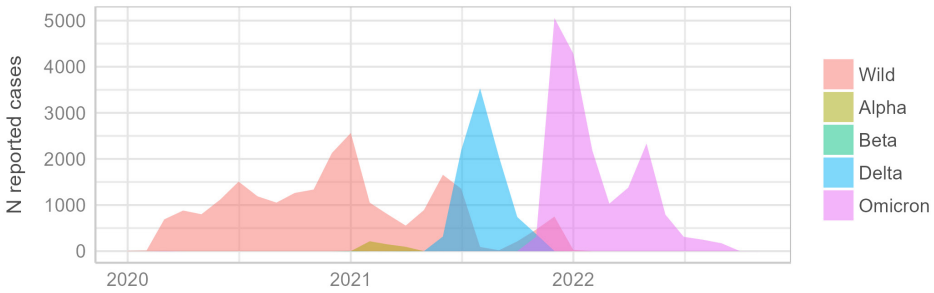
When analysis was limited to data from South Africa, the findings were in line with the overall analysis. Notably, there was a demonstrated association, i.e. an increased risk, between HIV status and age for disease severity and in-hospital mortality, as detailed in **Tables S23** and **S24**.

3.6 Variants of concern, vaccination and reinfection of children hospitalized with COVID-19

Using the hospital admission date and country-specific reports on the progression of the SARS CoV 2 mutations, as detailed in the Methods section and **Table S25**, we ascertained that of the 50 351 paediatric patients included in our analysis, 458 (0.91%) were hospitalized during the Alpha period, 14 (0.03%) during the Beta period, 9192 (18.26%) during the Delta period and 18112 (35.97%) during the Omicron period (each period corresponding to the dominant circulation of the respective variant) (**see Fig. 13**). These details are presented in **Table S26**.

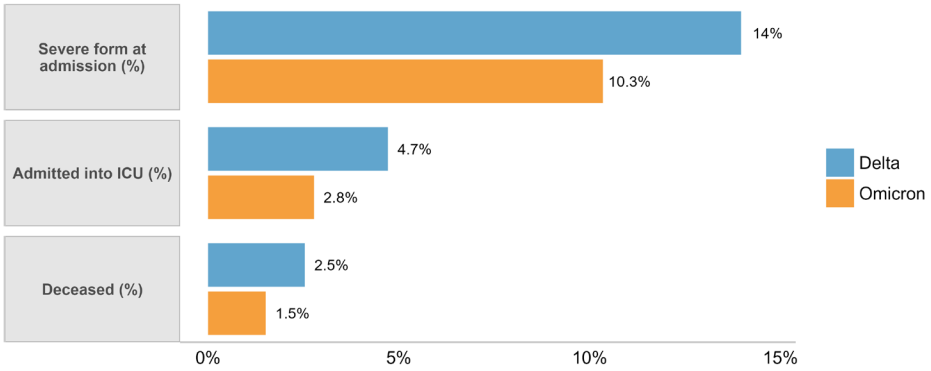
Due to the limited data available on the predominance of other variants, our analyses primarily focused on the Delta and Omicron periods.

Fig. 13. **Cases of hospitalized children with COVID-19, by likely variant of concern from January 2020 to June 2022**



Our findings demonstrate that, compared with the Omicron period, the Delta period was associated with higher proportions of severe disease (14% vs 10.3%), higher ICU admission rates (4.7% vs 2.8%) and higher in-hospital mortality rates (2.5% vs 1.5%) (see **Fig. 14**). The Omicron period was associated with lower risk of severe and critical disease and 14-day in-hospital mortality (aOR = 0.66; CI: 0.59, 0.74; $P < 0.001$) and (aHR = 0.61; CI 0.45, 0.83; $P = 0.002$), respectively compared with the Delta period (see **Table S27** and **S28**).

Fig. 14. Disease severity and outcomes by likely variant amongst children hospitalized with COVID-19



Data pertaining to reinfection and vaccination status were available for only a small fraction of the records, specifically 703 (1.4%) and 674 (1.3%) respectively. Due to this limited availability, we did not carry out further analyses related to these variables.

4. Discussion

Overall, our findings suggest that children admitted to the hospital with COVID-19 generally presented with milder disease and better outcomes compared with adults aged 20–45 years. Age emerged as a significant factor in in-hospital mortality, with the highest mortality observed in neonates – a pattern common to many diseases. Notably, 17% of hospitalized children with COVID-19 presented at hospital admission with severe to critical disease.

The most frequently reported symptom was fever, along with respiratory, gastrointestinal and neurological manifestations. Among neurological presentations, seizures were most common, occurring in about a third of children aged 1–4 years.

Children admitted to hospital with COVID-19 who also presented with underlying conditions faced a two- to five-fold increased risk of severe or critical disease and in-hospital mortality. Our analyses showed that a higher risk of mortality was associated with having more than one underling condition.

Among children hospitalized with COVID-19, children living with HIV were proportionally twice as likely than those without HIV to present with severe disease. Among all paediatric age groups children living with HIV have a higher in-hospital mortality as compared with those with no HIV.

Patients admitted during the Delta variant period were more likely to experience severe disease, higher ICU admission and have higher in-hospital mortality rates compared with those admitted during the Omicron variant period.

4.1 Data in context of the known literature

This report presents the largest geographically representative data on children hospitalized with COVID-19 from diverse populations allowing characterization and associated risk description.

These data demonstrate that COVID-19 presents as a milder disease in children compared with adults, a finding consistent with several other studies *(17-20)*. These studies attribute these observations to various hypothesized factors, including less-intense immune response to the virus in children (i.e. minor cytokine release syndrome), variations in the expression of the angiotensin-converting enzyme 2 receptor, and viral interference (concurrent infection and microbiota differences) in the respiratory tract of young children which may result in lower viral loads in children than adults *(17-20)*. Moreover, the observed increased in in-hospital mortality during the first two periods of spikes in case hospitalizations over the studied period could be a result of inadequate resources for case management or because of a circulating variant with severe disease which was similar to the trends seen in adults, as indicated by recent surveys *(21, 22)*.

This analysis also revealed that neonates had the highest death rate among children, with rates rising in older children. This “U-shaped” pattern, is consistent with findings from other studies and mirrors historical patterns of childhood mortality as reported by the United Nations Children’s Fund in 2021 *(23, 24)*. The increased mortality rate in neonates compared with older children may be attributable to a multitude of congenital and early life factors representing physiological and immunological vulnerability. Direct measures to improve immunity, such as maternal immunization, could potentially improve neonatal outcomes related to COVID-19. This improvement could be due to direct transfer of immunity as well as indirect benefits on the growth and development of the unborn child stemming from maternal well-being.

Our findings showed that children hospitalized with COVID-19 predominantly presented with a range of symptoms similar to adults, with the most common features being fever, cough, vomiting, fatigue and headache *(25)*. However, seizure has been reported more frequently as a primary manifestation in children than adults hospitalized with COVID-19 (26-29). COVID-19 infection can cause an excessive excitation or drastic reduction of inhibition in the nervous system, potentially increasing the susceptibility to seizures in children *(26, 30)*. While seizures in children can sometimes be benign, as commonly seen in febrile seizure, they may also signal significant neurological injury. This could indicate underlying complications of infection in the nervous system with potential acute and chronic consequences. A recent report of disorders such as microcephaly and other neurodevelopmental conditions could signal potential unknown consequence of COVID-19 among children *(31-35)*. These findings underscore the need for effective measures to prevent and mitigate COVID-19 infection in maternal and paediatric populations.

Children who presented with COVID-19 and underlying conditions such as HIV, hypertension, chronic cardiac disease, diabetes and pulmonary disease were likely to present with severe form of the disease at the time of admission. Notably, cases diagnosed with chronic kidney disease, HIV, chronic cardiac disease (not hypertension) and malignant neoplasm were approximately four times more likely to die during hospitalization. Those with tuberculosis and diabetes had three times and two times the mortality risk, respectively. Children with one or two underlying conditions have twice the mortality risk, while those with three or more underlying conditions had a seven-fold increase. These observations underscore the need to scale-up vaccination and care for children with these conditions, as they can exacerbate COVID-19 infection and increase mortality.

Of note, we observed higher rates of HIV among hospitalized newborns as compared with other age groups, possibly due to screening programmes like Prevention of Mother to Child Transmission. As reported in other studies, some patients with controlled HIV had better COVID-19 outcomes *(36, 37)*. Hence, it is suggested that all children living with HIV should receive ART and prevention of other infectious diseases interventions could help mitigate the impact of COVID-19 among this population. Moreover, prioritizing the screening and effective management of underlying conditions in children with COVID-19 may potentially reduce poor outcomes.

Our analysis also showed that children infected during the Omicron variant period presented with less severe disease upon hospital admission compared to those infected during the Delta variant period. However, the symptomatologic presentation did not significantly differ between the two periods. These findings confirm the observations of other studies and reports *(38-40)*.

4.2 Limitations

The data collected as part of the Global Clinical Platform represent a convenience sample, based on the availability of cases, collaborators, infrastructure and willingness to contribute. Despite the very large size of the database (more than 1 million records), the degree to which bias is introduced, and the direction of effect, is difficult to ascertain. The large sample size of this assessment and outcomes may partly mitigate such effects as they may relate more to random than sampling error *(41)*.

It is clear that the data strongly represent some countries, notably South Africa, which therefore contribute disproportionately to the findings. Additionally, study population were not systematically selected between and within contributing countries. Interpretation and extrapolation to under-represented areas should therefore be undertaken with caution.

The platform is constructed to be as accessible to collaborators as possible; those facilities, organizations and countries which contribute may not have the resources to systematically and fully capture data. This leads to a degree of missingness in the dataset, which we have described here. The ability to retrospectively enter data is an explicit compromise which maximizes the sources, and hopefully the representation of data. However, this may also contribute to shortfalls in completeness.

The stand-alone nature of much clinical data means that we cannot collect metadata or linked data at the individual level. This leads to indirectness in the analysis, for example the use of proxy indicators of VOC (derived at the country level). We have made explicit where this has been done, and the assumptions on which we employed aggregate data. Ideally, linkage to individual virus sequencing at the level of the patient would be employed, but this would also highly limit the sample size, and the possibility of inclusion of data from highly resource-limited settings where such advanced diagnostics are not available.

Lastly, key questions about outcomes for all patients with COVID-19 cannot be answered using data collected at the hospital facility, especially for the paediatric population; the denominator is unknown. This is a function of both the study design and declining rates and completeness of community testing as the pandemic progresses *(42)*.

4.3 Conclusion

After more than 3 years of response to COVID-19 as a Public Health Emergency of International Concern, WHO declared an end to the emergency response in May 2023, with COVID-19 now an established and ongoing health issue. Understanding risk factors associated with patient and health care important outcomes continues to be critical in guiding practice as viral variants and clinical patterns of disease change over time. In this study, we found differences and similarities among children hospitalized with COVID-19 and adults and within the paediatric subgroups. We found that children generally presented with milder disease compared with adults; and among children, under-5 year olds, especially neonates, present with the highest disease severity and mortality.

The study found that severity and in-hospital mortality were associated with underlying conditions with those having multiple underlying conditions at higher risk of mortality. Compared with the Delta variant, Omicron was associated with lower disease severity, lower rates of ICU admission and lower in-hospital mortality. There is a continued need to prioritize the accessibility and administration of COVID-19 vaccines for pregnant women and children at risk which will reduce severity, hospitalization and mortality.

For treatment of those who become ill as a result of SARS CoV 2 infection, we must ensure functional and resilient health care systems through capacity building the health workforce, scaling up oxygen systems, and ensuring adequate medical equipment and supplies. For children, the development and provision of paediatric formulations of COVID-19 therapeutics is lacking. Lastly, continuous vigilance and surveillance of disease will allow us to better understand and manage the disease at the level of the patient, and the broader health system.

5. Funding

The WHO Global Clinical Platform for COVID-19 was supported by WHO through R&D German grant. Funding for ISARIC is provided by the United Kingdom Foreign, Commonwealth and Development Office and Wellcome [215091/Z/18/Z, 222410/Z/21/Z, 225288/Z/22/Z]; the Bill & Melinda Gates Foundation [OPP1209135] and the University of Oxford's COVID-19 Research Response Fund [0009109].

6. Clinical characteristics and health outcomes for children hospitalized with COVID-19: supplementary material

Table S1. Number of children hospitalised with COVID-19 reported by country

	Characteristic						
Country	Overall, N = 50 351*	<1 month, N = 1400*	1–11 months, N = 9586*	1–4 years, N = 10 823*	5–9 years, N = 6318*	10–14 years, N = 7503*	15–19 years, N = 14 721*
South Africa	35 601 (71%)	1207 (86%)	6655 (69%)	7774 (72%)	4490 (71%)	5112 (68%)	10 363 (70%)
United Kingdom	8572 (17%)	0 (0%)	1890 (20%)	1618 (15%)	1003 (16%)	1528 (20%)	2533 (17%)
Colombia	1869 (3.7%)	73 (5.2%)	415 (4.3%)	484 (4.5%)	237 (3.8%)	230 (3.1%)	430 (2.9%)
Malaysia	883 (1.8%)	6 (0.4%)	31 (0.3%)	75 (0.7%)	70 (1.1%)	194 (2.6%)	507 (3.4%)
Brazil	716 (1.4%)	31 (2.2%)	101 (1.1%)	209 (1.9%)	174 (2.8%)	91 (1.2%)	110 (0.7%)
Malawi	693 (1.4%)	22 (1.6%)	239 (2.5%)	258 (2.4%)	47 (0.7%)	35 (0.5%)	92 (0.6%)
Nigeria	421 (0.8%)	7 (0.5%)	9 (<0.1%)	68 (0.6%)	69 (1.1%)	85 (1.1%)	183 (1.2%)
Ecuador	246 (0.5%)	3 (0.2%)	45 (0.5%)	62 (0.6%)	51 (0.8%)	41 (0.5%)	44 (0.3%)
Zimbabwe	188 (0.4%)	9 (0.6%)	27 (0.3%)	9 (<0.1%)	7 (0.1%)	42 (0.6%)	94 (0.6%)
Cameroon	159 (0.3%)	0 (0%)	2 (<0.1%)	88 (0.8%)	44 (0.7%)	10 (0.1%)	15 (0.1%)
Guinea	146 (0.3%)	0 (0%)	5 (<0.1%)	19 (0.2%)	25 (0.4%)	24 (0.3%)	73 (0.5%)
Jordan	115 (0.2%)	3 (0.2%)	26 (0.3%)	12 (0.1%)	10 (0.2%)	12 (0.2%)	52 (0.4%)
Canada	100 (0.2%)	3 (0.2%)	14 (0.1%)	36 (0.3%)	9 (0.1%)	21 (0.3%)	17 (0.1%)
Panama	96 (0.2%)	11 (0.8%)	41 (0.4%)	19 (0.2%)	12 (0.2%)	7 (<0.1%)	6 (<0.1%)
Italy	82 (0.2%)	1 (<0.1%)	7 (<0.1%)	28 (0.3%)	14 (0.2%)	20 (0.3%)	12 (<0.1%)
India	76 (0.2%)	8 (0.6%)	11 (0.1%)	18 (0.2%)	9 (0.1%)	6 (<0.1%)	24 (0.2%)
Ireland	50 (<0.1%)	6 (0.4%)	12 (0.1%)	12 (0.1%)	5 (<0.1%)	5 (<0.1%)	10 (<0.1%)
Dominican Republic	48 (<0.1%)	0 (0%)	8 (<0.1%)	8 (<0.1%)	18 (0.3%)	8 (0.1%)	6 (<0.1%)
Germany	36 (<0.1%)	1 (<0.1%)	10 (0.1%)	6 (<0.1%)	7 (0.1%)	7 (<0.1%)	5 (<0.1%)
Bangladesh	28 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	28 (0.2%)
Spain	25 (<0.1%)	3 (0.2%)	4 (<0.1%)	7 (<0.1%)	1 (<0.1%)	1 (<0.1%)	9 (<0.1%)
United States of America	24 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1%)	22 (0.1%)
Gambia	21 (<0.1%)	5 (0.4%)	7 (<0.1%)	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)	4 (<0.1%)
France	19 (<0.1%)	0 (0%)	2 (<0.1%)	2 (<0.1%)	5 (<0.1%)	0 (0%)	10 (<0.1%)
Poland	17 (<0.1%)	0 (0%)	2 (<0.1%)	3 (<0.1%)	4 (<0.1%)	8 (0.1%)	0 (0%)
Burkina Faso	16 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	16 (0.1%)
Indonesia	16 (<0.1%)	1 (<0.1%)	7 (<0.1%)	2 (<0.1%)	3 (<0.1%)	3 (<0.1%)	0 (0%)
Netherlands (Kingdom of the)	12 (<0.1%)	0 (0%)	1 (<0.1%)	2 (<0.1%)	0 (0%)	0 (0%)	9 (<0.1%)
Israel	11 (<0.1%)	0 (0%)	2 (<0.1%)	1 (<0.1%)	0 (0%)	1 (<0.1%)	7 (<0.1%)
Zambia	9 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	1 (<0.1%)	3 (<0.1%)	4 (<0.1%)
Democratic Republic of the Congo	8 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	7 (<0.1%)
Norway	8 (<0.1%)	0 (0%)	6 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1%)

Table S1. *continued*

Country	Characteristic						
	Overall, N = 50 351*	<1 month, N = 1400*	1–11 months, N = 9586*	1–4 years, N = 10 823*	5–9 years, N = 6318*	10–14 years, N = 7503*	15–19 years, N = 14 721*
Peru	8 (<0.1%)	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)	2 (<0.1%)	5 (<0.1%)
Kuwait	7 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	1 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Korea, Republic of	6 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (<0.1%)
Ghana	4 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)	3 (<0.1%)
Niger	3 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1%)
Philippines	3 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1%)
Hungary	2 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)	1 (<0.1%)
Ukraine	2 (<0.1%)	0 (0%)	2 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Greece	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)
Japan	1 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Singapore	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)
Sudan	1 (<0.1%)	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)
Türkiye	1 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*n (%)

Table S2. Number of children hospitalised with COVID-19 reported by country

Age group	Characteristic		
	Overall N = 50 252*	Male N = 25 156†	Female N = 25 096†
<1 month	1386	733 (53%)	653 (47%)
1–11 months	9562	5387 (56%)	4175 (44%)
1–4 years	10 805	6081 (56%)	4724 (44%)
5–9 years	6308	3549 (56%)	2759 (44%)
10–14 years	7486	3795 (51%)	3691 (49%)
15–19 years	14 705	5611 (38%)	9094 (62%)

*N; †n (%)

Table S3. Multivariate regression analysis of association between age category and severity of disease

Characteristic	Severity		Logistic mixed effects model		
	Mild N = 119 328*	Severe N = 28 485*	OR	95% CI	p-value
HIV					
No	110 252 (81%)	26 156 (19%)	1.00	—	
Yes	9076 (80%)	2329 (20%)	1.05	1.00, 1.10	0.048
Chronic cardiac disease (not hypertension)					
No	117 861 (81%)	27 883 (19%)	1.00	—	
Yes	1467 (71%)	602 (29%)	1.36	1.22, 1.50	<0.001
Diabetes					
No	109 675 (81%)	25 175 (19%)	1.00	—	
Yes	9653 (74%)	3310 (26%)	1.29	1.23, 1.35	<0.001
Hypertension					
No	109 725 (82%)	24 459 (18%)	1.00	—	
Yes	9603 (70%)	4026 (30%)	1.64	1.57, 1.71	<0.001
Pulmonary disease (including asthma)					
No	110 582 (81%)	26 112 (19%)	1.00	—	
Yes	8746 (79%)	2373 (21%)	1.16	1.10, 1.22	<0.001
Age group					
20–45 years	94 977 (79%)	24 760 (21%)	1.00	—	
15–19 years	7053 (89%)	858 (11%)	0.52	0.48, 0.56	<0.001
10–14 years	3728 (89%)	474 (11%)	0.48	0.43, 0.53	<0.001
5–9 years	3224 (87%)	486 (13%)	0.52	0.47, 0.58	<0.001
1–4 years	5645 (86%)	919 (14%)	0.59	0.55, 0.63	<0.001
1–11 months	4231 (83%)	856 (17%)	0.72	0.66, 0.78	<0.001
<1 month	470 (78%)	132 (22%)	0.98	0.80, 1.20	0.8
Sex					
Male	49 403 (77%)	14 643 (23%)	1.00	—	
Female	69 925 (83%)	13 842 (17%)	0.64	0.62, 0.66	<0.001

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S4. **Multivariate regression analysis of association between age category and 14 day in hospital mortality**

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 138 720*	Yes N = 6193*	HR	95% CI	p-value
HIV					
No	129 030 (96%)	4745 (3.5%)	1.00	—	
Yes	9690 (87%)	1448 (13%)	2.70	2.54, 2.87	<0.001
Chronic cardiac disease (not hypertension)					
No	136 864 (96%)	6051 (4.2%)	1.00	—	
Yes	1856 (93%)	142 (7.1%)	1.72	1.45, 2.05	<0.001
Diabetes					
No	126 992 (96%)	5164 (3.9%)	1.00	—	
Yes	11 728 (92%)	1029 (8.1%)	1.81	1.69, 1.95	<0.001
Hypertension					
No	126 389 (96%)	5103 (3.9%)	1.00	—	
Yes	12 331 (92%)	1090 (8.1%)	1.36	1.27, 1.46	<0.001
Pulmonary disease (including asthma)					
No	128 291 (96%)	5748 (4.3%)	1.00	—	
Yes	10 429 (96%)	445 (4.1%)	1.12	1.01, 1.23	0.025
Chronic kidney disease					
No	137 055 (96%)	5956 (4.2%)	1.00	—	
Yes	1665 (88%)	237 (12%)	2.30	2.00, 2.64	<0.001
Malignant neoplasm					
No	137 583 (96%)	6086 (4.2%)	1.00	—	
Yes	1137 (91%)	107 (8.6%)	3.22	2.64, 3.92	<0.001
Age group					
20–45 years	111 412 (95%)	5835 (5.0%)	1.00	—	
15–19 years	7652 (99%)	107 (1.4%)	0.34	0.28, 0.41	<0.001
10–14 years	4083 (99%)	56 (1.4%)	0.32	0.24, 0.41	<0.001
5–9 years	3626 (99%)	30 (0.8%)	0.18	0.12, 0.25	<0.001
1–4 years	6442 (99%)	47 (0.7%)	0.16	0.12, 0.21	<0.001
1–11 months	4949 (98%)	84 (1.7%)	0.37	0.29, 0.45	<0.001
<1 month	556 (94%)	34 (5.8%)	1.14	0.81, 1.60	0.4
Sex					
Male	59 486 (95%)	3019 (4.8%)	1.00	—	
Female	79 234 (96%)	3174 (3.9%)	0.66	0.63, 0.70	<0.001

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S5. Multivariate regression analysis of association between age category and 14 day in hospital mortality, with severity additionally included as a model covariate

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 138 720*	Yes N = 6193*	HR	95% CI	p-value
HIV					
No	129 030 (96%)	4745 (3.5%)	1.00	—	
Yes	9690 (87%)	1448 (13%)	2.76	2.60, 2.93	<0.001
Chronic cardiac disease (not hypertension)					
No	136 864 (96%)	6051 (4.2%)	1.00	—	
Yes	1856 (93%)	142 (7.1%)	1.56	1.31, 1.85	<0.001
Diabetes					
No	126 992 (96%)	5164 (3.9%)	1.00	—	
Yes	11 728 (92%)	1029 (8.1%)	1.75	1.63, 1.88	<0.001
Hypertension					
No	126 389 (96%)	5103 (3.9%)	1.00	—	
Yes	12 331 (92%)	1090 (8.1%)	1.25	1.16, 1.34	<0.001
Pulmonary disease (including asthma)					
No	128 291 (96%)	5748 (4.3%)	1.00	—	
Yes	10 429 (96%)	445 (4.1%)	1.11	1.00, 1.22	0.046
Chronic kidney disease					
No	137 055 (96%)	5956 (4.2%)	1.00	—	
Yes	1665 (88%)	237 (12%)	2.31	2.02, 2.65	<0.001
Malignant neoplasm					
No	137 583 (96%)	6086 (4.2%)	1.00	—	
Yes	1137 (91%)	107 (8.6%)	3.02	2.48, 3.67	<0.001
Age group					
20–45 years	111 412 (95%)	5835 (5.0%)	1.00	—	
15–19 years	7652 (99%)	107 (1.4%)	0.37	0.31, 0.45	<0.001
10–14 years	4083 (99%)	56 (1.4%)	0.37	0.28, 0.48	<0.001
5–9 years	3626 (99%)	30 (0.8%)	0.20	0.14, 0.29	<0.001
1–4 years	6442 (99%)	47 (0.7%)	0.18	0.13, 0.24	<0.001
1–11 months	4949 (98%)	84 (1.7%)	0.39	0.32, 0.49	<0.001
<1 month	556 (94%)	34 (5.8%)	1.16	0.83, 1.62	0.4
Sex					
Male	59 486 (95%)	3019 (4.8%)	1.00	—	
Female	79 234 (96%)	3174 (3.9%)	0.71	0.68, 0.75	<0.001
Severity					
mild	113 594 (97%)	3739 (3.2%)	1.00	—	
severe	25 126 (91%)	2454 (8.9%)	2.43	2.31, 2.56	<0.001

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S6. **Multivariate regression analysis of association between age category and 28 day in hospital mortality (instead of 14 days)**

	Deceased within 28 days		Cox mixed effects model		
Characteristic	No N = 137 278*	Yes N = 7635*	HR	95% CI	p-value
HIV					
No	127 754 (95%)	6021 (4.5%)	1.00	—	
Yes	9524 (86%)	1614 (14%)	2.44	2.31, 2.58	<0.001
Chronic cardiac disease (not hypertension)					
No	135 461 (95%)	7454 (5.2%)	1.00	—	
Yes	1817 (91%)	181 (9.1%)	1.68	1.44, 1.96	<0.001
Diabetes					
No	125 780 (95%)	6376 (4.8%)	1.00	—	
Yes	11 498 (90%)	1259 (9.9%)	1.76	1.65, 1.88	<0.001
Hypertension					
No	125 197 (95%)	6295 (4.8%)	1.00	—	
Yes	12 081 (90%)	1340 (10.0%)	1.37	1.28, 1.46	<0.001
Pulmonary disease (including asthma)					
No	126 976 (95%)	7063 (5.3%)	1.00	—	
Yes	10 302 (95%)	572 (5.3%)	1.14	1.04, 1.24	0.004
Chronic kidney disease					
No	135 667 (95%)	7344 (5.1%)	1.00	—	
Yes	1611 (85%)	291 (15%)	2.25	1.98, 2.54	<0.001
Malignant neoplasm					
No	136 190 (95%)	7479 (5.2%)	1.00	—	
Yes	1088 (87%)	156 (13%)	3.64	3.09, 4.29	<0.001
Age group					
20–45 years	110 019 (94%)	7228 (6.2%)	1.00	—	
15–19 years	7630 (98%)	129 (1.7%)	0.32	0.27, 0.38	<0.001
10–14 years	4074 (98%)	65 (1.6%)	0.29	0.23, 0.37	<0.001
5–9 years	3623 (99%)	33 (0.9%)	0.15	0.11, 0.21	<0.001
1–4 years	6435 (99%)	54 (0.8%)	0.14	0.11, 0.19	<0.001
1–11 months	4944 (98%)	89 (1.8%)	0.31	0.25, 0.38	<0.001
<1 month	553 (94%)	37 (6.3%)	1.01	0.73, 1.39	>0.9
Sex					
Male	58 763 (94%)	3742 (6.0%)	1.00	—	
Female	78 515 (95%)	3893 (4.7%)	0.66	0.63, 0.69	<0.001

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S7. Multivariate regression analysis of association between age category and severity of disease, excluding South African data

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 36 787*	Severe N = 10 104*	OR	95% CI	p-value
Diabetes					
No	32 798 (79%)	8799 (21%)	1.00	—	
Yes	3989 (75%)	1305 (25%)	1.26	1.16, 1.36	<0.001
Hypertension					
No	33 876 (79%)	8957 (21%)	1.00	—	
Yes	2911 (72%)	1147 (28%)	1.32	1.22, 1.43	<0.001
Pulmonary disease (including asthma)					
No	31 816 (79%)	8637 (21%)	1.00	—	
Yes	4971 (77%)	1467 (23%)	1.28	1.20, 1.38	<0.001
Malignant neoplasm					
No	35 958 (78%)	9940 (22%)	1.00	—	
Yes	829 (83%)	164 (17%)	0.62	0.52, 0.75	<0.001
Chronic liver disease					
No	35 990 (78%)	9953 (22%)	1.00	—	
Yes	797 (84%)	151 (16%)	0.69	0.58, 0.83	<0.001
Chronic neurological disorder					
No	35 269 (79%)	9551 (21%)	1.00	—	
Yes	1518 (73%)	553 (27%)	1.47	1.32, 1.63	<0.001
Age group					
20–45 years	30 778 (79%)	8335 (21%)	1.00	—	
15–19 years	2398 (88%)	330 (12%)	0.59	0.52, 0.67	<0.001
10–14 years	1191 (82%)	254 (18%)	0.81	0.70, 0.95	0.008
5–9 years	679 (70%)	290 (30%)	1.42	1.21, 1.66	<0.001
1–4 years	909 (64%)	516 (36%)	1.91	1.68, 2.16	<0.001
1–11 months	793 (70%)	333 (30%)	1.11	0.96, 1.29	0.2
<1 month	39 (46%)	46 (54%)	2.55	1.52, 4.28	<0.001
Sex					
Male	17 837 (75%)	5909 (25%)	1.00	—	
Female	18 950 (82%)	4195 (18%)	0.60	0.57, 0.63	<0.001

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S8. **Multivariate regression analysis of association between age category and 14 day in hospital mortality, excluding South African data**

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 42 060*	Yes N = 730*	HR	95% CI	p-value
HIV					
No	41 553 (98%)	663 (1.6%)	1.00	—	
Yes	507 (88%)	67 (12%)	2.11	1.56, 2.86	<0.001
Chronic cardiac disease (not hypertension)					
No	40 759 (98%)	659 (1.6%)	1.00	—	
Yes	1301 (95%)	71 (5.2%)	1.92	1.47, 2.52	<0.001
Diabetes					
No	37 388 (98%)	578 (1.5%)	1.00	—	
Yes	4672 (97%)	152 (3.2%)	1.85	1.52, 2.26	<0.001
Hypertension					
No	38 565 (98%)	588 (1.5%)	1.00	—	
Yes	3495 (96%)	142 (3.9%)	1.45	1.17, 1.78	<0.001
Pulmonary disease (including asthma)					
No	36 194 (98%)	613 (1.7%)	1.00	—	
Yes	5866 (98%)	117 (2.0%)	1.29	1.05, 1.59	0.015
Chronic kidney disease					
No	41 028 (98%)	647 (1.6%)	1.00	—	
Yes	1032 (93%)	83 (7.4%)	2.51	1.93, 3.26	<0.001
Malignant neoplasm					
No	41 176 (98%)	672 (1.6%)	1.00	—	
Yes	884 (94%)	58 (6.2%)	3.45	2.60, 4.58	<0.001
Chronic liver disease					
No	41 226 (98%)	682 (1.6%)	1.00	—	
Yes	834 (95%)	48 (5.4%)	2.43	1.78, 3.32	<0.001
Chronic neurological disorder					
No	40 204 (98%)	656 (1.6%)	1.00	—	
Yes	1856 (96%)	74 (3.8%)	2.12	1.63, 2.75	<0.001
Age group					
20–45 years	34 935 (98%)	662 (1.9%)	1.00	—	
15–19 years	2468 (99%)	19 (0.8%)	0.48	0.30, 0.75	0.002
10–14 years	1341 (99%)	13 (1.0%)	0.59	0.34, 1.03	0.062
5–9 years	899 (99%)	7 (0.8%)	0.37	0.17, 0.77	0.008
1–4 years	1322 (99%)	10 (0.8%)	0.41	0.22, 0.77	0.005
1–11 months	1022 (98%)	17 (1.6%)	0.77	0.47, 1.25	0.3
<1 month	73 (97%)	2 (2.7%)	0.54	0.13, 2.17	0.4
Sex					
Male	21 006 (98%)	417 (1.9%)	1.00	—	
Female	21 054 (99%)	313 (1.5%)	0.73	0.63, 0.85	<0.001

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S9. Description of symptoms for the whole paediatric population and stratified per age group

	Age group						
Characteristic	Overall, N = 14 757*	<1 month, N = 194*	1–11 months, N = 2932*	1–4 years, N = 3050*	5–9 years, N = 1828*	10–14 years, N = 2392*	15–19 years, N = 4361*
History of fever	6612 / 11 965 (55%)	58 / 142 (41%)	1759 / 2520 (70%)	1597 / 2546 (63%)	752 / 1446 (52%)	877 / 1863 (47%)	1569 / 3448 (46%)
Lower chest wall indrawing	100 / 2294 (4.4%)	10 / 86 (12%)	38 / 330 (12%)	27 / 478 (5.6%)	9 / 392 (2.3%)	9 / 333 (2.7%)	7 / 675 (1.0%)
Headache	1330 / 7610 (17%)	0 / 0 (NA%)	0 / 0 (NA%)	59 / 1429 (4.1%)	200 / 1225 (16%)	356 / 1689 (21%)	715 / 3267 (22%)
Altered consciousness/ confusion	469 / 9508 (4.9%)	4 / 124 (3.2%)	91 / 2190 (4.2%)	85 / 2101 (4.0%)	81 / 1137 (7.1%)	92 / 1444 (6.4%)	116 / 2512 (4.6%)
Abdominal pain	1348 / 9872 (14%)	4 / 121 (3.3%)	47 / 1907 (2.5%)	155 / 2047 (7.6%)	287 / 1183 (24%)	370 / 1606 (23%)	485 / 3008 (16%)
Runny nose	1544 / 10 184 (15%)	10 / 130 (7.7%)	610 / 2216 (28%)	439 / 2085 (21%)	104 / 1170 (8.9%)	140 / 1595 (8.8%)	241 / 2988 (8.1%)
Wheezing	648 / 8947 (7.2%)	5 / 73 (6.8%)	181 / 1819 (10.0%)	282 / 1688 (17%)	49 / 1044 (4.7%)	62 / 1505 (4.1%)	69 / 2818 (2.4%)
Skin rash	675 / 10 691 (6.3%)	2 / 139 (1.4%)	252 / 2337 (11%)	171 / 2215 (7.7%)	100 / 1233 (8.1%)	100 / 1684 (5.9%)	50 / 3083 (1.6%)
Joint pain (arthralgia)	141 / 2532 (5.6%)	9 / 103 (8.7%)	4 / 406 (1.0%)	8 / 517 (1.5%)	14 / 349 (4.0%)	24 / 355 (6.8%)	82 / 802 (10%)
Skin ulcers	66 / 2122 (3.1%)	1 / 99 (1.0%)	16 / 386 (4.1%)	26 / 549 (4.7%)	5 / 394 (1.3%)	8 / 252 (3.2%)	10 / 442 (2.3%)
Fatigue / malaise	2243 / 10 246 (22%)	27 / 137 (20%)	459 / 2063 (22%)	394 / 2101 (19%)	283 / 1198 (24%)	392 / 1652 (24%)	688 / 3095 (22%)
Lymphadenopathy	7 / 1427 (0.5%)	0 / 66 (0%)	3 / 285 (1.1%)	0 / 341 (0%)	2 / 219 (0.9%)	0 / 162 (0%)	2 / 354 (0.6%)
Inability to walk	43 / 2244 (1.9%)	0 / 0 (NA%)	0 / 0 (NA%)	7 / 580 (1.2%)	11 / 384 (2.9%)	10 / 408 (2.5%)	15 / 872 (1.7%)
Sore throat	1040 / 7714 (13%)	0 / 0 (NA%)	0 / 0 (NA%)	138 / 1522 (9.1%)	136 / 1252 (11%)	239 / 1699 (14%)	527 / 3241 (16%)
Vomiting / Nausea	2567 / 11 037 (23%)	10 / 144 (6.9%)	492 / 2382 (21%)	490 / 2293 (21%)	392 / 1275 (31%)	491 / 1737 (28%)	692 / 3206 (22%)
Diarrhoea	1415 / 11 423 (12%)	9 / 155 (5.8%)	380 / 2462 (15%)	306 / 2385 (13%)	160 / 1312 (12%)	206 / 1778 (12%)	354 / 3331 (11%)
Chest pain	728 / 9589 (7.6%)	12 / 124 (9.7%)	24 / 1791 (1.3%)	47 / 1932 (2.4%)	57 / 1156 (4.9%)	139 / 1573 (8.8%)	449 / 3013 (15%)
Conjunctivitis	168 / 10 195 (1.6%)	2 / 134 (1.5%)	54 / 2169 (2.5%)	32 / 2092 (1.5%)	33 / 1179 (2.8%)	33 / 1606 (2.1%)	14 / 3015 (0.5%)
Muscle aches (myalgia)	748 / 7283 (10%)	0 / 0 (NA%)	0 / 0 (NA%)	57 / 1389 (4.1%)	105 / 1189 (8.8%)	164 / 1615 (10%)	422 / 3090 (14%)
Loss of taste	310 / 6353 (4.9%)	0 / 0 (NA%)	0 / 0 (NA%)	7 / 1014 (0.7%)	17 / 981 (1.7%)	48 / 1423 (3.4%)	238 / 2935 (8.1%)
Loss of smell	334 / 6538 (5.1%)	0 / 0 (NA%)	0 / 0 (NA%)	9 / 1071 (0.8%)	15 / 1029 (1.5%)	50 / 1465 (3.4%)	260 / 2973 (8.7%)
Bleeding (Haemorrhage)	26 / 2247 (1.2%)	2 / 88 (2.3%)	1 / 439 (0.2%)	3 / 581 (0.5%)	5 / 411 (1.2%)	4 / 270 (1.5%)	11 / 458 (2.4%)
Seizures (anytime)	525 / 3158 (17%)	4 / 109 (3.7%)	73 / 541 (13%)	219 / 741 (30%)	82 / 442 (19%)	74 / 436 (17%)	73 / 889 (8.2%)
Cough	5051 / 12 195 (41%)	48 / 185 (26%)	1252 / 2582 (48%)	1281 / 2606 (49%)	443 / 1471 (30%)	606 / 1855 (33%)	1421 / 3496 (41%)

*n / N (%)

Table S10. Description of comorbidities for the whole paediatric population and stratified per age group

Characteristic	Age groups						
	Overall, N = 50 351*	<1 month, N = 1400*	1–11 months, N = 9586*	1–4 years, N = 10 823*	5–9 years, N = 6318*	10–14 years, N = 7503*	15–19 years, N = 14 721*
HIV	985 / 31 884 (3.1%)	34 / 703 (4.8%)	140 / 5715 (2.4%)	182 / 7287 (2.5%)	90 / 4128 (2.2%)	110 / 4815 (2.3%)	429 / 9236 (4.6%)
Chronic cardiac disease (not hypertension)	467 / 31 256 (1.5%)	5 / 694 (0.7%)	104 / 5741 (1.8%)	116 / 7346 (1.6%)	75 / 4144 (1.8%)	69 / 4630 (1.5%)	98 / 8701 (1.1%)
Diabetes	1106 / 33 031 (3.3%)	16 / 718 (2.2%)	63 / 5865 (1.1%)	115 / 7555 (1.5%)	140 / 4310 (3.2%)	267 / 5022 (5.3%)	505 / 9561 (5.3%)
Hypertension	582 / 32 105 (1.8%)	20 / 715 (2.8%)	60 / 5548 (1.1%)	90 / 7241 (1.2%)	78 / 4219 (1.8%)	83 / 4920 (1.7%)	251 / 9462 (2.7%)
Pulmonary disease (including asthma)	2351 / 30 141 (7.8%)	10 / 645 (1.6%)	205 / 5438 (3.8%)	541 / 6943 (7.8%)	451 / 3994 (11%)	464 / 4511 (10%)	680 / 8610 (7.9%)
Tuberculosis	367 / 25 776 (1.4%)	4 / 680 (0.6%)	41 / 4836 (0.8%)	97 / 6295 (1.5%)	46 / 3473 (1.3%)	47 / 3629 (1.3%)	132 / 6863 (1.9%)
Asplenia	5 / 1407 (0.4%)	0 / 46 (0%)	0 / 244 (0%)	1 / 328 (0.3%)	2 / 207 (1.0%)	1 / 185 (0.5%)	1 / 397 (0.3%)
Chronic kidney disease	285 / 31 359 (0.9%)	3 / 699 (0.4%)	38 / 5786 (0.7%)	44 / 7392 (0.6%)	49 / 4151 (1.2%)	71 / 4637 (1.5%)	80 / 8694 (0.9%)
Malignant neoplasm	367 / 30 522 (1.2%)	1 / 654 (0.2%)	13 / 5653 (0.2%)	103 / 7142 (1.4%)	89 / 3970 (2.2%)	94 / 4534 (2.1%)	67 / 8569 (0.8%)
Chronic liver disease	98 / 9818 (1.0%)	1 / 131 (0.8%)	14 / 1618 (0.9%)	19 / 2053 (0.9%)	15 / 1273 (1.2%)	22 / 1687 (1.3%)	27 / 3056 (0.9%)
Chronic neurological disorder	599 / 10 021 (6.0%)	1 / 169 (0.6%)	44 / 1705 (2.6%)	138 / 2127 (6.5%)	137 / 1318 (10%)	146 / 1695 (8.6%)	133 / 3007 (4.4%)

*n / N (%)

Table S11. Multivariate regression analysis of comorbidities associated with severity of disease

Characteristic	Severity		Logistic mixed effects model		
	Mild N = 24 351*	Severe N = 3725*	OR	95% CI	p-value
HIV					
No	23 929 (87%)	3620 (13%)	1.00	—	
Yes	422 (80%)	105 (20%)	2.04	1.62, 2.57	<0.001
Chronic cardiac disease (not hypertension)					
No	24 090 (87%)	3601 (13%)	1.00	—	
Yes	261 (68%)	124 (32%)	1.68	1.32, 2.13	<0.001
Diabetes					
No	23 653 (87%)	3570 (13%)	1.00	—	
Yes	698 (82%)	155 (18%)	1.31	1.07, 1.60	0.009
Hypertension					
No	24 046 (87%)	3623 (13%)	1.00	—	
Yes	305 (75%)	102 (25%)	1.75	1.36, 2.26	<0.001
Pulmonary disease (including asthma)					
No	22 839 (87%)	3399 (13%)	1.00	—	
Yes	1512 (82%)	326 (18%)	1.27	1.11, 1.45	<0.001
Age group					
15–19 years	7053 (89%)	858 (11%)	1.00	—	
<1 month	470 (78%)	132 (22%)	2.42	1.94, 3.02	<0.001
1–11 months	4231 (83%)	856 (17%)	1.65	1.48, 1.84	<0.001
1–4 years	5645 (86%)	919 (14%)	1.32	1.19, 1.47	<0.001
5–9 years	3224 (87%)	486 (13%)	1.16	1.03, 1.32	0.018
10–14 years	3728 (89%)	474 (11%)	0.98	0.86, 1.11	0.7
Sex					
Male	12 285 (86%)	2002 (14%)	1.00	—	
Female	12 066 (88%)	1723 (12%)	0.87	0.81, 0.94	<0.001

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S12. **Multivariate regression analysis of comorbidities associated with 14 day in hospital mortality**

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 28 048*	Yes N = 379*	HR†	95% CI	p-value
HIV					
No	27 554 (99%)	336 (1.2%)	1.00	—	
Yes	494 (92%)	43 (8.0%)	5.05	3.62, 7.03	<0.001
Chronic cardiac disease (not hypertension)					
No	27 665 (99%)	358 (1.3%)	1.00	—	
Yes	383 (95%)	21 (5.2%)	4.85	3.02, 7.77	<0.001
Diabetes					
No	27 187 (99%)	354 (1.3%)	1.00	—	
Yes	861 (97%)	25 (2.8%)	2.26	1.48, 3.44	<0.001
Chronic kidney disease					
No	27 829 (99%)	366 (1.3%)	1.00	—	
Yes	219 (94%)	13 (5.6%)	4.32	2.40, 7.80	<0.001
Malignant neoplasm					
No	27 737 (99%)	369 (1.3%)	1.00	—	
Yes	311 (97%)	10 (3.1%)	3.61	1.87, 6.97	<0.001
Age group					
15–19 years	7776 (99%)	113 (1.4%)	1.00	—	
<1 month	564 (94%)	34 (5.7%)	3.55	2.41, 5.25	<0.001
1–11 months	5153 (98%)	90 (1.7%)	1.18	0.89, 1.58	0.2
1–4 years	6654 (99%)	52 (0.8%)	0.54	0.39, 0.76	<0.001
5–9 years	3707 (99%)	32 (0.9%)	0.58	0.39, 0.86	0.007
10–14 years	4194 (99%)	58 (1.4%)	0.96	0.70, 1.33	0.8
Sex					
Male	14 283 (99%)	196 (1.4%)	1.00	—	
Female	13 765 (99%)	183 (1.3%)	0.89	0.73, 1.10	0.3

*n (%); †not shown: country included as a random effects variable; HR = Hazard Ratio; CI = Confidence Interval

Table S13. Multivariate regression analysis of association between burden of comorbidity and severity of disease

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 28 401*	Severe N = 6509*	OR†	95% CI	p-value
Comorbidity burden					
No underlying condition	23 145 (83%)	4835 (17%)	1.00	—	
1 or 2 conditions	5058 (76%)	1607 (24%)	1.41	1.30, 1.52	<0.001
3+ conditions	198 (75%)	67 (25%)	1.79	1.32, 2.42	<0.001
Age group					
15–19 years	8732 (86%)	1478 (14%)	1.00	—	
<1 month	550 (69%)	249 (31%)	2.46	2.03, 2.98	<0.001
1–11 months	4804 (77%)	1402 (23%)	1.59	1.45, 1.75	<0.001
1–4 years	6238 (79%)	1662 (21%)	1.37	1.25, 1.50	<0.001
5–9 years	3624 (80%)	902 (20%)	1.19	1.06, 1.32	0.002
10–14 years	4453 (85%)	816 (15%)	0.99	0.89, 1.10	0.9
Sex					
Male	14 151 (80%)	3476 (20%)	1.00	—	
Female	14 250 (82%)	3033 (18%)	0.89	0.83, 0.95	<0.001

*n (%); †not shown: country included as a random effects variable; OR = Odds Ratio; CI = Confidence Interval

Table S14. Multivariate regression analysis of association between burden of underlying conditions and 14 day in hospital mortality

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 33 882*	Yes N = 614*	HR†	95% CI	p-value
Comorbidity burden					
No underlying condition	27 315 (99%)	378 (1.4%)	1.00	—	
1 or 2 conditions	6333 (97%)	214 (3.3%)	2.85	2.39, 3.39	<0.001
3+ conditions	234 (91%)	22 (8.6%)	8.49	5.48, 13.1	<0.001
Age group					
15–19 years	9901 (98%)	204 (2.0%)	1.00	—	
<1 month	736 (94%)	51 (6.5%)	2.95	2.16, 4.03	<0.001
1–11 months	6016 (98%)	136 (2.2%)	1.12	0.89, 1.40	0.3
1–4 years	7712 (99%)	78 (1.0%)	0.48	0.37, 0.63	<0.001
5–9 years	4401 (99%)	52 (1.2%)	0.52	0.38, 0.71	<0.001
10–14 years	5116 (98%)	93 (1.8%)	0.88	0.69, 1.12	0.3
Sex					
Male	17 072 (98%)	314 (1.8%)	1.00	—	
Female	16 810 (98%)	300 (1.8%)	0.92	0.78, 1.08	0.3

*n (%); †not shown: country included as a random effects variable; HR = Hazard Ratio; CI = Confidence Interval

Table S15. Multivariate regression analysis of comorbidities associated with 28 day in hospital mortality (instead of 14 days)

	Deceased within 28 days		Cox mixed effects model		
Characteristic	No N = 27 996*	Yes N = 431*	HR	95% CI	p-value
HIV					
No	27 509 (99%)	381 (1.4%)	1.00	—	
Yes	487 (91%)	50 (9.3%)	5.21	3.83, 7.09	<0.001
Chronic cardiac disease (not hypertension)					
No	27 615 (99%)	408 (1.5%)	1.00	—	
Yes	381 (94%)	23 (5.7%)	4.60	2.93, 7.20	<0.001
Diabetes					
No	27 139 (99%)	402 (1.5%)	1.00	—	
Yes	857 (97%)	29 (3.3%)	2.25	1.52, 3.33	<0.001
Chronic kidney disease					
No	27 778 (99%)	417 (1.5%)	1.00	—	
Yes	218 (94%)	14 (6.0%)	3.92	2.23, 6.90	<0.001
Malignant neoplasm					
No	27 691 (99%)	415 (1.5%)	1.00	—	
Yes	305 (95%)	16 (5.0%)	5.25	3.10, 8.91	<0.001
Age group					
15–19 years	7753 (98%)	136 (1.7%)	1.00	—	
<1 month	561 (94%)	37 (6.2%)	3.22	2.22, 4.66	<0.001
1–11 months	5147 (98%)	96 (1.8%)	1.05	0.80, 1.37	0.7
1–4 years	6647 (99%)	59 (0.9%)	0.51	0.37, 0.69	<0.001
5–9 years	3703 (99%)	36 (1.0%)	0.53	0.37, 0.77	<0.001
10–14 years	4185 (98%)	67 (1.6%)	0.91	0.67, 1.22	0.5
Sex					
Male	14 253 (98%)	226 (1.6%)	1.00	—	
Female	13 743 (99%)	205 (1.5%)	0.86	0.71, 1.04	0.11

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S16. Multivariate regression analysis of comorbidities associated with severity of disease, excluding South Africa

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 5834*	Severe N = 1699*	OR	95% CI	p-value
HIV					
No	5813 (78%)	1671 (22%)	1.00	—	
Yes	21 (43%)	28 (57%)	2.84	1.43, 5.66	0.003
Hypertension					
No	5741 (78%)	1647 (22%)	1.00	—	
Yes	93 (64%)	52 (36%)	1.53	1.02, 2.30	0.039
Pulmonary disease (including asthma)					
No	5218 (78%)	1467 (22%)	1.00	—	
Yes	616 (73%)	232 (27%)	1.47	1.22, 1.78	<0.001
Malignant neoplasm					
No	5624 (77%)	1663 (23%)	1.00	—	
Yes	210 (85%)	36 (15%)	0.53	0.36, 0.77	0.001
Chronic neurological disorder					
No	5550 (79%)	1464 (21%)	1.00	—	
Yes	284 (55%)	235 (45%)	3.69	3.01, 4.51	<0.001
Age group					
15–19 years	2304 (88%)	306 (12%)	1.00	—	
<1 month	37 (48%)	40 (52%)	4.37	2.49, 7.68	<0.001
1–11 months	779 (71%)	321 (29%)	2.23	1.82, 2.74	<0.001
1–4 years	896 (64%)	504 (36%)	3.41	2.83, 4.10	<0.001
5–9 years	660 (70%)	282 (30%)	2.49	2.02, 3.07	<0.001
10–14 years	1158 (82%)	246 (18%)	1.46	1.19, 1.78	<0.001
Sex					
Male	2996 (76%)	953 (24%)	1.00	—	
Female	2838 (79%)	746 (21%)	0.80	0.70, 0.91	<0.001

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S17. Multivariate regression analysis of comorbidities associated with 14 day in hospital mortality, excluding South Africa

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 7488*	Yes N = 77*	HR	95% CI	p-value
HIV					
No	7452 (99%)	71 (0.9%)	1.00	—	
Yes	36 (86%)	6 (14%)	4.96	1.88, 13.1	0.001
Chronic cardiac disease (not hypertension)					
No	7226 (99%)	62 (0.9%)	1.00	—	
Yes	262 (95%)	15 (5.4%)	4.17	2.18, 7.97	<0.001
Diabetes					
No	7101 (99%)	66 (0.9%)	1.00	—	
Yes	387 (97%)	11 (2.8%)	2.43	1.20, 4.92	0.014
Pulmonary disease (including asthma)					
No	6618 (99%)	59 (0.9%)	1.00	—	
Yes	870 (98%)	18 (2.0%)	1.96	1.12, 3.43	0.019
Chronic kidney disease					
No	7322 (99%)	66 (0.9%)	1.00	—	
Yes	166 (94%)	11 (6.2%)	5.15	2.59, 10.2	<0.001
Malignant neoplasm					
No	7245 (99%)	71 (1.0%)	1.00	—	
Yes	243 (98%)	6 (2.4%)	2.68	1.09, 6.55	0.031
Chronic neurological disorder					
No	6980 (99%)	60 (0.9%)	1.00	—	
Yes	508 (97%)	17 (3.2%)	4.22	2.28, 7.82	<0.001
Age group					
15–19 years	2542 (99%)	24 (0.9%)	1.00	—	
<1 month	74 (97%)	2 (2.6%)	0.84	0.19, 3.79	0.8
1–11 months	1123 (98%)	18 (1.6%)	1.36	0.71, 2.61	0.4
1–4 years	1396 (99%)	11 (0.8%)	0.75	0.36, 1.56	0.4
5–9 years	947 (99%)	9 (0.9%)	0.79	0.36, 1.74	0.6
10–14 years	1406 (99%)	13 (0.9%)	1.05	0.52, 2.10	0.9
Sex					
Male	3929 (99%)	39 (1.0%)	1.00	—	
Female	3559 (99%)	38 (1.1%)	0.97	0.61, 1.54	>0.9

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S18. Multivariate regression analysis of comorbidities associated with severity of disease, limited to South Africa, including tuberculosis among covariates

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 18 376*	Severe N = 2042*	OR	95% CI	p-value
HIV					
No	17 978 (90%)	1964 (9.8%)	1.00	—	
Yes	398 (84%)	78 (16%)	1.78	1.37, 2.27	<0.001
Chronic cardiac disease (not hypertension)					
No	18 321 (90%)	2009 (9.9%)	1.00	—	
Yes	55 (63%)	33 (38%)	5.01	3.17, 7.79	<0.001
Diabetes					
No	17 991 (90%)	1981 (9.9%)	1.00	—	
Yes	385 (86%)	61 (14%)	1.53	1.14, 2.01	0.003
Hypertension					
No	18 169 (90%)	1997 (9.9%)	1.00	—	
Yes	207 (82%)	45 (18%)	1.59	1.10, 2.23	0.010
Chronic kidney disease					
No	18 340 (90%)	2030 (10.0%)	1.00	—	
Yes	36 (75%)	12 (25%)	2.15	1.02, 4.22	0.034
Malignant neoplasm					
No	18 323 (90%)	2030 (10.0%)	1.00	—	
Yes	53 (82%)	12 (18%)	2.42	1.23, 4.41	0.006
Age group					
15–19 years	4733 (90%)	541 (10%)	1.00	—	
<1 month	430 (83%)	89 (17%)	1.87	1.46, 2.39	<0.001
1–11 months	3423 (86%)	551 (14%)	1.46	1.29, 1.67	<0.001
1–4 years	4710 (92%)	426 (8.3%)	0.82	0.71, 0.93	0.003
5–9 years	2530 (92%)	208 (7.6%)	0.72	0.61, 0.85	<0.001
10–14 years	2550 (92%)	227 (8.2%)	0.77	0.65, 0.91	0.002
Sex					
Male	9231 (90%)	1069 (10%)	1.00	—	
Female	9145 (90%)	973 (9.6%)	0.90	0.82, 0.99	0.035

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S19. Multivariate regression analysis of comorbidities associated with 14 day in hospital mortality, limited to South Africa, including tuberculosis among covariates

	Deceased within 14 days		Cox mixed effects model		
Characteristic	No N = 19 951*	Yes N = 291*	HR	95% CI	p-value
HIV					
No	19 532 (99%)	254 (1.3%)	1.00	—	
Yes	419 (92%)	37 (8.1%)	4.93	3.37, 7.21	<0.001
Chronic cardiac disease (not hypertension)					
No	19 869 (99%)	285 (1.4%)	1.00	—	
Yes	82 (93%)	6 (6.8%)	4.44	1.97, 9.99	<0.001
Diabetes					
No	19 502 (99%)	277 (1.4%)	1.00	—	
Yes	449 (97%)	14 (3.0%)	2.26	1.31, 3.91	0.004
Tuberculosis					
No	19 705 (99%)	273 (1.4%)	1.00	—	
Yes	246 (93%)	18 (6.8%)	2.83	1.67, 4.77	<0.001
Malignant neoplasm					
No	19 893 (99%)	287 (1.4%)	1.00	—	
Yes	58 (94%)	4 (6.5%)	5.76	2.13, 15.6	<0.001
Age group					
15–19 years	5110 (98%)	90 (1.7%)	1.00	—	
<1 month	477 (94%)	32 (6.3%)	4.36	2.89, 6.58	<0.001
1–11 months	3870 (98%)	68 (1.7%)	1.20	0.86, 1.66	0.3
1–4 years	5073 (99%)	38 (0.7%)	0.49	0.33, 0.72	<0.001
5–9 years	2706 (99%)	23 (0.8%)	0.53	0.33, 0.84	0.007
10–14 years	2715 (99%)	40 (1.5%)	0.88	0.60, 1.28	0.5
Sex					
Male	10 059 (99%)	150 (1.5%)	1.00	—	
Female	9892 (99%)	141 (1.4%)	0.88	0.70, 1.12	0.3

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S20. Multivariate regression analysis of the association between HIV status and disease severity

Characteristic	Severity		Logistic mixed effects model		
	Mild N = 25 363*	Severe N = 4446*	OR	95% CI	p-value
HIV					
No	24 903 (85%)	4316 (15%)	1.00	—	
Yes	460 (78%)	130 (22%)	1.70	1.39, 2.07	<0.001
Hypertension					
No	25 037 (85%)	4330 (15%)	1.00	—	
Yes	326 (74%)	116 (26%)	2.16	1.73, 2.67	<0.001
Age group					
<5y	10 464 (83%)	2206 (17%)	1.00	—	
5–9 years	3305 (86%)	554 (14%)	0.79	0.71, 0.87	<0.001
10–14 years	3985 (87%)	572 (13%)	0.68	0.61, 0.75	<0.001
15–19 years	7609 (87%)	1114 (13%)	0.69	0.63, 0.74	<0.001
Sex					
Male	12 679 (84%)	2361 (16%)	1.00	—	
Female	12 684 (86%)	2085 (14%)	0.91	0.86, 0.98	0.007

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S21. Multivariate regression analysis of the association between HIV status and 14 day in hospital mortality

Characteristic	Deceased within 14 days		Cox mixed effects model		
	No N = 29 096*	Yes N = 422*	HR	95% CI	p-value
HIV					
No	28 568 (99%)	368 (1.3%)	1.00	—	
Yes	528 (91%)	54 (9.3%)	7.12	5.32, 9.52	<0.001
Hypertension					
No	28 687 (99%)	399 (1.4%)	1.00	—	
Yes	409 (95%)	23 (5.3%)	3.32	2.17, 5.08	<0.001
Sex					
Male	14 652 (99%)	218 (1.5%)	1.00	—	
Female	14 444 (99%)	204 (1.4%)	0.91	0.75, 1.11	0.3
Age group					
<5y	12 373 (99%)	182 (1.4%)	1.00	—	
5–9 years	3781 (99%)	37 (1.0%)	0.65	0.46, 0.93	0.017
10–14 years	4440 (99%)	64 (1.4%)	0.96	0.72, 1.28	0.8
15–19 years	8502 (98%)	139 (1.6%)	0.97	0.78, 1.22	0.8

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S22. Multivariate regression analysis of the association between HIV status and 28 day in hospital mortality (instead of 14 days)

	Deceased within 28 days		Cox mixed effects model		
Characteristic	No N = 29 045*	Yes N = 473*	HR	95% CI	p-value
HIV					
No	28 524 (99%)	412 (1.4%)	1.00	—	
Yes	521 (90%)	61 (10%)	7.17	5.45, 9.43	<0.001
Hypertension					
No	28 637 (98%)	449 (1.5%)	1.00	—	
Yes	408 (94%)	24 (5.6%)	3.04	2.01, 4.60	<0.001
Sex					
Male	14 623 (98%)	247 (1.7%)	1.00	—	
Female	14 422 (98%)	226 (1.5%)	0.88	0.73, 1.06	0.2
Age group					
<5 years	12 357 (98%)	198 (1.6%)	1.00	—	
5–9 years	3778 (99%)	40 (1.0%)	0.65	0.46, 0.91	0.012
10–14 years	4431 (98%)	73 (1.6%)	1.01	0.77, 1.32	>0.9
15–19 years	8479 (98%)	162 (1.9%)	1.05	0.85, 1.30	0.6

*n (%); HR = Hazard Ratio; CI = Confidence Interval

Table S23. Multivariate regression analysis of the association between HIV status and disease severity, limited to South African data

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 18,537*	Severe N = 2,069*	OR†	95% CI	p-value
HIV					
No	18,127 (90%)	1,987 (9.9%)	1.00	—	
Yes	410 (83%)	82 (17%)	1.81	1.41, 2.30	<0.001
Chronic cardiac disease (not hypertension)					
No	18,481 (90%)	2,036 (9.9%)	1.00	—	
Yes	56 (63%)	33 (37%)	5.04	3.21, 7.77	<0.001
Hypertension					
No	18,314 (90%)	2,021 (9.9%)	1.00	—	
Yes	223 (82%)	48 (18%)	1.81	1.29, 2.47	<0.001
Age group					
<5 years	8,604 (89%)	1,076 (11%)	1.00	—	
5–9 years	2,554 (92%)	209 (7.6%)	0.64	0.55, 0.75	<0.001
10–14 years	2,569 (92%)	230 (8.2%)	0.71	0.61, 0.82	<0.001
15–19 years	4,810 (90%)	554 (10%)	0.91	0.81, 1.01	0.089
Sex					
Male	9,298 (90%)	1,081 (10%)	1.00	—	
Female	9,239 (90%)	988 (9.7%)	0.90	0.82, 0.99	0.035

*n (%); †not shown: country included as a random effects variable; OR = Odds Ratio; CI = Confidence Interval

Table S24. Multivariate regression analysis of the association between HIV status and 14 day in hospital mortality, limited to South African data

Characteristic	Deceased within 14 days		Cox mixed effects model		
	No N = 20,275*	Yes N = 306*	HR†	95% CI	p-value
HIV					
No	19,828 (99%)	267 (1.3%)	1.00	—	
Yes	447 (92%)	39 (8.0%)	5.85	4.15, 8.25	<0.001
Chronic cardiac disease (Not Hypertension)					
No	20,192 (99%)	300 (1.5%)	1.00	—	
Yes	83 (93%)	6 (6.7%)	3.57	1.55, 8.23	0.003
Hypertension					
No	20,014 (99%)	296 (1.5%)	1.00	—	
Yes	261 (96%)	10 (3.7%)	1.94	1.01, 3.73	0.048
Age group					
<5 years	9,524 (99%)	142 (1.5%)	1.00	—	
5–9 years	2,736 (99%)	24 (0.9%)	0.57	0.37, 0.88	0.011
10–14 years	2,749 (98%)	45 (1.6%)	1.05	0.75, 1.47	0.8
15–19 years	5,266 (98%)	95 (1.8%)	1.05	0.80, 1.38	0.7
Sex					
Male	10,209 (98%)	157 (1.5%)	1.00	—	
Female	10,066 (99%)	149 (1.5%)	0.91	0.73, 1.15	0.4

*n (%); †not shown: country included as a random effects variable; HR = Hazard Ratio; CI = Confidence Interval

Table S25. Countries with ninety percent predominant SARS-CoV2 variant of the COVID-19 population using GISAID genetic sequencing data

	GISAID genetic sequencing data								
Country	Alpha (start)	Alpha (end)	Beta (start)	Beta (end)	Gamma (start)	Gamma (end)	Delta (start)	Delta (end)	Omicron (start)
Bangladesh							06/24/2021	12/20/2021	01/15/2022
Brazil					04/01/2021	07/08/2021	09/13/2021	12/10/2021	01/02/2022
Burkina Faso									01/11/2022
Cameroon									01/03/2022
Canada							07/29/2021	12/03/2021	12/27/2021
Colombia							10/30/2021	11/21/2021	01/07/2022
Democratic Republic of the Congo									01/04/2022
Dominican Republic							10/08/2021	12/11/2021	12/29/2021
Ecuador							10/14/2021	11/29/2021	01/11/2022
France							07/22/2021	12/05/2021	01/09/2022
Gambia							06/26/2021	12/14/2021	12/18/2021
Germany							07/27/2021	12/13/2021	01/15/2022
Greece	03/12/2021	06/08/2021					07/26/2021	12/07/2021	01/12/2022
Guinea							07/25/2021	10/26/2021	01/04/2022
Hungary							07/16/2021	12/16/2021	01/11/2022
India							06/25/2021	12/04/2021	01/13/2022
Indonesia							07/10/2021	12/08/2021	01/14/2022
Ireland	02/20/2021	05/26/2021					07/12/2021	12/03/2021	12/27/2021
Israel							07/10/2021	12/04/2021	01/03/2022
Italy							07/29/2021	12/01/2021	01/21/2022
Japan									01/30/2022
Jordan							07/12/2021	12/05/2021	01/26/2022
Kuwait							07/04/2021	09/06/2021	02/20/2022
Malawi							05/31/2021	11/04/2021	11/18/2021
Malaysia							07/19/2021	11/30/2021	01/25/2022
Netherlands (Kingdom of the)	03/22/2021	05/26/2021					07/15/2021	12/11/2021	01/10/2022
Niger									01/21/2022
Nigeria							07/29/2021	10/24/2021	12/27/2021
Norway	03/20/2021	06/06/2021					07/25/2021	11/30/2021	01/06/2022
Panama							10/16/2021	12/12/2021	01/05/2022
Peru							10/22/2021	12/11/2021	01/11/2022
Philippines							08/15/2021	09/29/2021	12/02/2021
Poland	03/24/2021	06/02/2021					08/04/2021	12/26/2021	01/19/2022
Republic of Korea							08/05/2021	12/22/2021	01/22/2022
Russian Federation							06/16/2021	12/09/2021	01/30/2022
Singapore							05/23/2021	12/04/2021	01/09/2022
South Africa							07/14/2021	10/14/2021	11/26/2021
Spain							07/28/2021	11/29/2021	01/14/2022
Sudan							07/20/2021	10/01/2021	12/15/2021

Table S25. *continued*

	GISAID genetic sequencing data								
Country	Alpha (start)	Alpha (end)	Beta (start)	Beta (end)	Gamma (start)	Gamma (end)	Delta (start)	Delta (end)	Omicron (start)
Türkiye							09/06/2021	12/22/2021	01/13/2022
Ukraine							07/20/2021	12/23/2021	01/23/2022
United Kingdom	01/30/2021	04/21/2021					06/09/2021	12/06/2021	12/26/2021
United States of America							07/22/2021	12/06/2021	12/31/2021
Zambia			01/15/2021	04/01/2021			05/22/2021	10/01/2021	10/29/2021
Zimbabwe			01/12/2021	05/11/2021			06/19/2021	10/19/2021	11/10/2021

Table S26. **Description of reported cases by variant of concern**

	Age group						
Characteristic	Overall, N = 50 351*	<1 month, N = 1400*	1–11 months, N = 9586*	1–4 years, N = 10 823*	5–9 years, N = 6318*	10–14 years, N = 7503*	15–19 years, N = 14 721*
Variant of concern (90% threshold)							
alpha	458 (0.9%)	0 (0%)	87 (0.9%)	100 (0.9%)	77 (1.2%)	92 (1.2%)	102 (0.7%)
beta	14 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1%)	10 (<0.1%)
delta	9192 (18%)	284 (20%)	1515 (16%)	1570 (15%)	1047 (17%)	1621 (22%)	3155 (21%)
omicron	18 112 (36%)	372 (27%)	4201 (44%)	4690 (43%)	2566 (41%)	2300 (31%)	3983 (27%)
other	22 575 (45%)	743 (53%)	3783 (39%)	4463 (41%)	2628 (42%)	3487 (46%)	7471 (51%)

*n (%)

Table S27. Multivariate regression analysis of comorbidities associated with severity of disease, limited to alpha and omicron data and including VOC as a covariate

	Severity		Logistic mixed effects model		
Characteristic	Mild N = 13 776*	Severe N = 1617*	OR	95% CI	p-value
HIV					
No	13 541 (90%)	1562 (10%)	1.00	—	
Yes	235 (81%)	55 (19%)	2.10	1.51, 2.90	<0.001
Chronic cardiac disease (not hypertension)					
No	13 666 (90%)	1569 (10%)	1.00	—	
Yes	110 (70%)	48 (30%)	2.10	1.45, 3.02	<0.001
Hypertension					
No	13 624 (90%)	1578 (10%)	1.00	—	
Yes	152 (80%)	39 (20%)	2.14	1.46, 3.14	<0.001
Variant of concern (90% threshold)					
Delta	3820 (86%)	632 (14%)	1.00	—	
Omicron	9956 (91%)	985 (9.0%)	0.66	0.59, 0.74	<0.001
Age group					
15–19 years	3202 (91%)	325 (9.2%)	1.00	—	
<1 month	236 (83%)	49 (17%)	2.47	1.75, 3.48	<0.001
1–11 months	2666 (86%)	429 (14%)	2.11	1.79, 2.49	<0.001
1–4 years	3643 (90%)	412 (10%)	1.42	1.20, 1.67	<0.001
5–9 years	2064 (91%)	207 (9.1%)	1.20	1.0, 1.46	0.057
10–14 years	1965 (91%)	195 (9.0%)	1.03	0.85, 1.25	0.7
Sex					
Male	7114 (89%)	906 (11%)	1.00	—	
Female	6662 (90%)	711 (9.6%)	0.85	0.76, 0.95	0.003

*n (%); OR = Odds Ratio; CI = Confidence Interval

Table S28. Multivariate regression analysis of comorbidities associated with 14 day in hospital mortality, limited to alpha and omicron data and including VOC as a covariate

Characteristic	Deceased within 14 days		Cox mixed effects model		
	No N = 15 534*	Yes N = 185*	HR	95% CI	p-value
HIV					
No	15 252 (99%)	157 (1.0%)	1.00	—	
Yes	282 (91%)	28 (9.0%)	6.43	4.19, 9.88	<0.001
Chronic cardiac disease (not hypertension)					
No	15 379 (99%)	181 (1.2%)	1.00	—	
Yes	155 (97%)	4 (2.5%)	3.47	1.24, 9.69	0.018
Variant of concern (90% threshold)					
Delta	4484 (98%)	81 (1.8%)	1.00	—	
Omicron	11 050 (99%)	104 (0.9%)	0.61	0.45, 0.83	0.002
Age group					
15–19 years	3550 (99%)	49 (1.4%)	1.00	—	
<1 month	273 (94%)	18 (6.2%)	3.67	2.11, 6.37	<0.001
1–11 months	3135 (98%)	51 (1.6%)	1.32	0.88, 1.98	0.2
1–4 years	4112 (99%)	24 (0.6%)	0.50	0.31, 0.83	0.007
5–9 years	2295 (99%)	15 (0.6%)	0.57	0.32, 1.03	0.063
10–14 years	2169 (99%)	28 (1.3%)	1.06	0.66, 1.69	0.8
Sex					
Male	8095 (99%)	99 (1.2%)	1.00	—	
Female	7439 (99%)	86 (1.1%)	0.90	0.67, 1.21	0.5

*n (%); HR = Hazard Ratio; CI = Confidence Interval

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