International Pediatric COVID-19 Severity over the Course of the Pandemic

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Key Points (100 words)

Question Were the dominant circulating SARS-CoV-2 variants of concern (VOCs) associated with differences in COVID-19 severity among hospitalized children?

Findings This multi-center retrospective cohort study including 31,785 hospitalized children with SARS-CoV-2 infection, suggesting that whilst ICU admission decreased over the course of the pandemic in all age groups, ventilatory and oxygen support did not decrease over time in children aged <5 years.

Meaning These data will inform mechanistic and intervention research, as well as public health policy, which must be aware of the importance of considering different pediatric age groups when assessing the severity of disease in future SARS-CoV-2 waves.

Abstract (350 words)

Importance SARS-CoV-2 variants have emerged over the COVID-19 pandemic. The implications for COVID-19 severity in children world-wide are unclear.

Objective Whether the dominant circulating SARS-CoV-2 variants of concern (VOCs) were associated with differences in COVID-19 severity among hospitalized children.

Design, Setting, and Participants Clinical data from hospitalized children and adolescents (<18 years) who were SARS-CoV-2 positive were obtained from 9

countries during three different time frames. Time frames one (T1), two (T2), three (T3) were defined to represent periods of dominance by the ancestral virus, pre-Omicron VOCs and Omicron respectively. Age groups for analysis were under 6 months, 6 months to <5 years and 5 to <18 years. Children with an incidental positive test for SARS-CoV-2 were excluded.

Exposures SARS-CoV-2 hospitalization during the stipulated time frame.

Main Outcomes and Measures The severity of disease was assessed by admission to intensive care unit (ICU), the need for ventilatory support or oxygen therapy.

Results Among 31,785 hospitalized children and adolescents, the median age was 4 [IQR 1-12] years, and 16,639 (52.3%) were male. In children <5 years of age, across successive SARS-CoV-2 waves, there was a reduction in ICU admission (T3 vs T1: Risk Ratio [RR], 0.56; 95% CI, 0.42-0.75 [< 6 months]; RR 0.61, 95% CI; 0.47–0.79 [6 months to < 5 years]), but not ventilatory support or oxygen therapy. In contrast, ICU admission (T3 vs T1: RR, 0.39, 95% CI, 0.32–0.48), ventilatory support (T3 vs T1: RR, 0.37; 95% CI, 0.27–0.51) and oxygen therapy (T3 vs T1: RR, 0.47; 95% CI, 0.32-0.70) decreased across SARS-CoV-2 waves in children 5 to <18 years old. The results were consistent when data was restricted to unvaccinated children.

Conclusions and Relevance This study provides valuable insights into the impact of SARS-CoV-2 VOCs on the severity of COVID-19 in hospitalized children across different age groups and countries, suggesting that while ICU admissions decreased across the pandemic in all age groups, ventilatory and oxygen support generally did not decrease over time in children aged <5 years. These findings highlight the importance of considering different pediatric age groups when assessing disease severity in COVID-19.

Introduction

Since the emergence of SARS-CoV-2 in late 2019, there have been numerous studies characterizing disease severity in both adults and children[1-3]. Several distinct SARS-CoV-2 variants have since emerged, with the most clinically significant known as variants of concern (VOCs). Whilst differences have and still do exist regarding the dominant viral variant amongst countries, the COVID-19 pandemic globally can be broadly classified as being dominated by the ancestral strain, Alpha/Beta/Delta variant and the Omicron variant[4].

In adults, the emergence of VOCs, in particular the Omicron variant, has been associated with altered disease severity relative to the ancestral virus[5]. Indeed, infections with the Omicron variant remained associated with reduced morbidity and mortality in adults compared to those with the Delta variant[6-8]. Importantly, whilst these data may reflect changes in the virus over time, they could also reflect the increased protection from vaccination that was increasingly available over the course of the pandemic as well as increasing protection from prior SARS-CoV-2 infection.

The role of VOCs, particularly Omicron, in severe COVID-19 amongst children remains less well defined. For example, whilst some studies suggest that pediatric ICU admission rates during the Omicron wave peaked at approximately 3.5 times the peak rate during the Delta wave[9, 10], others found no difference or a reduction in ICU admission of children across COVID-19 waves[11-13]. Severe croup associated with SARS-CoV-2 infection was a new phenotype first observed in young children (<5 years old) during the Omicron wave[10] whilst the use of mechanical ventilation and the use of non-invasive ventilation were reduced[12, 14-16]. It is difficult to discern if any of these differences are the result of functional changes in the virus or reflect changes in the host through increased immunity or changes in health care. This is complicated by the fact that in children vaccination was initially prioritized for children >12 years

old, with younger children either not being vaccinated or vaccinated at a later point in the pandemic.

Understanding disease severity following VOC infection in children is further limited by the single-center design of most available studies. Moreover, pediatric studies have largely focused on only a subset of children or group all children under the age of 18 years as a single cohort, precluding the analysis of age-specific differences in disease and vaccination status. Studies across the age spectrum in children are urgently needed to inform public health policies. Here, we review morbidity among pediatric hospitalized patients (separated by different age groups) among periods of dominance by different VOCs.

Methods

Study design

This is a multi-centre observational study using retrospective clinical data of hospitalized children and adolescents (<18 years) who were SARS-CoV-2 positive. De-identified data from hospitalized pediatric COVID-19 patients were requested from UK, Portugal, Italy, Switzerland, South Africa, Brazil, USA, Thailand and Australia between January 1, 2020, and March 31, 2022. Results were stratified by age to investigate potential age differences during the course of the COVID-19 pandemic. The age categories were defined as: < 6 months, 6 months to < 5 years, and 5 years to <18 years. The primary outcome was disease severity as defined by the need for (1) ICU admission (2) ventilatory support (3) oxygen therapy. The study was approved by the University of Queensland and local human research ethics committee. No further informed consent by participants was required. This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Reporting Guidelines[17].

Data source

Ten databases (from nine countries) provided data (eTable1). To provide site-specific estimates for each research population, each site adhered to a standardized data collection and analysis process. All transfer of data to the University of Queensland was subject to a data transfer agreement.

Data collection

We collected data on hospitalized pediatric patients under 18 years of age with PCR-confirmed SARS-CoV-2 infection from 10 sites across 9 countries (eTable 1). Data were requested from three timeframes: timeframe one (T1) which was defined as the period in which ancestral SARS-CoV-2 was dominant, T2 defined as the period in which pre-Omicron VOCs were dominant and T3 defined as the period in which Omicron-derived VOCs were dominant. The dates used to define T1, T2 and T3 in each participating site were derived from the corresponding national SARS-CoV-2 genome surveillance, where a VOC was considered to be dominant in the community if it constituted >70% of the collected SARS-CoV-2 sequences[18]. The specific time periods and date of pediatric COVID-19 vaccine roll out for each country are shown in eTable 2 and 3. The data collection materials are described in eMethods.

Statistical analysis

Descriptive statistics (n [%] or median [interquartile range, IQR]) were used for the characteristics of patients across the entirety of the study period and within each time frame and age category. To examine statistically differences of comparisons between different time frames, we used the χ^2 test for categorical variables, Fisher's exact test for variables with small sample sizes (n<5), and the student's t-test or the Mann–Whitney U test for continuous variables as appropriate. A P value of less than ·05 was used as the criterion for statistical significance. Adjusted estimates of three outcomes were calculated for each site and time frame (eMethods). Each independent covariable included in the adjusted models were combined in a meta-

analysis. Risk ratios were summarized using fixed and random effects models, with the random effects estimates presented in the text. All analyses were performed with R software (version 4.1.1).

Results

Characteristics of Patients Included in the Study

A total of 31,785 children and adolescents were included (eTable 4). The median age was 4 [IQR 1-12] years and 16,639 (52.3%) patients were male. When data were stratified by time period, we identified 5,438 (17.1%) children hospitalized during T1 (ancestral cohort), 15,205 (47.8%) in T2 (pre-Omicron cohort), and 11,142 (35.1%) in T3 (Omicron cohort). More boys than girls were admitted for COVID-19 in each time period. The median age was lower in T3 (3 years [IQR 1-11]) compared to T1 and T2 (5 years [IQR 1-13]).

Most hospitalizations (>75%) were among children and adolescents not known to be vaccinated, regardless of time frames (T1, T2, or T3). Only 64 of 14,841 (0.4%) of hospitalized adolescents were vaccinated in T2 — although this number rose to just over 72 of 8,582 (0.8%) when Omicron infections first accelerated in T3. Across the three time periods, 2,737 (8.6%) of hospitalized children were admitted to ICU, 5,209 (16.4%) required oxygen support and 1,125 (3.5%) required ventilatory support. ICU admission was more frequent in patients during T1 (13.5%) and T2 (9.3%) compared to patients in T3 (5.5%). Ventilatory support, and oxygen therapy were all more frequent during both T1 and T2, relative to T3. Supplementary eTable 5 - eTable 13 show the distribution of pediatric cases for each site in three time periods by age, sex, symptoms on hospital admission, comorbidities, outcomes, and COVID-19 vaccination status. The most frequently reported symptoms in all sites were fever and cough during all time frames. When looking at the proportion of ICU admission, oxygen support or ventilatory support across different ages, most outcome events

across multiple sites were noted in children under 6 months of age (eFigure 1). In contrast, events appeared to be evenly distributed across other ages. We therefore elected to stratify the data according to three age groups: children younger than 6 months, children 6 months to <5 years, 5 years to <18 years. Site-specific estimates of odds ratios for ICU admission, ventilation and oxygen therapy using unadjusted and adjusted models are shown in eTable 14.

COVID-19 severity amongst hospitalized children under 6 months old

The association between study periods and COVID-19 severity amongst hospitalized children under 6 months of age is shown in Figure 1. The relative risk of ICU admission was significantly lower in T3 vs T1 (random effects adjusted risk ratio, 0.56, 95% CI, 0.42-0.75). No difference was noted in the proportion of oxygen therapy during the pandemic in this age group (Figure 1). Children under 6 months of age were less likely to be ventilated during T3 compared to during T1 (RR, 0.57; 95% CI, 0.36-0.90). The I^2 statistic ranged from 0-68% across all the analyses, which suggested limited-modest heterogeneity across study sites.

Figure 1 shows that South African site 1 (SA_1) contributed the largest cases to the analysis of ICU admission, ventilatory support and oxygen amongst children under 6 months who were hospitalized with COVID-19. To assess if this one site was influencing the observed results, a sensitivity analysis was performed excluding the South African site 1. In the absence of South African site 1 the same patterns in ICU admission, ventilatory support and oxygen therapy were observed. Namely, the proportion of ICU admission was significantly lower in T3 vs T1 (RR, 0.58, 95% CI, 0.34–0.99) (eFigure 2). However, the relative risk of ventilatory support and oxygen therapy did not change over the course of the pandemic in this age group.

COVID-19 severity amongst hospitalized children aged 6 months to < 5 years old

The association between time frame and COVID-19 severity amongst hospitalized children aged 6 months to < 5 years old is shown in Figure 2. In this age group, the relative risk of ICU admission was significantly lower in T2 vs T1 (RR, 0.78; 95% CI, 0.62–0.98). Similarly, children aged 6 months to < 5 years in T3 were approximately 24% less likely to be admitted to the ICU as were children aged 6 months to < 5 years in T2 (RR, 0.76; 95% CI, 0.62–0.93). The relative risk of ICU admission was also reduced in this age group in T3 vs T1 (RR, 0.61; 95% CI, 0.47–0.79). The reduced relative risk of ICU admission in T3 vs T1 was maintained if a sensitivity analysis was performed excluding South African site 1 (eFigure 3). No significant difference was noted in the relative risk of ventilatory support or oxygen therapy over the course of the pandemic in this age group (Figure 2). Findings did not change when the major contributing site, South African site 1, was excluded from the analysis (eFigure 3). In the aforementioned analyses, the I^2 statistic ranged from 0%-67% indicating limited-modest heterogeneity across study sites.

COVID-19 severity amongst hospitalized children aged 5 to <18 years old

The association between time period and COVID-19 severity amongst hospitalized children older than five years is shown in Figure 3. In this age group, ICU admission rate decreased significantly over study time period, namely T2 vs T1 (RR, 0.75; 95% CI, 0.64–0.88), T3 vs T2 (RR, 0.53; 95% CI, 0.40–0.71), and T3 vs T1 (RR, 0.39; 95% CI, 0.32–0.48)(Figure 3); an observation which held true even if South African site 1 was excluded from the analysis (eFigure 4)

Although the RRs for oxygen therapy did not differ between T2 vs T1 in individuals aged 5 to <18 years (RR, 1.08; 95% CI, 0.78–1.49) with a considerable heterogeneity between sites (I^2 value, 72%), significant reductions in the risk of oxygen therapy were seen in T3 compared to T1 (RR, 0.47; 95% CI, 0.32–0.70), and

T3 compared to T2 (RR, 0.45; 95% CI, 0.40–0.50) . This difference was maintained if South African site 1 was excluded from the analysis (eFigure 4).

In contrast to the analysis of children < 5 years of age (Figure 2 & 3), the risk ratio of ventilatory support decreased over the course of the pandemic in children among 5 to <18 years old (Figure 3, T3 vs T1 RR; 0.37; 95% CI, 0.27–0.51). When South African site 1 was excluded from the analysis this remained true for the comparison of T3 vs T2 (RR, 0.51; 95% CI, 0.35–0.74) and the comparison of T3 vs T1 (RR, 0.41; 95% CI, 0.27–0.62) (eFigure 4).

Together, these data suggest that risk of ICU admission decreased over the course of the pandemic for all ages groups, but while risks for ventilatory support and oxygen therapy remained generally unchanged for children <5 years of age, those risks also decreased over the course of the pandemic for ages 5 to <18 years. To determine if these results were influenced by COVID-19 vaccination in children aged 5-18, a sensitivity analysis was performed where only unvaccinated children 5 to <18 years were included. ICU admission, oxygen therapy and ventilatory support still consistently decreased over the course of the pandemic in unvaccinated hospitalized children aged 5 to <18 years (Figure 4).

Direct comparison of COVID-19 severity between different pediatric age groups

Finally, to understand age dependent differences in the severity of COVID-19 in the three different time frames the risk of ICU admission, oxygen support and ventilatory support were compared directly between children <6 months, children 6 months to <5 years and children 5 to <18 years (eFigure 5). No notable differences were recorded in any of the three outcomes (in any time frame) between children <6 months and children 6 months to <5 years (eFigure 5). In contrast, compared to children 6 months to <5 years, children aged 5 to < 18 years had a significantly higher risk of

ICU admission (RR, 1.72; 95% CI, 1.38–2.14), ventilatory support (RR, 1.81; 95% CI, 1.30–2.51) and oxygen support during T1 (RR, 1.35; 95% CI, 1.12–1.63) (eFigure 5) compared to those aged 6 months to <5 years. Together, these data suggest that within each of the selected time frames of the study disease severity was equivalent between hospitalized children <6 months and hospitalized children aged 6 months to <5 years. In contrast, children 5 years and older had more severe disease compared to younger children in T1.

Discussion

This study found that hospitalized children aged <5 years had a reduced proportion of COVID-19 ICU admissions with successive variants whilst proportions of ventilatory support only decreased in T3 vs T1 among children under 6 months, and oxygen therapy did not change. In contrast, hospitalized children aged 5 to <18 years had a lower proportion of ICU admission, ventilatory support and oxygen support over the course of the entire COVID-19 pandemic. These same trends were observed amongst hospitalized children aged 5 to <18 years who had not been vaccinated. Together, these data indicate that there were age-dependent differences in disease severity across the course of the COVID-19 pandemic amongst hospitalized children.

Recent studies of COVID-19 vaccination during pregnancy suggest the transplacental transfer of SARS-CoV-2–specific antibodies[19]. Accordingly, maternal vaccination during pregnancy for COVID-19 has been associated with reduced hospitalization of children <6 months[20]. It may be that the reduced rate of ICU admission over the course of the COVID-19 pandemic in children <6 months is reflective of maternal vaccination and/or infection (more likely to occur in T2 and T3). It is possible that this same effect was not seen in terms of ventilatory support and oxygen support because maternal vaccination may be most efficacious in protecting

from more severe outcomes of SARS-CoV-2 infection (i.e., ICU admission) and not more moderate outcomes (i.e., ventilatory and oxygen support).

Children aged 6 months to <5 years represent an important subgroup to understand disease severity in the absence of COVID-19 vaccination. It is widely accepted that at >6 months transplacental antibodies have waned, although antibodies can be transferred via breastfeeding following maternal infection or vaccination[21]. In the time period studied herein, vaccination was not licensed for children under 5 years. We found that children in this age group experienced a reduced ICU admission over the pandemic. This may reflect the protective effect of prior infection on the severe outcomes of disease, changes in clinical practice, case reporting or changes in the virulence of the virus over time. Indeed, these data are consistent with a US study documenting reduced ICU admissions in children < 5 years in the Omicron wave relative to the prior Delta wave[12]. It is interesting to note the same trend was not observed over time in terms of the ventilatory support and oxygen support in children aged 6 months to <5 years. This could be affected by clinical threshold and/or availability of ventilation support etc. Although, our study did not directly investigate the impact of multisystem inflammatory syndrome in children (MIS-C) on ICU admissions, it is possible that differential incidences of MIS-C resulted in ICU admission in the absence of ventilation[22]. Therefore, it is important to acknowledge that broad statements about disease severity over the course of the pandemic need to be carefully nuanced.

Children > 5 years experienced a reduction in ICU admission, ventilatory support and oxygen therapy over the course of the pandemic. Noting that only a low number of hospitalized children in this study were vaccinated, these same trends were observed amongst unvaccinated children > 5 years. These data suggest that other factors such as prior infection, changes in viral virulence or changes in clinical practice may have played a more significant role in the observed trends. Indeed, it is tempting to

speculate that older children may have an immune response more akin to that of adults such that observed patterns of decreased virulence during the Omicron wave in adults[6-8] could be extrapolated to this age group.

In a direct comparison of disease severity between the different age groups, disease severity (in terms of ICU admission and ventilatory support) was elevated in older children in T1. These data are consistent with previous studies from the US, Canada, Iran and Costa Rica showing that older children and adolescents had more severe illness when hospitalized with COVID-19 compared to younger children during the early stages of the pandemic[23 24].

This study has a number of strengths. Internationally, there has been considerable variation in the rate of SARS-CoV-2 infection, clinical practice and medical capacity. It is therefore important, albeit difficult, to consider global patterns in disease severity in both adult and pediatric populations. This speaks to the benefit of conducting a multi-center meta-analysis of disease severity. In the present study whilst we did observe site-to-site variations in disease severity the majority of the analyses showed low-moderate inter-study heterogeneity (mean/median I^2 value recorded 25/14%), confirming the robustness of our findings.

There are also important limitations of the present study. Firstly, it is important to emphasize that the population studied herein were hospitalized children, therefore the rates of ICU admission, ventilatory support and oxygen support cannot be generalized to children in the community. It is also important to acknowledge that these data were collected up until March 2022 and may therefore not represent more recent evolution in SARS-CoV-2 variants. We acknowledge that the inability to collect reinfection status for all individuals limited a meaningful analysis of the impact of previous SARS-CoV-2 infection on COVID-19 severity[25] . In the present study we utilized Multiple Imputation using Chained Equations [26] to address missing data from the South African and Australian sites where approximately 40% of individuals had

random missing values in the comorbidities variable. Whilst this may have induced bias, removing SA_1 yielded similar results, providing reassurance about the findings' robustness. Finally, data was also limited to certain sites on different continents (e.g., Brazil, South Africa and Thailand), and might not be representative across the continent (e.g., North America and Australia). Despite this limitation, this study represents the first multi-center analysis of COVID-19 severity in children over the course of the pandemic.

Conclusions

In conclusion, this study provides valuable insights into the impact of SARS-CoV-2 VOCs on the severity of COVID-19 in hospitalized children across different age groups and countries. The results suggest that while ICU admissions decreased over the course of the pandemic in all age groups, ventilatory and oxygen support did not decrease over time in children aged <5 years. Moreover, the risk ratios of disease severity, including ICU admission, ventilatory support, and oxygen therapy, decreased across SARS-CoV-2 waves in those aged 5 to <18 years old. These findings highlight the importance of considering different pediatric age groups when assessing disease severity in SARS-CoV-2.

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Access to data statement

A/Prof Short had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

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Study supervision: Short.

Data Sharing Statement

Deidentified participant data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. This work includes data provided by the COVID-19 Data Platform. DOI citations: Infectious Diseases Data Observatory. 2022. "IDDO_COVID19_DAC_2022-01-05" created 2022-03-11 PID https://doi.org/10.48688/0f1w-t125. Subset of The IDDO Data Repository (dataset). PID https://doi.org/10.48688/cpwp-ft84.

Infectious Diseases Data Observatory (2017): The IDDO Data Repository. Exaptive. (dataset). https://doi.org/10.48688/cpwp-ft84.

Additional Contributions:

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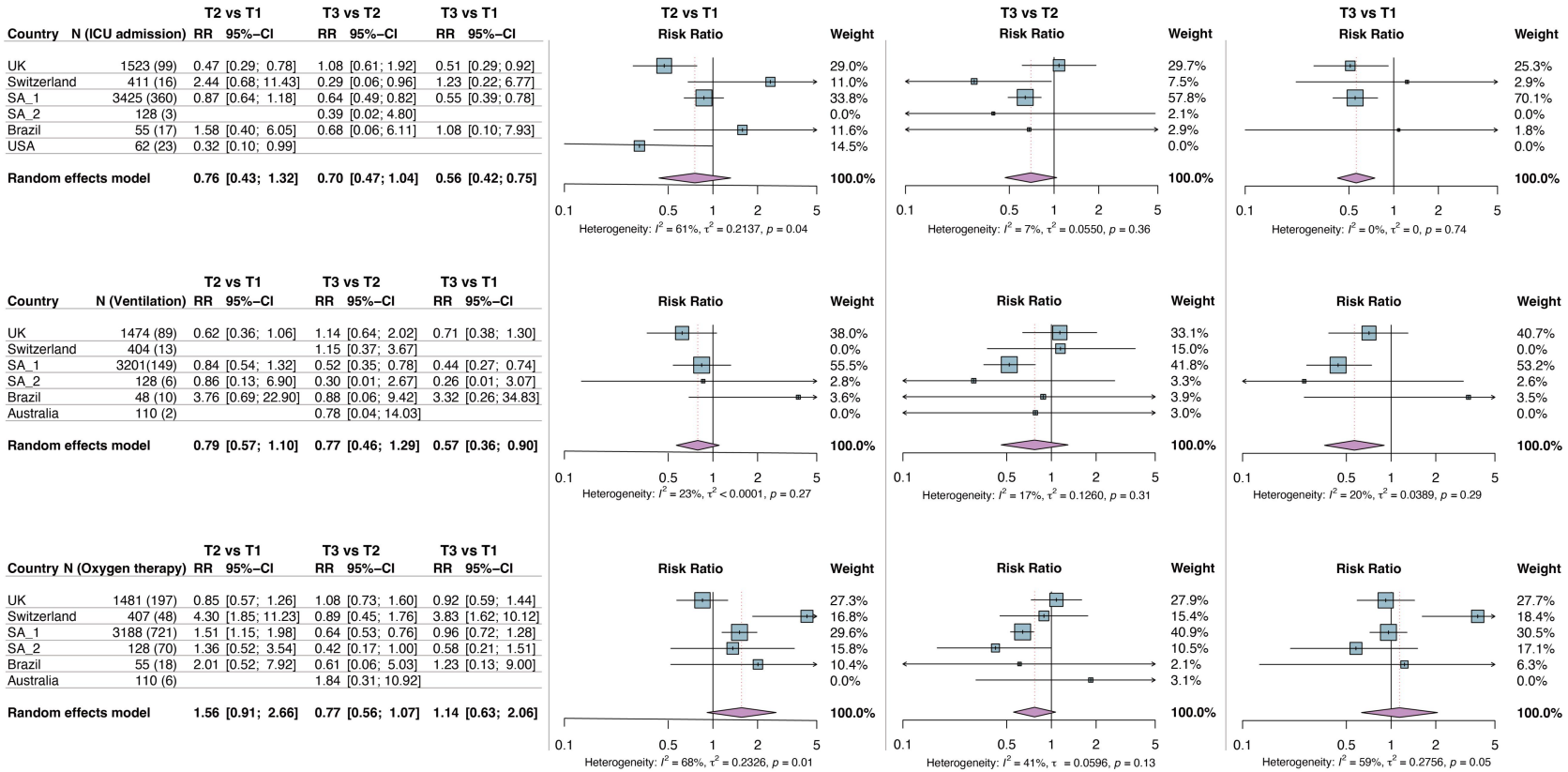

Figure 1. Meta-analysis risk ratios for ICU admission, noninvasive/invasive mechanical ventilatory support, oxygen therapy among pediatric patients under 6 months old. Models were adjusted for sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder(yes/no), childhood cancer(yes/no), immunological disease or immunosuppression(yes/no), diabetes (yes/no), HIV positive(yes/no), tuberculosis(yes/no), and prematurity (<37 weeks) (yes/no) as appropriate. SA_1 data were obtained from South Africa DATCOV, SA_2 data were obtained from South Africa NICD. Data from USA (T3); Thailand (T1); Australia (T1) was not included in this model because data were not available.

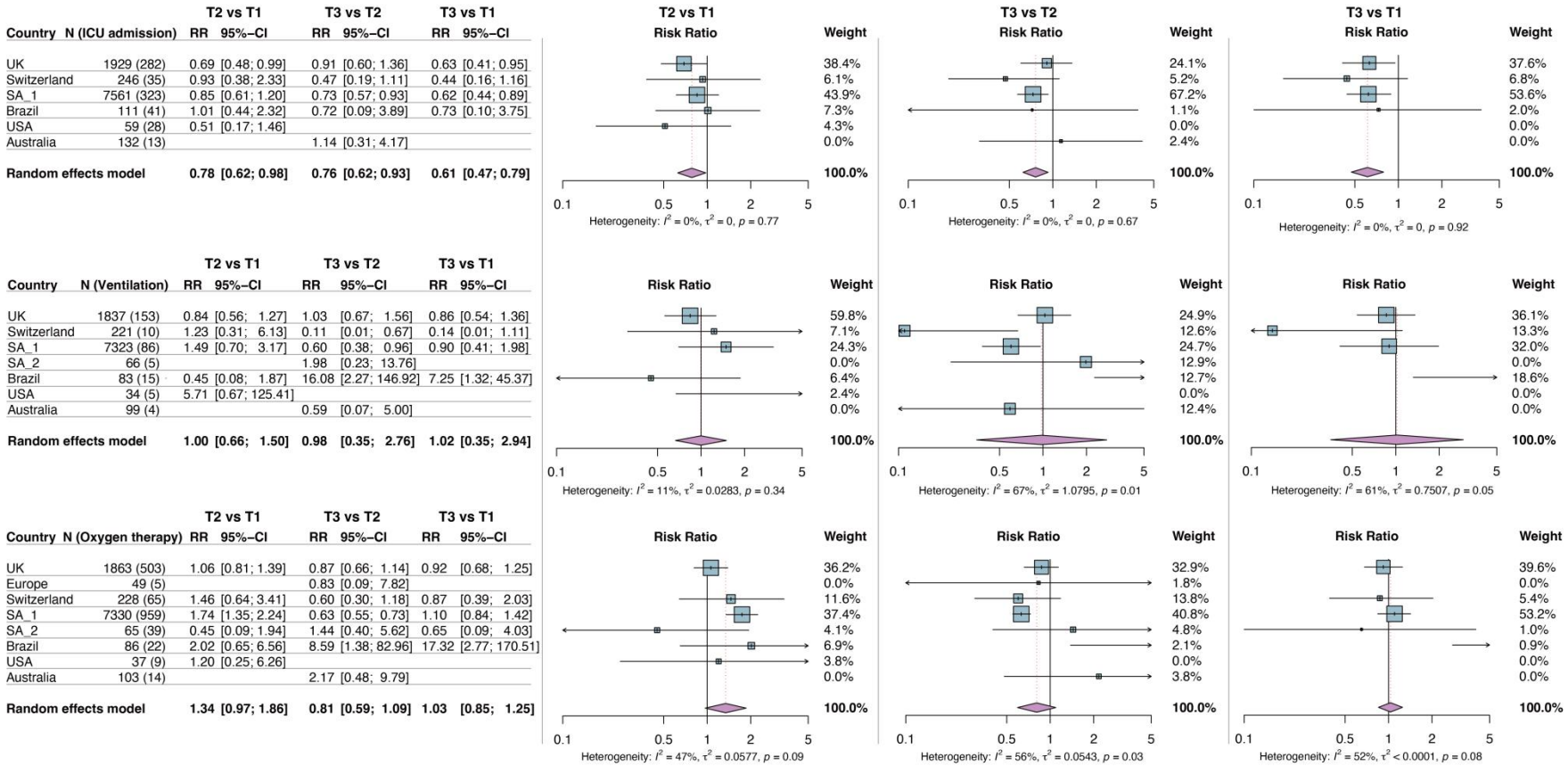

Figure 2. Meta-analysis risk ratios for ICU admission, noninvasive/invasive mechanical ventilatory support, oxygen therapy among pediatric patients aged 6 months to < 5 years. Models were adjusted for sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder(yes/no), childhood cancer(yes/no), immunological disease or immunosuppression(yes/no), diabetes (yes/no), HIV positive(yes/no), tuberculosis(yes/no), and prematurity (<37 weeks) (yes/no) as appropriate. SA_1 data were obtained from South Africa DATCOV, SA_2 data were obtained from South Africa NICD. Data from USA (T3); Thailand (T1); Australia (T1) was not included in this model because data were not available.

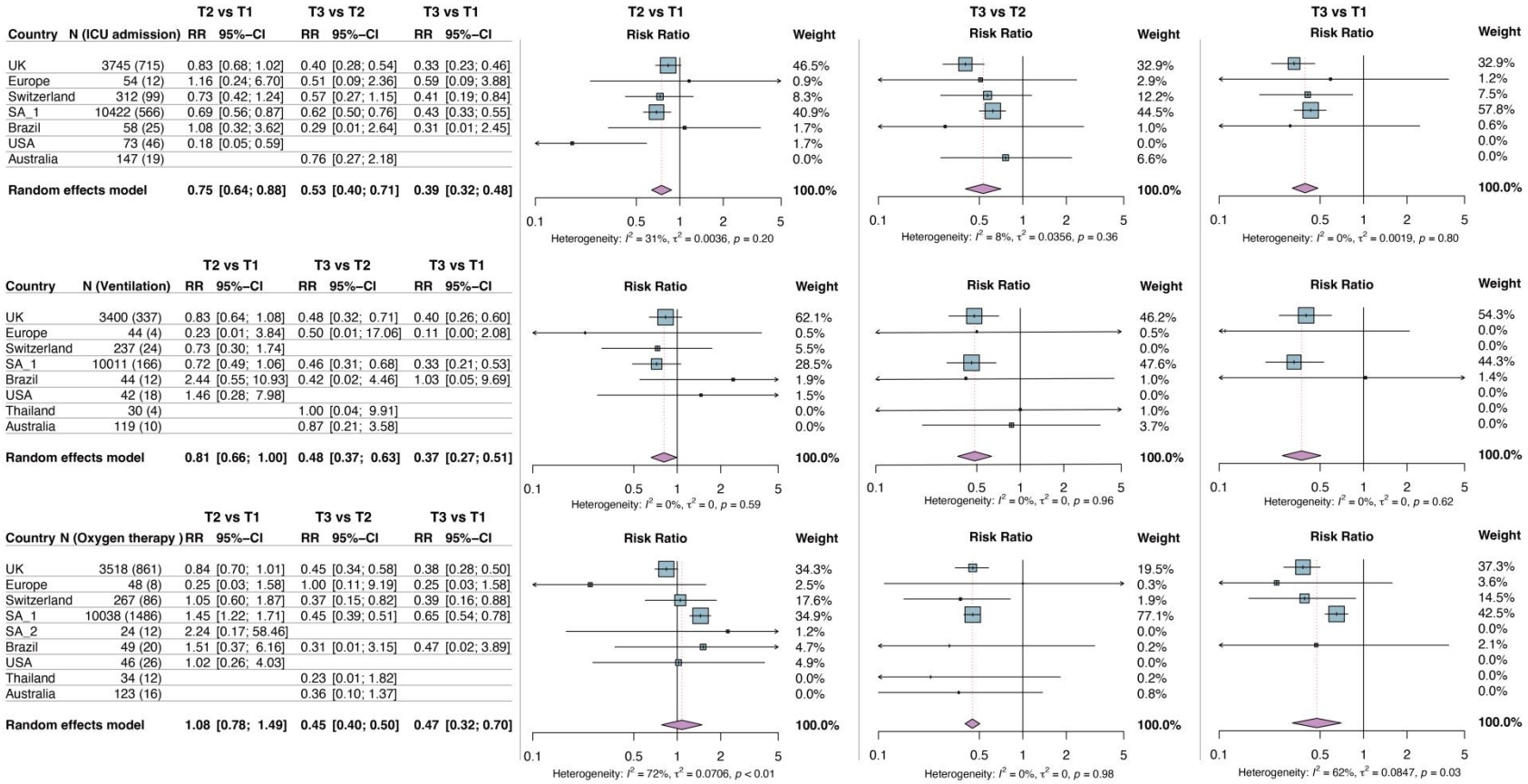

Figure 3. Meta-analysis risk ratios for ICU admission, noninvasive/invasive mechanical ventilatory support, oxygen therapy among pediatric patients aged 5 to <18 years. Models were adjusted for sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder(yes/no), childhood cancer(yes/no), immunological disease or immunosuppression(yes/no), diabetes (yes/no), HIV positive(yes/no), tuberculosis(yes/no), and prematurity (<37 weeks) (yes/no) as appropriate. SA_1 data were from South Africa DATCOV, SA_2 data were from South Africa NICD. Data from USA (T3); Thailand (T1); Australia (T1) was not included in this model because data were not available.

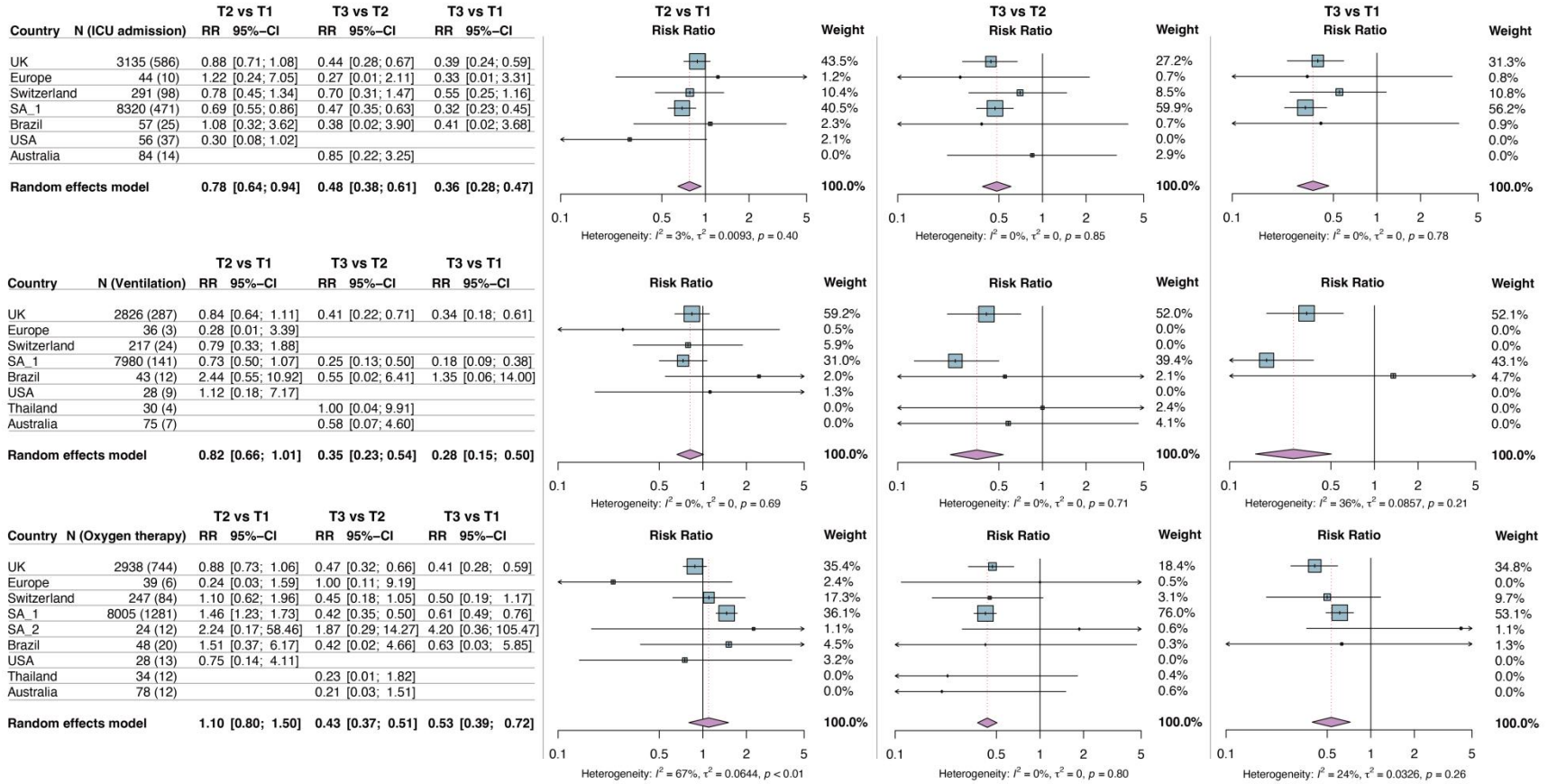

Figure 4. Meta-analysis risk ratios for ICU admission, noninvasive/invasive mechanical ventilatory support, oxygen therapy among pediatric patients aged 5 to <18 years without COVID-19 vaccination. Models were adjusted for sex (male/female), preexisting cardiovascular disease (yes/no), asthma (yes/no), neurological disorder(yes/no), childhood cancer(yes/no), immunological disease or immunosuppression(yes/no), diabetes (yes/no), HIV positive(yes/no), tuberculosis(yes/no), and prematurity (<37 weeks) (yes/no) as appropriate. SA_1 data were obtained from South Africa DATCOV, SA_2 data were obtained from South Africa NICD. Data from USA (T3); Thailand (T1); Australia (T1) was not included in this model because data were not available.