Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity

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ABSTRACT

Background The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.

Methods The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.

Results A total of 12,860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% (=3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities (tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent systematic reviews identified a potential- ly higher paediatric mortality per population from COVID-19 in low-income to middle-income countries (LMICs) compared with high-income countries (HICs) but concluded that heterogeneity of published studies limits firm conclusions. Correspondingly, lethality of other acute respiratory infections has been shown to be higher in LMIC.

WHAT THIS STUDY ADDS

⇒ By using harmonised data collection tools of a study population of over 12,000 children, this study can directly compare inpatient management and outcomes in HIC and LMIC. Analysis finds higher mortality in LMIC, although a lower proportion receive intensive care unit admission and ventilation prior to death. Disparity in access to care and lack of available advanced medical therapies are highlighted and provide areas for collaborative efforts between clinicians, administrators and likely government groups to improve outcomes in LMIC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While intensified by the pandemic, a lack of adequate resources to care for children with acute respiratory infections in LMIC is likely a general concern that requires allocation of resources. Reducing the gap in our ability to care for sick children in LMICs versus HICs will inevitably improve global outcomes during both pandemic and interpandemic periods.

Conclusion Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.
INTRODUCTION

The clinical presentation, severity and outcomes of acute COVID-19 are different in children compared with adults. While a higher proportion of children are asymptomatic or less severely ill than in many adult reports, severe manifestations do occur. While cardiac compromise in the form of multisystem inflammatory syndrome in children (MIS-C) is often described, acute respiratory distress syndrome (ARDS) and other organ dysfunction also occurs in children. The risk factors for severe disease in in paediatrics are incompletely understood. Furthermore, there is a lack of global data to improve understanding of the COVID-19 burden in children who live in low-income to middle-income countries (LMICs) versus those in high-income countries (HICs) sites.

One systematic review that summarised the difference in paediatric COVID-19 morbidity and mortality in HICs and LMICs has been published. However, most studies' samples analysed fewer than 100 patients, and over half the data came from the USA and China. Furthermore, due to heterogeneous reporting of data in the included studies, the authors were limited in their ability to pool the data. Nearly all studies were conducted in one region or only presented data of children admitted to institutions across the globe contributing to the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) database according to ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infection. Fields for analysis were extracted from the complete dataset gathered from Research Electronic Data Capture (V.8.11.11, Vanderbilt University, Nashville, Tennessee, USA). Variables of interest were classified into four domains: comorbidities, presenting signs and symptoms, complications and treatments. Comorbidity was defined as any history of pre-existing medical conditions that were not otherwise related to COVID-19 natural history and reported at admission date. Complications referred to any medical condition detected during patients' stay that was not present at admission. Therapies included were drugs, oxygen and use of other treatments such as invasive mechanical ventilation (IMV). Ethnicity was collapsed into five categories (black or African American, white, Asian, mixed/others and missing/unknown) following the Centers for Disease Control and Prevention National Health Interview Survey glossary.

METHODS

Data were collected from hospitalised patients under 19 years of age with confirmed or clinically suspected COVID-19 between 1 January 2020 and 31 March 2021 admitted to institutions across the globe contributing to the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) database according to ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infection. Fields for analysis were extracted from the complete dataset gathered from Research Electronic Data Capture (V.8.11.11, Vanderbilt University, Nashville, Tennessee, USA).

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| Income group          | Country name | n  | %   |
|-----------------------|--------------|----|-----|
| High-income country   | UK           | 3099 | 24.1 |
| High-income country   | Poland       | 304  | 2.4  |
| High-income country   | Canada       | 164  | 1.3  |
| High-income country   | Spain        | 87   | 0.7  |
| High-income country   | Germany      | 25   | 0.2  |
| High-income country   | USA          | 22   | 0.2  |
| High-income country   | Ireland      | 21   | 0.2  |
| High-income country   | France       | 18   | 0.1  |
| High-income country   | Australia    | 17   | 0.1  |
| High-income country   | Chile        | 16   | 0.1  |
| High-income country   | Israel       | 12   | 0.1  |
| High-income country   | Netherlands  | 11   | 0.1  |
| High-income country   | Italy        | 8    | 0.1  |
| High-income country   | Greece       | 4    | 0.0  |
| High-income country   | Belgium      | 3    | 0.0  |
| High-income country   | Portugal     | 3    | 0.0  |
| High-income country   | Bolivia      | 1    | 0.0  |
| High-income country   | Kuwait       | 1    | 0.0  |
| High-income country   | Norway       | 1    | 0.0  |
| High-income country   | New Zealand  | 1    | 0.0  |
| High-income country   | Saudi Arabia | 1    | 0.0  |
| Lower-middle income country | South Africa | 7621 | 59.3 |
| Lower-middle income country | Malaysia    | 627  | 4.9  |
| Lower-middle income country | Malawi        | 296  | 2.3  |
| Lower-middle income country | Romania    | 135  | 1.0  |
| Lower-middle income country | Colombia  | 112  | 0.9  |
| Lower-middle income country | Indonesia   | 73   | 0.6  |
| Lower-middle income country | Peru        | 49   | 0.4  |
| Lower-middle income country | Pakistan   | 35   | 0.3  |
| Lower-middle income country | India       | 24   | 0.2  |
| Lower-middle income country | Honduras | 21   | 0.2  |
| Lower-middle income country | Argentina | 18   | 0.1  |
| Lower-middle income country | Mexico      | 11   | 0.1  |
| Lower-middle income country | Brazil     | 10   | 0.1  |
| Lower-middle income country | Nepal       | 6    | 0.0  |
| Lower-middle income country | Russia      | 3    | 0.0  |
income groups were dichotomised into HICs and LMICs according to the latest World Bank classification.

Date of admission was defined as the date of hospitalisation. Descriptive statistics were described as frequencies (n) and proportions for categorical data, mean±SD or median (IQR) for continuous data, and number of available data (N) for each variable. Demographic characteristics, comorbidities, complications and treatments were compared between country income groups using χ² or Fisher’s exact test as indicated. Kaplan-Meier survival curves were plotted and compared using the log-rank test. Multivariable Cox proportional hazards regression models were fitted to identify mortality predictors. In-hospital survival analysis was performed to obtain 28-day and 90-day survival rates. Intensive care unit (ICU) admission and IMV requirement served as proxies for morbidity. Time-to-event analyses were performed to identify morbidity and mortality defining periods: (1) from hospital admission until ICU admission, (2) ICU admission to first intubation, (3) ICU admission to ICU discharge or death, (4) ICU discharge to hospital discharge or death. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.25 (IBM Corp).

RESULTS
There were 12 860 children, originating from 36 countries, 15 of which (41.7%) were LMICs and 21 (58.3%) HICs (table 1). Seventy per cent (n=9041) of participants were from LMICs and 29.7% (n=3819) cases were from HICs. The majority of participants were contributed from 670 cites in South Africa (59.3%) and 346 sites in the UK (24.1%), followed by Malaysia (4.9%), Poland (2.4%) and Malawi (2.3%) (figure 1 and table 1). COVID-19 status was laboratory confirmed in 69.7%; this rate was higher in HICs (73.0%) in comparison with that in LMICs (68.3%) (table 2).

Adolescents aged between 12 and 17 years were the largest age group in LMICs (25.6%) and overall (24.0%), followed by infants younger than 1 year of age (21%). Infants were the largest group in HICs (29.4%). Males (50.8%) and females (49.2%) were similarly represented. Black or African-American participants formed more than one-third of the study population and 52% of LMICs children (table 2).

In total, 425 (3.3%) participants died. The mortality rate was higher in LMICs compared with HICs (4% vs 1.7%) (table 2). Reported mortality in the UK was 52 children (1.2%), which does not differ significantly (p=0.98) from the rest of HICs. Mortality in South Africa, numbering 268 children (3.5%), differed significantly (p=0.001) from 93 (6.5%) mortality in the rest of LMICs. The total admissions and mortality rates across the study period based on country groups (UK, South Africa and other countries) were presented in figure 2. The curves showed bimodal with peaks of mortality rates coinciding with admissions during July 2020 and January 2021. Available case data in early 2020 was limited compared with later time points. In contrast to South Africa and other countries, mortality rate in the UK did not rise significantly with the first and second wave of case admissions during April–May 2020 and October 2020–January 2021.

Children in LMICs had significantly greater and earlier mortality (adjusted HR (aHR) (95% CI) 4.73 (3.16 to 7.10), p<0.001). The 28-day and 90-days survival among all participants were 96.7% (10 339/10 692) and 96.5% (9 642/11 024), respectively. Survival was higher at both 28 (98.3% (3049/3101)) and 90 days (98.1% (3137/3199)) in HICs than LMICs (96.0% (7290/7591) and 95% (7505/7825), respectively).

The availability of information on comorbidities varied between countries of origin. The prevalence of several comorbidities was significantly higher in HICs including chronic neurological disease, seizures, diabetes and chronic cardiac disease. Infectious diseases such as tuberculosis and HIV/AIDS were significantly higher in LMICs (table 3).

The most common presenting symptoms overall include fever (20%), cough (16.1%) and shortness of breath (10.5%). Between-group’s comparisons showed that cough (HIC 14.0% vs LMIC 26.1%), shortness of breath (9.2% vs 16.4%), runny nose (4.2% vs 8.6%), loss of smell or taste (0.7% vs 2.9%), anorexia (0.1% vs 0.8%) and inability to walk (0.1% vs 0.2%) were more common among patients in LMICs.

Complications during hospitalisation are shown in table 4. Patients in LMICs had more bacterial and cryptocogenic pneumonia and ARDS, as well as other organ involvement such as brain with stroke or heart with cardiac arrest. The rates of complications were generally higher than that of HICs, except for cardiac arrhythmia and disseminated intravascular coagulation in which HICs rates were statistically higher.

The two most commonly administered therapies were antibiotics in 41.2% of participants, followed by corticosteroids in 11.4%. Antivirus was administered in 5.3% of subjects, with higher percentage observed in HIC, especially of remdesivir, which is more than twice that of LMIC. Adjunctive and supportive treatments were generally performed more often in HICs. No participants in LMICs were treated with extracorporeal membrane
oxygenation, as compared with 10 participants in HICs (table 5).

Participants in LMICs were most often admitted to the ICU within the first day of admission, with those who died being admitted earlier than survivors (LMICs vs HICs: 0 (0–1) vs 0 (0–2.5) day respectively, p=0.03) . While time to IMV was not significantly different for survivors versus non-surgeons, although non-surgeons in HICs had longer stays than in LMIC (3 (1–6) vs 9.5 (4.5–19.2) days respectively in HIC and 0 (0–4) vs 4 (0.7–7.2) days respectively in LMIC, p<0.05). Mortality was significantly higher (p<0.001) in LMICs compared with HICs for participants who received IMV (43.6% vs 7.3%) or who required ICU admission (16.7% vs 3.5). Nearly 2.3% and 6.1% participants died without ICU and/or IMV support in LMIC in comparison with the respective 1.3% and 1.4% in HICs (table 6).

Multivariable analysis was done to evaluate factors associated with mortality. Significant risk factors found were: aged <1 year (aHR (95% CI)=1.80 (1.01 to 3.22)), low-middle income group (4.73 (3.16 to 7.10)), comorbidities such as chronic kidney disease (3.74 (2.20 to 6.35)) or cardiac disease (2.42 (1.50 to 3.91)) and invasive mechanical ventilator requirement (3.46 (2.27 to 5.28)) or exposure to antibiotics (2.07 (1.34 to 3.22)). The use of antiviral agents (aHR=0.55 (0.32 to 0.96)) was the only factor inversely associated with mortality (figure 3).
DISCUSSION

We present a large international cohort of children hospitalised with COVID-19. We found that mortality was significantly higher in LMICs in comparison with HICs. Disparate care patterns were also observed, with patients in LMICs reported to receive most adjunctive and supportive therapies less frequently than patients in HICs. While these findings may represent differences in practice, they may also represent variation in available supports for children based on income status of the country. Such disparities have been described in adult COVID-19 patients, but limited data exist for children. 11–20

Prior reports have focused on specific aspects of illness such as infection or cardiac dysfunction, have included small cohorts of children or are limited to certain countries or regions. 11–20

While the findings may be criticised as mainly representing data from two countries, the UK and South Africa (SA), these countries are good examples of HICs and LMICs. Statistical analysis showed no significant difference of mortality between UK and the rest of HICs. Although mortality in SA was significantly lower than the rest of LMICs, both mortalities from SA and non-SA LMICs were significantly higher than HICs group. Low number of subjects from non-SA LMICs was disproportionate to that of SA, thus conclusion can not be drawn from observed difference in mortality between them. Furthermore, as data supplied from the UK and South Africa comes from national COVID-19 research databases recruiting from a high number of sites in the UK and South Africa, and in this sense may be more representative of country income differences, as opposed to enrolment of single sites (eg, a national referral centre) in different countries. The inclusion of children from many other countries, although relatively small cohorts form each country in comparison, does allow understanding of care patterns in areas around the world.

More participants from HICs could be admitted to ICU and received IMV than LMICs patients. While the small numbers available for analysis in some categories limit our confidence in these findings, in LMICs they do give IMV and dying within shorter periods of time than HICs. Not only were children in LMICs hospitalised with COVID-19 more likely to die, they were also shown to die earlier in their hospitalisation. Despite possible confounding effects from missing data relating to severity of illness at presentation (vital signs, organ failure scores), a positive association between LMICs and mortality were consistently observed in analysis of children admitted to the ICU and those receiving IMV.

Several independent risk factors for mortality were identified in addition to country economic group. Mortality was lowest for patients aged between 1 and 5 years and higher among patients of age <1 or >5 years. This finding confirmed the U-shaped mortality pattern shown in several other reports, although infancy is not always recognised as a risk factor in small studies. 11–20 Comorbidities such as chronic kidney and cardiac diseases were also shown to be independent risk factors as reported by others. 19 23 24

| Country income | HICs | LMICs | Total |
|----------------|------|-------|-------|
|                | N    | n     | %     | N    | n     | %     | N    | n     | %     | P value |
| Chronic neurological disorder* | 2588 | 191  | 7.4 | 902 | 14  | 1.6 | 3490 | 205 | 5.9 | 0.001 |
| Seizure* | 2490 | 111  | 4.5 | 899 | 16  | 1.8 | 3389 | 127 | 3.7 | 0.001 |
| Smoking | 2091 | 82   | 3.9 | 1509 | 46  | 3.0 | 3600 | 128 | 3.6 | 0.215 |
| Diabetes* | 2592 | 95   | 3.7 | 4468 | 149 | 3.3 | 7060 | 244 | 3.5 | 0.001 |
| Chronic cardiac disease* | 2587 | 141 | 5.5 | 3578 | 48 | 1.3 | 6165 | 189 | 3.1 | 0.001 |
| Obesity* | 2438 | 90   | 3.7 | 1736 | 39  | 2.2 | 4174 | 129 | 3.1 | 0.001 |
| Tuberculosis* | 290 | – | – | 3649 | 102 | 2.8 | 3939 | 102 | 2.6 | 0.001 |
| Chronic haematological disease* | 2475 | 77 | 3.1 | 899 | 9 | 1.0 | 3374 | 86 | 2.5 | 0.001 |
| HIV/AIDS* | 2562 | 1 | <0.01 | 4382 | 142 | 3.2 | 6944 | 143 | 2.1 | 0.001 |
| Rare diseases and inborn errors of metabolism | 1823 | 36 | 2.0 | 0 | – | – | 1823 | 36 | 2.0% | 0.715 |
| Malnutrition | 2539 | 35 | 1.4 | 901 | 26 | 2.9% | 3440 | 61 | 1.8% | 0.412 |
| Malignant neoplasm* | 2571 | 64 | 2.5 | 4164 | 27 | 0.8% | 6735 | 91 | 1.4% | 0.001 |
| Rheumatological disorder* | 2491 | 45 | 1.8 | 898 | 2 | 0.2% | 3389 | 47 | 1.4% | 0.001 |
| Chronic kidney disease* | 2596 | 59 | 2.3 | 4147 | 28 | 0.7 | 6743 | 87 | 1.3 | 0.001 |
| Liver disease | 2623 | 12 | 0.5 | 902 | – | – | 3525 | 12 | 0.3 | 0.866 |

*Significant with p-value <0.05 using Chi-square test.

HICs, high-income countries; LMICs, low-income to middle-income countries; N, denominators; n, total patients with comorbidities.
infectious in nature, is another possible cause of the relationship between LMICs and mortality. Chronic respiratory failure has been associated with death in COVID-19 adult patients, with some evidence that this occurs in paediatric cases as well. Our data also provided information on tuberculosis, which has not specifically identified as comorbidity in children with COVID-19 in other reports. Similarly, data on the impact of HIV in children is sparse, and our review finds this to be an important risk factor and more prevalent in LMICs.

More patients receiving antiviral therapy were found in HICs versus LMICS. In fact, remdesivir, which is recommended for severe hospitalised COVID-19, was used in exceptionally lower percentage of LMIC subjects. We can only speculate that period of this study occurred when evidence based on antiviral efficacy was still scarce especially in children, or it may indicate lack of access to drug or lack familiarity with recommendations. The recommendations for antiviral use in children with severe COVID-19 from the National Institutes of Health have suggested use for patients over the age of 12 years; this recommendation would not have applied to infants who had a higher risk of mortality in our study. Further investigation of the impact of antivirals in children of all ages should be considered. The efficacy and the cost benefit of these expensive medications in resource-limited sites are needed; if valuable, improving access should then be at the core of discussions.

Table 4 Comparison of complications between country income groups

| Country income | HICs | LMICs | Total |
|----------------|------|-------|-------|
|                | N    | n    | %    | N    | n    | %    | N    | n    | %    | P value |
| Bacterial pneumonia* | 3497 | 11 | 3.3 | 1107 | 10 | 9.2 | 4604 | 21 | 4.7 | <0.001 |
| ARDS* | 3153 | 31 | 1.0 | 4972 | 26 | 7 | 8125 | 29 | 8 | 3.7 | <0.001 |
| AKI | 3624 | 11 | 3.0 | 1410 | 49 | 3.5 | 5034 | 15 | 9 | 3.2 | 0.477 |
| Seizure | 3627 | 10 | 2.8 | 1412 | 39 | 2.8 | 5039 | 14 | 2 | 2.8 | 0.958 |
| Pleural effusion | 3511 | 82 | 2.3 | 1110 | 36 | 3.2 | 4621 | 11 | 8 | 2.6 | 0.118 |
| Myocarditis and pericarditis* | 2858 | 42 | 1.5 | 427 | 22 | 5.2 | 3285 | 64 | 1.9 | <0.001 |
| Bronchiolitis | 3620 | 57 | 1.6 | 1412 | 21 | 1.5 | 5032 | 78 | 1.6 | 0.922 |
| Cardiac arrhythmia* | 3635 | 70 | 1.9 | 1407 | 13 | 0.9 | 5042 | 83 | 1.6 | 0.017 |
| Endocarditis* | 692 | 5 | 0.7 | 487 | 14 | 2.9 | 1179 | 19 | 1.6 | 0.008 |
| Cardiac arrest* | 3535 | 19 | 0.5 | 1412 | 55 | 3.9 | 4947 | 74 | 1.5 | <0.001 |
| DIC* | 3498 | 48 | 1.3 | 4668 | 58 | 1.2 | 8166 | 10 | 4 | 1.3 | 0.850 |
| Meningitis and encephalitis* | 3621 | 16 | 0.4 | 1413 | 20 | 1.4 | 5034 | 36 | 0.7 | <0.001 |
| Pneumothorax | 3530 | 15 | 0.4 | 1109 | 9 | 0.8 | 4639 | 24 | 0.5 | 0.185 |
| Stroke/cerebrovascular complication† | 3527 | 7 | 0.2 | 1109 | 11 | 1.0 | 4636 | 18 | 0.4 | 0.001 |
| Pulmonary embolism | 1928 | 4 | 0.2 | 293 | 2 | 0.7 | 2221 | 6 | 0.3 | 0.182 |
| Cardiac ischaemia | 3510 | 7 | 0.2 | 1110 | 4 | 0.4 | 4620 | 11 | 0.2 | 0.309 |
| Myocardial infarction | 312 | 1 | 0.3 | 298 | – | – | 610 | 1 | 0.2 | 1.000 |
| Sepsis | – | – | – | 3862 | 8 | 0.2 | 3862 | 8 | 0.2 | – |
| DVT | 1606 | 1 | 0.1 | 3 | – | – | 1609 | 1 | 0.1 | 1.000 |
| COP† | 3398 | – | – | 1110 | 5 | 0.5 | 4508 | 5 | 0.1 | 0.001 |

*Significant with p-value <0.05 using χ² test.
†Fisher’s exact test.
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COP, cryptogenic organising pneumonia; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; HICs, high-income countries; LMICs, low-income to middle-income countries; n, total patients with complications; N, denominators.
The higher prevalence of complications of respiratory disease such as ARDS, bacterial and cryptogenic organising pneumonia, and the impact of organ dysfunction outside the lung such as increased rates of myocarditis, pericarditis, endocarditis, meningitis, encephalitis, stroke and cardiac arrest observed in LMICs are also likely factors in the high death rates. Patients with MIS-C were not specifically reported in the time period of this report.

Our study has the strength of a common reporting format in participating centres around the world. We describe a relatively large number of children and are able to provide both comparisons of patient characteristics and outcomes and evaluate risk factors for outcomes using common definitions. Limitation of this study includes a predominance of patients from one LMICs and one HICs, South Africa and UK, potentially limiting the generalisability of our findings to all countries. In addition, we did not adjust for pandemic era. Inevitably, we have missing data for a number of variables, including comorbidities, which limits the effective sample size of analyses examining relationships with patient characteristics and outcomes. Lack of data on nutritional status of children on each group, which may explain disparity between country income groups, was another limitation of the study. Moreover, considerable proportion of non-confirmed cases also limits the impact of this study on public health policy.

In conclusion, we found many differences in characteristics, treatments and outcomes among children from LMICs and HICs with infants had higher death rates than other children. Patients less frequently receive IMV and other supportive therapies in LMICs, which likely represents disparities in access to healthcare that influence outcomes. Reducing the gap in our ability to care

| Table 5 | Treatment profile of study participants |
|---------|----------------------------------------|
| **Country income** | **HICs** | **LMICs** | **Total** |
|  | N  | n  | %  | N  | n  | %  | N  | n  | %  | P value |
| Antibiotics* | 3685 | 2189 | 59.4 | 4349 | 1122 | 25.8 | 8034 | 3311 | 41.2 | <0.001 |
| Corticosteroid* | 3663 | 564 | 15.4 | 4905 | 417 | 8.5 | 8568 | 981 | 11.4 | <0.001 |
| HFNC* | 3380 | 282 | 8.3 | 3967 | 147 | 3.7 | 7347 | 429 | 5.8 | <0.001 |
| IMV* | 3620 | 235 | 6.5 | 4684 | 204 | 4.3 | 8304 | 439 | 5.3 | <0.001 |
| Antivirus* | 3672 | 271 | 7.4 | 4341 | 172 | 4.0 | 8013 | 443 | 5.5 | <0.001 |
| Remdesivir | 3672 | 96 | 2.6 | 4341 | 17 | 0.4 | 8013 | 113 | 1.4 |
| Neuraminidase inhibitor | 3672 | 32 | 0.9 | 4341 | 17 | 0.4 | 8013 | 113 | 1.4 |
| Inotropic/vasopressor* | 3451 | 201 | 5.8 | 4961 | 174 | 3.5 | 8412 | 375 | 4.4 | <0.001 |
| Prone positioning* | 3532 | 64 | 1.8 | 4647 | 39 | 0.8 | 8179 | 103 | 1.2 | <0.001 |
| Anticoagulant | 3819 | 50 | 1.3 | 9041 | 88 | 1.0 | 12860 | 138 | 1.1 | 0.091 |
| NIV* | 3627 | 53 | 1.5 | 4966 | 17 | 0.3 | 8593 | 70 | 0.8 | <0.001 |
| RRT | 3573 | 19 | 0.5 | 4334 | 27 | 0.6 | 7907 | 46 | 0.6 | 0.084 |
| ECMO† | 3608 | 10 | 0.3 | 1086 | – | – | 4694 | 10 | 0.2 | <0.001 |

*Significant with p value <0.05 using χ² test.
†Fisher’s exact test.

| Table 6 | Mortality based on ICU admission and IMV use |
|---------|----------------------------------------|
| **Mortality based on country income** | **HICs** | **LMICs** | **Total** |
|  | N  | n  | %  | N  | n  | %  | N  | n  | %  |
| ICU* | Yes | 679 | 24 | 3.5 | 1037 | 173 | 16.7 | 1716 | 197 | 11.5 |
| No | 3140 | 40 | 1.3 | 8004 | 188 | 2.3 | 11144 | 228 | 2.0 |
| IMV* | Yes | 235 | 17 | 7.2 | 204 | 89 | 43.6 | 439 | 106 | 24.1 |
| No | 3385 | 47 | 1.4 | 4480 | 272 | 6.1 | 7865 | 319 | 4.0 |

*Significant with p value <0.05 using χ² test.

HICs, high-income countries; ICU, intensive care unit; IMV, invasive mechanical ventilation; LMICs, low-income to middle-income countries; N, denominator (total patients with or without ICU/IMV); n, total mortality.
for sick children in LMICs versus HICs will inevitably improve global outcomes during both pandemic and interpandemic periods.

Figure 3  Adjusted HR and 95% CI of mortality risk factors in all participants.
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