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Epidemiology and clinical features of SARS-CoV-2 infection in children and adolescents in the pre-Omicron era: A global systematic review and meta-analysis

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Background Data on paediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are limited, especially from the early pandemic period. Moreover, children are not considered to be at high risk for severe outcomes of coronavirus disease 2019 (COVID-19). In this systematic review and meta-analysis, we estimated the SAR-CoV-2 positivity rate, identified risk factors, and described the severity and mortality outcomes of SARS-CoV-2 infections in children aged ≤18 years until December 2021, prior to the Omicron era.

Methods We searched MEDLINE, Embase, Global Health, CINAHL, China National Knowledge Infrastructure, Wanfang, CQvip, and the World Health Organization (WHO) COVID-19 global literature databases for primary studies recruiting children aged ≤18 years with a diagnosis of SARS-CoV-2 infection confirmed either by molecular or antigen tests. We used the Joanna Briggs Institute critical appraisal tools to appraise the study quality and conducted meta-analyses using the random effects model for all outcomes except for race/ethnicity as risk factors of SARS-CoV-2 infection.

Results We included 237 studies, each reporting at least one of the study outcomes. Based on data from 117 studies, the pooled SARS-CoV-2 positivity rate was 9.30% (95% confidence interval (CI) = 7.15–11.73). Having a comorbidity was identified as a risk factor for SARS-CoV-2 infection (risk ratio (RR) = 1.33; 95% CI = 1.04–1.71) based on data from 49 studies. Most cases in this review presented with mild disease (n = 50; 52.47% (95% CI = 44.03–60.84)). However, 20.70% of paediatric SARS-CoV-2 infections were hospitalised (67 studies), 7.19% required oxygen support (57 studies), 4.26% required intensive care (93 studies), and 2.92% required assisted ventilation (63 studies). The case fatality ratio (n = 119) was 0.87% (95% CI = 0.54–1.28), which included in-hospital and out-of-hospital deaths.

Conclusions Our data showed that children were at risk for SARS-CoV-2 infections and severe outcomes in the pre-Omicron era. These findings underscore the need for effective vaccination strategies for the paediatric population to protect against the acute and long-term sequelae of COVID-19.

Registration PROSPERO: CRD42022327680.

The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic on 11 March 2020 [1]. WHO estimates suggest that there have been over 663 million confirmed COVID-19 cases, including at least 6 million reported deaths as of 19 January 2023 [2]. Since the emergence of the first case in Wuhan, China in late 2019, numerous SARS-CoV-2 variants have emerged and have been circulating globally. The Omicron variant, (also called variant B.1.1.529), was first reported to WHO on 24 November 2021 and has been circulating ever since [3]. There is a large volume of data on the epidemiology and economic impact of SARS-CoV-2 infections; unfortunately, comprehensive data on the burden of SARS-CoV-2 infections in children and adolescents are limited, particularly in the pre-Omicron era.

The United Nations (UN) defines children as persons under the age of 18 years [4] and adolescents as persons between the ages of 10 and 19 years [5]. Evidence suggests that individuals under 20 years of age represented 33% of the 2020 global population and contributed to 21% of all reported COVID-19 cases since the beginning of the pandemic until the end of 2022 [6]. Although these numbers indicate that the incidence of COVID-19 is low in this compared to other age groups, a lack of data from this population has been identified as a challenge for developing precise estimates [6]. Moreover, the case numbers represent just one aspect of the disease burden. A comprehensive determination of the burden of COVID-19 is incomplete without estimating the disease severity and highest level of management or care required by cases. Furthermore, it is important to identify vulnerable groups within this population to prioritise protection and prevention measures, access to health care, or even treatment.

Therefore, we aimed to estimate the burden of SARS-CoV-2 infections (in terms of test positivity, severity of clinical presentation, and the level of care required) in children and adolescents aged ≤18 years from published literature reporting data from the pre-Omicron era, and to report data on risk factors for SARS-CoV-2 infections and related mortality in this population. This systematic review of existing evidence and synthesis of knowledge will help improve our understanding of the burden of SARS-CoV-2 infections in children and adolescents globally and help shape and inform protection and prevention policies and management guidelines.

METHODS

We registered the protocol for this systematic review in PROSPERO (CRD42022327680) and followed the PRISMA-P 2020 guidelines in reporting our findings [7] (Table S12–13 in the **Online Supplementary Document**). We did not seek formal ethical approval as this review was based on data from open-access published primary studies.

Literature search

We searched MEDLINE, Embase, Global Health, CINAHL, and the WHO COVID-19 global literature databases on 27 February 2022 using pre-developed search strategies to identify studies reporting incidence, risk factors, severity, and outcomes of COVID-19 infection in children and adolescents aged ≤18 years. We also searched three Chinese literature databases (CNKI, Wanfang, and CQvip) on 21 March 2022 (Text S2 in the in the **Online Supplementary Document**).

Literature selection

Following deduplication, we uploaded the references retrieved from the searches in English language databases into Covidence (Veritas Health Innovation, Melbourne, Australia). A single reviewer (DK) then screened their titles and abstracts. During the screening, we observed that many studies defined children as those aged ≤18 years rather than those aged <18 years. Therefore, the review population included children and adolescents, i.e. those aged ≤18 years, as data were very commonly reported for this age group. A single reviewer screened the full text of the studies based on pre-defined inclusion criteria, depending on the study language (English: DK, Chinese: FZ or XW, Portuguese: JS, Spanish: KA). We included observational studies with a sample size of at least 100 children; presenting data on people aged ≤18 years; reporting on SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) or antigen tests; and reporting test positivity, severity, risk factors, or mortality due to SARS-CoV-2 infection or the differential impacts of SARS-CoV-2 variants. We set no criteria regarding settings (community, educational institutions, health care settings, etc.) (Text S1 in the **Online Supplementary Document**).

Data extraction

We designed a data extraction form in Microsoft Access to capture characteristics and outcomes for studies included in this systematic review and meta-analysis (see variables in Text S3 in the **Online Supplementary Document**). A single reviewer extracted the data into Microsoft Access (DK, JS, or KA) or Microsoft Excel (FZ), while a second reviewer cross-checked the extractions in MS Excel (English-language studies: NFI, Chinese-language studies: XW). Any disagreements between the two reviewers were resolved through discussion or by consulting a third reviewer (HN) if necessary.

Quality assessment

A single reviewer (DK, KA, or FZ) assessed the quality of the included studies using the modified Joanna Briggs Institute quality assessment checklists, according to each study's design [8] (Text S4 in the **Online Supplementary Document**). English language studies marked as good quality or poor quality by the first reviewer were re-assessed by the second reviewer (NFI). Studies were deemed to be of good quality if they had a score of 7–8 (cross-sectional studies), 8–10 (case-control studies and quasi-experimental studies), 9–11 (cohort studies), or 8–10 (diagnostic test accuracy studies); of fair quality if they had a score of 4–6 (cross-sectional studies), 4–7 (case-control studies and quasi-experimental studies), 6 and 8 (cohort studies), or 4–7 (diagnostic test accuracy studies); and of poor quality if they had a score of 0–3 (cross-sectional, case-control, quasi-experimental, and diagnostic test accuracy studies) or 0–5 (cohort studies). Any discrepancies were resolved by discussion or by consulting a third reviewer (HN). We used the quality scores to conduct sensitivity analysis.

Statistical analysis

We conducted all statistical analyses in *R*, version 4.2.1 (R Core Team, Vienna, Austria). Since we anticipated significant heterogeneity, we adopted the DerSimonian and Laird random effects model [9]. We applied the Freeman-Tukey double arcsine transformation for all analyses except for the analysis on race/ethnicity as a risk factor for SARS-CoV-2 infections, which we synthesised narratively due to a lack of standardised data. The Freeman-Tukey double arcsine transformation enabled the inclusion of zero event estimates. The transformation also standardises the variance, which was appropriate to our analyses, as there was substantial heterogeneity across study estimates. We derived the pooled proportion as back-transformed values as the weighted mean of the transformed proportions to report all the pooled estimates with their 95% confidence intervals (CIs). We assessed heterogeneity by calculating the I^2 and τ^2 values. For risk factors, we calculated the pooled risk ratio (RR) with their 95% CIs. We developed forest plots to display results from individual studies along with the pooled estimates.

Test positivity estimates

We generated a pooled estimate for the proportion of children and adolescents testing positive for SARS-CoV-2 either by antigen tests or PCR among all children and adolescents that were tested in each study. All nucleic acid amplification tests were coded as PCR, as we estimated this to be the most widely used nucleic acid test across settings. We then performed a leave-one-out meta-analysis to investigate the influence of each study on the overall estimate and to identify influential studies, and also conducted a sensitivity analysis to determine the pooled estimate for the proportion of positive cases by including only good-quality studies. We conducted subgroup analyses to report the test positivity by setting (community, health care, educational institution, or other), age groups, type of diagnostic test, and geographical location.

By age group

We also performed subgroup analyses by two age groups (<5 and 5 to ≤18 years), in which we included any studies that reported age-stratified data for these two groups. We then further split these age groups into two narrower age bands (<5-year-old group into those aged <1 and 1 to <5 years; 5 to ≤18-year-old group into those aged 5 to <11 and 11 to 18 years). If a study reported data for groups that overlapped over subgroups within a group, we classified the data in a way that they fell in the group where most of their sample can be expected to fall in (for example, those <3 years old were included in the 1 to <5-year-old group) to maximise the inclusion of data in the analysis. Age groups that could not be classified into either of our groups (because they fell exactly in between) were placed in the higher age group (for example, the <2-year-old group was placed in the 1 to <5-year-old group).

By regions

To assess regional differences, we conducted subgroup analysis by WHO regions [10] and World Bank income levels [11].

By SARS-CoV-2 variants

To investigate the differential impact of SARS-CoV-2 variants on the proportion of positive cases, we utilised open-access data [12]. These data represented the proportion of the total number of sequences (not cases), over time, that fell into the defined variant groups. Countries were displayed if they had at least 70 sequences for any variant being tracked, over at least 4 weeks. We allotted the most dominant variant, i.e. the one with the highest proportion of the total number of sequences occurring at the mid-study period of each study (month and year), which we calculated in Microsoft Excel.

By study settings

We classified settings as community, health care institution, educational institution, or other. Health facility setting included all studies reporting data from primary, secondary, or tertiary health care facilities including hospitals, COVID-19 isolation/quarantine centres, general practitioner clinics, paediatric clinics including well child visits, intensive care units (ICUs), paediatric intensive care units (PICUs), and health centres delivering specialised care (such as burns centres, oncology centres, etc.). If the setting was mixed or unclear, we classified it as 'other.'

By testing method

We conducted a subgroup analysis by testing method, i.e. PCR (including any nucleic acid tests), PCR or antigen tests, and antigen tests.

Risk factor analyses

We performed pooled analyses using risk factor data if at least two studies reported data on a particular risk factor. The pooled RRs were calculated with the 95% CI for each factor. Available data enabled us to conduct pooled analysis for age, sex, ethnicity, comorbidities, and pregnancy as risk factors for COVID-19 in people aged ≤18 years. We reported risk ratios for SARS-CoV-2 infection in four age groups (>1 year, 1 to <5 years, 5 to <10 years, and 10 to ≤18 years). However, the data reported in the studies were unstandardised; due to this heterogeneity, we classified the data from overlapping age bands so that they fell in the group where most of their sample can be expected to fall in. We compared the risk of SARS-CoV-2 infection in each of the groups to the other ages in the ≤18 years group. Some included studies also conducted adjusted analyses for several risk factors; in such cases, we were unable to pool the estimates of these adjusted analyses due to a lack of standardised data. Moreover, four studies reported on race or ethnicity; as we were unable to conduct a meta-analysis owing to the nature of these data (i.e. different groups of ethnicities/races reported in each study depending on their populations), we undertook a narrative synthesis for race or ethnicity as a risk for SARS-CoV-2 infection. We calculated the risk of SARS-CoV-2 infection in people having any of the following nine comorbidities: obesity, diabetes, immunosuppression, cardiovascular disease, asthma, epilepsy, renal disease, neurological condition, and congenital cardiac conditions.

Severity of disease

We assessed the severity of COVID-19 in children in two ways. We estimated the clinical management requirements (hospitalisation, ICU admissions, supplemental oxygen, and assisted ventilation) and provided a pooled estimate for the proportion of children (among those testing positive for SARS-CoV-2) requiring each of these. ICU admissions included ICU, PICU, and high dependency unit (HDU) admissions. Oxygen supplementation included all types of supplemental oxygen, including assisted ventilation, if details were unavailable. Assisted ventilation included all types of non-invasive and invasive mechanical ventilation, including continuous positive airway pressure, bilevel positive airway pressure, and tracheal intubation. If studies reported only on assisted ventilation without data on other types of supplemental oxygenation, we included them only for the analysis of assisted ventilation and not in the oxygen supplementation analysis. We included only studies that followed up at least 100 SARS-CoV-2 positive children and adolescents. We excluded studies that recruited only hospitalised children from the analysis of the proportion of children requiring hospitalisation. We could not assess the criteria for hospitalisation, ICU admission, and other requirements in individual studies, which is why we did not conduct further investigations and subgroup analyses based on WHO

region or country income levels. As there were limited data on dominant variants and therefore, we did not conduct any statistical tests to explore differences between the effects on severity by variants.

We also assessed severity based on the clinical presentation (asymptomatic, mild, moderate, and severe/critical disease). When studies combined two groups, we included the children from the combined group in the higher level of severity of the two groups (for example, moderate-severe disease cases were included in severe disease). We combined severe and critical COVID-19 disease as a single group due to overlapping definitions across studies and limited data on critical disease. The definitions of asymptomatic SARS-CoV-2 infections (without any clinical signs or symptoms), mild COVID-19 disease (upper respiratory infections), and moderate COVID-19 disease (non-severe pneumonia) were reasonably consistent across studies. If study authors did not report on the definitions used, these definitions were assumed.

Case fatality ratio

Lastly, we assessed the mortality outcomes in SARS-CoV-2 positive children. We calculated a pooled estimate of the proportion of SARS-CoV-2 positive children with fatal outcomes. The estimate likely included in-hospital and out-of-hospital deaths, as these details were rarely available in individual studies. To increase the confidence in our estimates, we only included studies that followed-up at least 100 SARS-CoV-2 children until the end of the study period or discharge or death (whichever occurred first). If studies differentiated between deaths caused due to COVID-19 and deaths due to other medical reasons in children and adolescents with SARS-CoV-2 infections, we extracted the data for deaths attributable to COVID-19 disease.

RESULTS

We identified 19 050 records through our searches in eight (including three Chinese) academic literature databases. Following the screening process, we included 237 studies in this systematic review [13-249] (**Figure 1**; Table S11 in the **Online Supplementary Document**). Our searches did not yield any studies that were entirely conducted in the Omicron era or after Omicron became the dominant variant. (Table S9 in the **Online Supplementary Document**).

Test positivity estimates

Based on 117 studies, we found the test positivity of SARS-CoV-2 to be 9.30% (95% CI = 7.15–11.73). The I^2 and τ^2 values suggested there was significant heterogeneity across the included study estimates. Three studies [55,88,241] were found to be influential in the estimates. The pooled SARS-CoV-2 test positivity after the exclusion of these studies was calculated as 8.13% (95% CI = 6.45–9.98, I^2 = 100%, τ^2 = 0.0300). When the analysis was restricted to good-quality studies only, the pooled SARS-CoV-2 test positivity was 9.04% (95% CI = 4.46–15.01, I^2 = 99%; τ^2 = 0.0172) (Figure S2 and Table S10 in the **Online Supplementary Document**).

Subgroup analysis of proportion positive estimates

Figure 2 illustrates the findings of the subgroup analyses according to age groups. The results of the subgroup analysis of SARS-CoV-2 proportion positive in children and adolescents by the WHO regions, country income groups, study setting, and testing method are summarised in **Table 1** and the plots available in Figures S3–6 in the supplementary materials **Online Supplementary Document**. The estimates were highest in the African region, middle income countries, health facility settings and in studies employing PCR. The estimates were lowest in the Western Pacific Region, high income countries, educational institutions and studies employing antigen testing.

We were unable to assess the effect of different SARS-CoV-2 variants, as there were limited data on the dominant variant in each country at the mid-study period. Most of the studies included in this review were conducted during the early pandemic period. Consequently, we could not provide reliable proportion positive estimates by SARS-CoV-2 variant subgroups (Figure S7 in the **Online Supplementary Document**.

Risk factors of SARS-CoV-2 infection in children aged ≤18 years

Age

We found the risk of SARS-CoV-2 infection to be lowest in the 1 to <5-year-old group (RR = 0.64; 95% CI = 0.49–0.83) compared with the remaining age groups. This was followed by the 5 to <10-year-old age group (RR = 0.82; 95% CI = 0.69–0.98) and the <1 year age group (RR = 0.88; 95% CI = 0.59–1.31). The risk

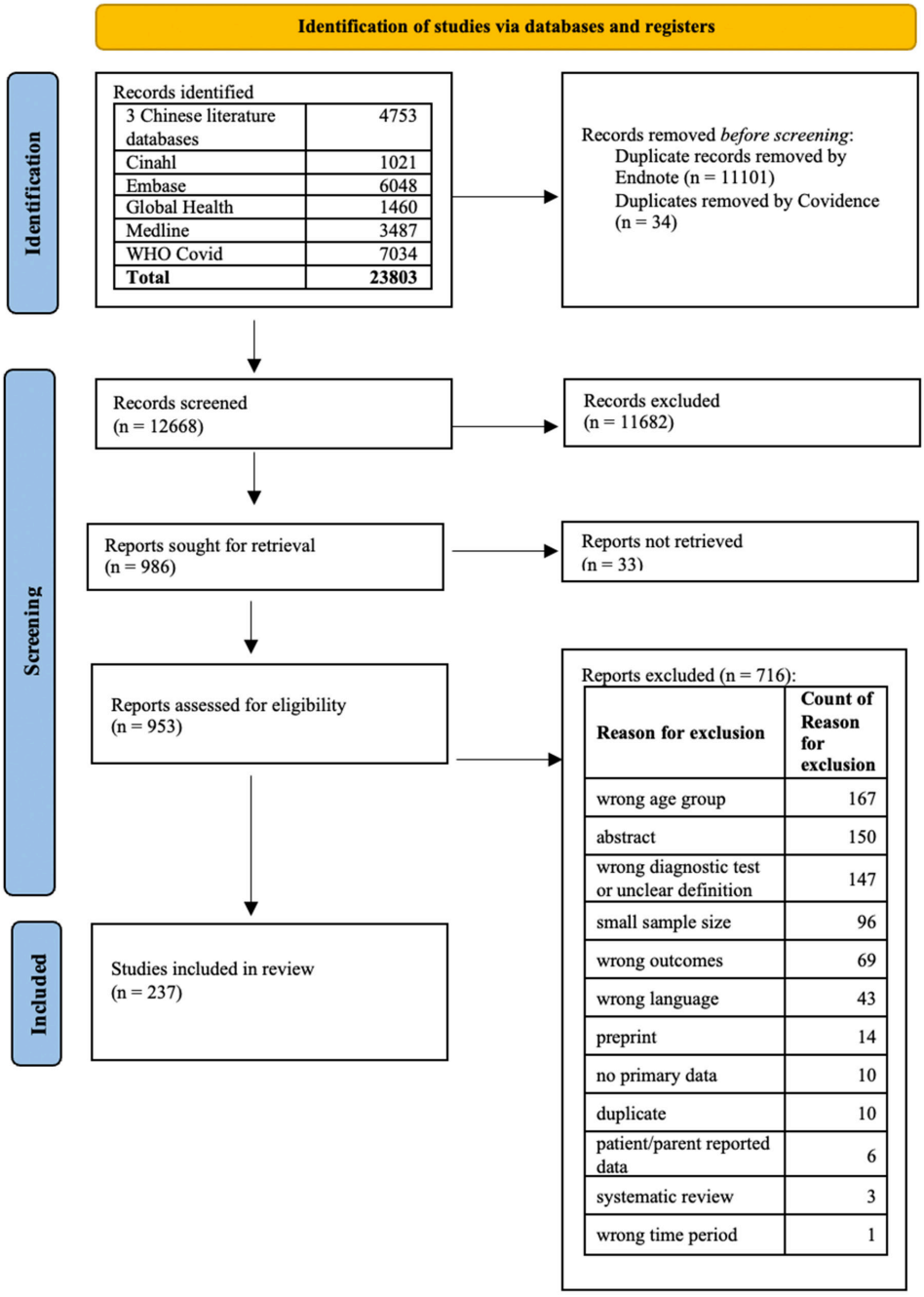
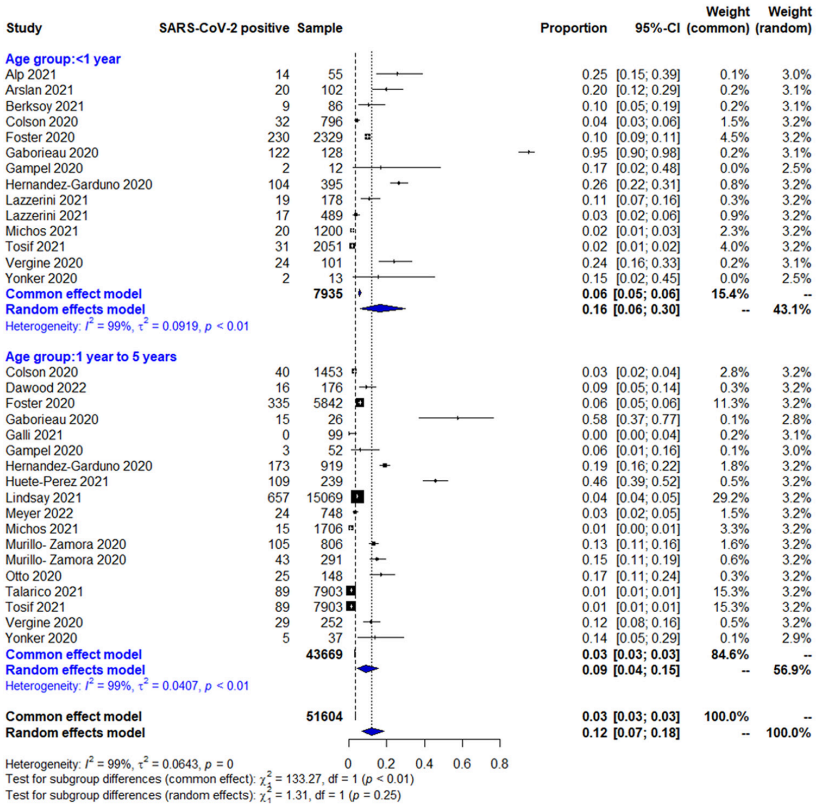


Figure 1. PRISMA flowchart.

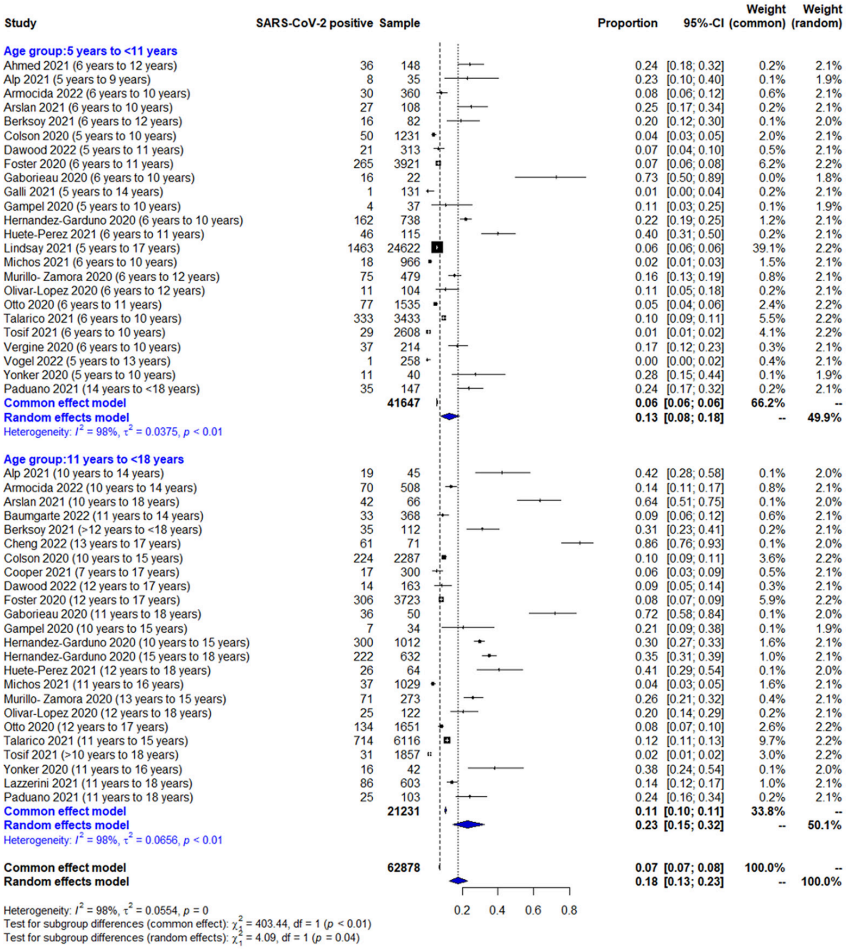
was highest in those aged between 10 years and ≤18 years (RR = 1.60; 95% CI = 1.23–2.08). Eleven studies [14,22,34,38,50,103,121,143,152,155,200] reported the mean or median age or age range in SARS-CoV-2 positive and SARS-CoV-2 negative children and adolescents. However, the *P*-value was not reported in all studies. Five studies [33,38,79,134,159] controlled for confounders and reported adjusted risk ratios (Tables S1–3 in the **Online Supplementary Document**).

Sex

Twenty-one studies [14,22,33,34,50,63,79,103,107,109,121,130,134,143,152,154,155,159,166,175,200] reported data on sex as a risk factor for SARS-CoV-2 infection in children. The results of this meta-analysis showed no evidence of an association between sex and SARS-CoV-2 infection in children aged ≤18 years. Of these 21 studies, four [33,34,79,159] conducted multivariate analyses to estimate the association between SARS-CoV-2 infection and sex after adjusting for other factors (Figure S8 and Table S4 in the **Online Supplementary Document**).



(A) Children aged <5 years divided into <1 year and 1 year to <5 year groups



(B) Children aged 5 to 18 years divided into 5 years to <11 years and 11 years to ≤18 years groups

Figure 2. Forest plot for subgroup analysis of SARS-CoV-2 proportion positive in people aged ≤18 years. **Panel A.** Children aged <5 years divided into <1-year and 1 to <5-year-old groups. **Panel B.** Children aged 5 to 18 years divided into 5 to <11-year and 11 to ≤18-year-old groups.

Table 1. Summary of results of subgroup analysis of SARS-CoV-2 test positivity in people aged ≤18 y

	Number of studies	Pooled estimate, (95% CI)	τ^2
WHO regions			
European region	62	7.83 (5.14–11.01)	0.0468
Western Pacific region	11	4.57 (0.62–11.71)	0.0499
Region of the Americas	28	13.28 (7.92–19.76)	0.0551
Eastern Mediterranean region	4	9.04 (3.08–17.57)	0.0192
African region	4	14.39 (14.27–14.51)	0.0000
Southeast Asian region	6	12.67 (7.64–18.73)	0.0104
Mixed*	1	31.03 (30.15–31.93)	-
Country income groups			
High income	77	5.95 (3.89–8.41)	0.0443
Upper middle-income	28	17.15 (12.53–22.31)	0.0300
Lower middle-income	10	15.84 (9.70–23.13)	0. 0213
Mixed†	2	32.72 (28.94–36.61)	0.0007
Study setting			
Health facility	86	10.01 (7.24–13.17)	0.0532
Other setting‡	20	9.58 (5.85–14.11)	0.0255
Community	2	9.76 (6.17–14.07)	0.0019
Educational institution	9	3.38 (0.57–8.20)	0.0246
Testing method			
PCR	106	9.67 (7.30–12.34)*	0.0490
PCR or antigen test	10	6.57 (3.02–11.33)	0.0182
Antigen test	1	3.38 (2.75–4.08)	-

CI – confidence interval, PCR – polymerase chain reaction, WHO – World Health Organization

*There was one multicentre study [87] which was conducted across more than one WHO region. It was put in the 'mixed' group.

†There were two studies [87,232] reporting findings from more than one country and those were from different income groups. They formed a separate 'mixed' group.

‡Other setting included those in which children were testing was unclear or it could be expected to have data from more than one setting (health facility, educational institution, and community) This included studies that reported surveillance data or data from testing laboratories. However, the setting in which the children were tested was, however, unclear. Such studies were classified as conducted in other settings [64,65,68,75,89,97,110,129,137,162,171,175,192,196,197,215,218,220,225].

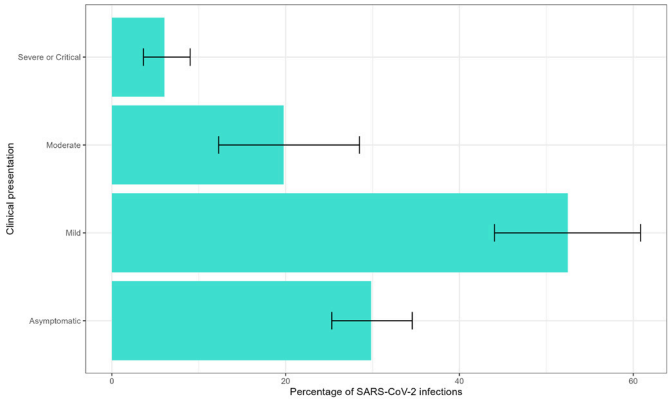


Figure 3. Severity of SARS-CoV-2 infection in children aged ≤18 years.

Ethnicity or race

Six studies [38,63,143,152,200,246] reported data on ethnicity or race as a risk factor for SARS-CoV-2 infection in the ≤18 years population. The findings for non-Hispanic White, Black, and Hispanic groups were variable across studies. The association between being Asian and the risk of SARS-CoV-2 infection was found to be statistically insignificant in all studies reporting data on Asians. However, the RR estimated varied across studies and ranged between 1.15 and 5.10. Some race/ethnicity groups (Secular Jews, Arabs, Ultraorthodox Jews, multiracial non-Latino) were reported by single studies. Three studies were conducted in the United States [38,200,246], and one in Israel [63], Brazil [143] and Spain [152] each (Table S5 in the **Online Supplementary Document**).

Comorbidities

The findings of the meta-analysis of comorbidities as a risk factor for SARS-CoV-2 infection are presented in **Table 2**. The results of another analysis that included combined data on at least one of the following comorbidities – obesity, diabetes, immunosuppression, cardiovascular disease, asthma, epilepsy, renal disease, neurologic condition, or congenital heart disease – showed that having any of these comorbidities was a risk factor for SARS-CoV-2 infection (RR = 1.33; 95% CI = 1. –1.71, $P < 0.001$).

The results of adjusted analyses for some comorbidities were reported by six studies [63,79,103,134,159,200] (Table S6 in the **Online Supplementary Document**).

Pregnancy

Based on two studies conducted in Mexico with a total sample size of 8297 [31,103] meta-analysis did not show an association of pregnancy with SARS-CoV-2 infection in people aged ≤18 years (RR = 1.19; 95% CI = 0.73–1.92; $P = 0.4807$).

Severity of SARS-CoV-2 infection in children and adolescents

Severity according to clinical presentation

Mild COVID-19 disease was the most common presentation of SARS-CoV-2 infection in those aged ≤18 years (52.47%). Meanwhile, 29.83% children with SARS-CoV-2 infection remained asymptomatic, followed by those presenting with moderate disease (19.77%) and lastly with severe/critical disease (6.05%) (**Figure 3**). Not all studies reported number of cases with each of these four presentations (asymptomatic, mild, moderate, and severe/critical disease). Therefore, the denominator populations for each of these outcomes are not identical (Figures S9–12, Tables S7–8 in the **Online Supplementary Document**).

Table 2. Comorbidities as a risk for SARS-CoV-2 infection

Comorbidity	Case definitions used	Number of studies included	Total sample size	RR (95% CI)	Direction of association
Obesity	Obesity as a comorbidity or obesity based on BMI	7	13 325	2.91 (1.68–5.04)	Risk increase.
Diabetes	Diabetes, diabetes mellitus type 1	6	13 416	2.30 (1.23–4.28)	Risk increase.
Immunosuppression	Immunosuppressed, immunodeficiency, primary immunodeficiencies, immunosuppressant use, immune thrombocytopenia, and common variable immune deficiency	6	13 509	1.14 (0.57–2.30)	No evidence of association.
Cardiovascular disease	Disease, cardiovascular conditions, and cardiac disease	5	13 538	1.07 (0.54–2.13)	No evidence of association.
Asthma	Includes asthma, asthma or reactive airway disease, and asthma or chronic lung disease	7	300 402	0.73 (0.46–1.17)	No evidence of association.
Epilepsy		3	608	1.90 (1.14–3.17)	Risk increase.
Renal disease	Chronic renal insufficiency, chronic renal failure, end-stage renal disease, renal disease, kidney-related comorbidity	4	11 285	1.04 (0.77–1.40)	No evidence of association.
Neurologic condition	Malformation, disabilities, neuromuscular diseases, neurological diseases except for epilepsy, neurologic condition, neuromuscular damage, neurological comorbidity	6	3885	0.79 (0.41–1.52)	No evidence of association.
Congenital cardiac disease	Any congenital cardiac disease	3	704	0.71 (0.34–1.49)	No evidence of association.

BMI – body mass index, CI – confidence interval, RR – risk ratio

Severity according to management requirements

Among those testing positive, the percentage of children requiring hospitalisation was 20.70% (95% CI = 15.04–26.99). In view of oxygen supplementation, our analysis showed that about 7.19% (95% CI = 4.66–10.20) of those testing positive for SARS-CoV-2 required some kind of oxygen supplementation for the management of clinical symptoms. For ICU admission, 4.26% (95% CI = 2.90–5.58) of children and adolescents with SARS-CoV-2 infection required ICU or PICU or HDU admission. Finally, the pooled percentage of children and adolescents with SARS-CoV-2 infections requiring assisted ventilation was 2.92% (95% CI = 1.79–4.30) (Figures S13–16 in the **Online Supplementary Document**).

Mortality outcomes

The pooled case fatality ratio was 0.87% (95% CI = 0.54–1.28) (Figure S17 in the **Online Supplementary Document**). Although most of these deaths can be considered as in-hospital deaths, these details, including the follow-up period, were unclear in most studies.

DISCUSSION

We undertook this systematic review and meta-analysis to assess the burden and epidemiology of SARS-CoV-2 infections in people aged ≤18 years to help guide prevention policies and treatment recommendations. Our findings suggest that about 9.30% of children and adolescents tested positive for SARS-CoV-2 infection by PCR or antigen tests in the pre-Omicron era, while around 29.83% of infections were asymptomatic. Likewise, 21 in 100 people who were aged ≤18 years and tested positive for SARS-CoV-2 required hospitalisation, 4 in 100 required ICU admission, and 1 in 100 resulted in death.

Our study showed that the pooled proportion positive estimates were slightly higher in studies only using PCR for diagnosis (9.67%) when compared with all included studies (9.30%). Well-designed large studies and surveillance systems are needed to better understand the true burden of COVID-19 in the paediatric population. Additionally, laboratory testing of SARS-CoV-2 should not be limited to those with symptoms of COVID-19 since at least about one-third of SARS-CoV-2 infected persons remain asymptomatic [250,251]. Without robust data on a representative sample for each country, we will not understand the true magnitude of COVID-19 and transmission patterns at the local and global levels. Importantly, early diagnosis and confirmation of infection will allow individuals to seek health care, therefore reducing disease severity and death.

Variability in sampling strategy and testing policies may have contributed to significant heterogeneity across studies. For example, three influential studies providing unusually high proportions of SARS-CoV-2 positives enrolled individuals within two weeks of exposure to a laboratory-confirmed COVID-19 household contact into the Household Exposure and Respiratory Virus Transmission and Immunity Study (HEARTS) with a convenient recruitment strategy [55] and evaluated a sample of children with a suspicion [241] or high suspicion of COVID-19, respectively [88]. Most studies conducted testing of all children visiting the health centre or educational institution, or individuals having symptoms, or a known contact with a COVID-19 case, or having residence in a geographical area of high COVID-19 incidence.

Our meta-analysis showed that the RR of SARS-CoV-2 positive test was higher in those aged 10 to ≤18 years compared to those <10 years. The number of COVID-19 cases and population by age-groups reported by the UN reflects a similar trend [6]. Globally, males have been shown to be at higher risk of severe COVID-19 disease and adverse outcomes compared to females, yet there does not seem to be strong evidence that suggests that test positivity is significantly higher in males compared to females in individuals of all ages [252]. We also did not detect an association of sex with SARS-CoV-2 test positivity (RR = 0.96; 95% CI = 0.87–1.05) in children and adolescents. Evidence on race/ethnicity as a risk factor for SARS-CoV-2 infections in this population was limited, with wide CIs, while the studies were reported from different countries and thus may not be directly comparable. Moreover, the findings must be interpreted with a caveat, since we did not adjust for demographic factors such as age, sex, deprivation, household size, and underlying health conditions in this analysis. Existing evidence, not limited to the paediatric and adolescent population, indicates that some ethnic communities are disproportionately affected by higher SARS-CoV-2 infection rates and adverse outcomes, and these disparities can often be attributed to pre-existing social inequalities [253]. Adults and children with certain underlying medical conditions are at higher risk of COVID-19 [254]. We found that having at least one of the following comorbidities – obesity, diabetes, immunosuppression, cardiovascular disease, asthma, epilepsy, renal disease, neurologic condition, or congenital heart disease – increased SARS-CoV-2 infection risk by 33% in people aged ≤18 years. In our meta-analysis, we did not observe a statistically significant association between immunosuppression and the risk of SARS-CoV-2 infection. It is plausible that this patient population was likely to have taken more precautions and preventive measures such as shielding, which may have confounded this association. Pregnancy and other comorbidities, like neurological disease, congenital cardiac disease, and renal disease, did not show a statistically significant association with SARS-CoV-2 infection. Like those immunosuppressed patients, pregnant women and patients living with these conditions can be expected to have had a heightened degree of precaution and better compliance to non-pharmacological interventions, particularly in the early pandemic period, when most of the data were collected. Thus, population behaviour factors that were beyond the scope of this systematic review may have confounded this association.

We estimated that about 20.70% of people aged ≤18 years who were positive for SARS-CoV-2 required admission to the hospital, but only 6.05% had severe or critical disease. This suggests that the criteria for hospitalisation were likely influenced by several other factors apart from the severity of COVID-19 disease. Importantly, criteria for hospitalisation were highly heterogeneous in different countries and changed over time. This discrepancy could be attributed to the fact that most countries adopted a very cautious approach at the beginning of the pandemic and set guidelines to hospitalise patients for monitoring and control of infection (isolation) rather than as a requirement for the management of the disease. Besides, we did not explore if the necessity for hospitalisation, ICU admission, oxygen supplementation, and mechanical ventilation was primarily driven by COVID-19 disease or other factors such as underlying health conditions. Therefore, these estimates should not be interpreted as hospitalisation, ICU admission, oxygen supplementation, and mechanical ventilation attributable to COVID-19 disease severity and are likely overestimates. Our findings suggest that about 0.87% of SARS-CoV-2 positive children had fatal outcomes. Children and adolescents with severe and critical disease are more likely to die than those with asymptomatic infection or mild and moderate COVID-19 disease. Only 35 studies reported the number of children and adolescents progressing to critical disease, and it may be expected that these studies were conducted in tertiary health facilities that have equipment and manpower to manage critically ill patients. For studies conducted in other settings, like communities, educational institutions, or primary health facilities, the case fatality ratio, requirement of oxygen supplementation, ICU admission, and assisted ventilation can be expected to be lower, as it is unlikely to have people with critical COVID-19 in these settings. It remains to be seen how the case fatality ratio changes according to disease severity and it would be of particular interest to see the disease severity estimates and death in children with specific underlying conditions. Again, most studies reported the case fatality ratios rather than the disease-attributable case fatality ratios. The estimate is, therefore, likely an overestimate of the true mortality estimate.

Our test-positive estimate of 9.30% is higher than the estimate provided by Jain et al. [255] for influenza in the same population (7.00%) between 2010 and 2012. Their estimates for respiratory syncytial virus, meanwhile, were higher (28.00%) compared to our estimates for SARS-Cov-2 in children aged ≤18 years. However, their study population was restricted to hospitalised children with a specific case definition of acute respiratory infections with radiologic evidence of pneumonia. One would expect higher chances of detection of respiratory virus in such populations presenting with acute respiratory illnesses and evidence of pneumonia as compared to our study population, which also included asymptomatic people who may or may not have had contact with a SARS-CoV-2 positive individual. Our study population was not restricted to those with acute respiratory illnesses, as we also wanted to estimate the proportion of cases with asymptomatic and mild disease presentation. The pooled proportion positive for influenza among hospitalised children and adolescents aged ≤18 years with respiratory illness was reported to be 9.50% (95% CI = 8.10–11.00) between 1982 and 2012 in another study [256]. Although we did not conduct a subgroup analysis for hospitalised patients, our subgroup analysis by study setting showed comparable estimates (10.01%; 95% CI = 7.24–13.17) in studies conducted in health facility settings (which also included outpatients). Considering the risk of COVID-19 is comparable to or higher than influenza, routine COVID-19 vaccination may need to be considered in children and adolescents, at risk of severe illness, as has been done in the case of influenza; moreover, COVID-19 vaccines such as mRNA vaccines have been shown to reduce both infection and severe outcomes such as hospitalisation and death in the paediatric population and have been demonstrated to be safe [257].

This is, to the best of our knowledge, the first systematic review to assess the global data on SARS-CoV-2 infections in children and adolescents. The study was guided by PRISMA-P guidelines and followed a predetermined protocol. We adopted a sensitive search strategy to retrieve relevant publications. However, our review has some limitations. We adopted a single reviewer screening approach that can lead to bias and increase the chance of human error. The differences in testing criteria and selection for inclusion of participants in individual studies led to very high heterogeneity in the included study estimates ($I^2 = 100\%$, $\tau^2 = 0 \cdot 0460$ for the test positivity estimates). We were unable to provide reliable estimates for subgroup analysis by SARS-CoV-2 variant, as most studies were conducted before reliable and large-scale genomic sequencing data became available. We did not explore the effect of non-pharmaceutical interventions or COVID-19 vaccination in children on our estimates. The vaccination policies were, again, highly variable across countries, including the type of vaccine, age criteria and the time of start of vaccination programmes. Lastly, we included no studies conducted in low-income countries in the proportion positive analysis. The two studies that were conducted across multiple countries also reported data either from high- or middle-income countries. This paucity of data also translates into vaccine coverage in low-income countries, as 69.20% of the global population had received at least one dose of the COVID-19 vaccine vs only 25.90% of people living in low-income countries as of 18 January 2023 [258]. Investment in research and surveillance activities in low-income countries is, therefore, warranted to help inform vaccination and other prevention policies and management strategies.

There were limited and unstandardised data on the long-term sequelae or complications of COVID-19 disease, so we did not undertake a synthesis for these outcomes. The portrayal of the burden of disease is incomplete without estimating the long-term sequelae or the incidence of long COVID-19 in this age group which seems to be more common than previously believed. This is a critical factor in comparing the risks and benefits of vaccinations, particularly because presentation with mild disease is very common in this age group [259]. Our analysis does not consider the impact of vaccination policies or non-pharmacological interventions and other preventive measures that were implemented or relaxed by different countries at different times and that had a likely impact on the burden of disease.

CONCLUSIONS

The detection of SARS-CoV-2 in children is not uncommon. Although many of the paediatric cases presented with asymptomatic or mild forms of disease with complete recovery, there is a considerable proportion of those requiring hospitalisation, oxygen support, and ICU admission. Moreover, it is essential to systematically investigate the long-term sequelae or incidence of long COVID-19 in this population and assess the differential impact of SARS-CoV-2 variants. Given the importance of COVID-19 in this population, more investment in research, diagnostics, treatment, and vaccines for this population is warranted.

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Additional material
Online Supplementary Document

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