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REVIEW ARTICLE

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SARS-CoV-2 infection in children and implications for vaccination

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The COVID-19 pandemic caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for more than 500 million cases worldwide as of April 2022. Initial estimates in 2020 found that children were less likely to become infected with SARS-CoV-2 and more likely to be asymptomatic or display mild COVID-19 symptoms. Our early understanding of COVID-19 transmission and disease in children led to a range of public health measures including school closures that have indirectly impacted child health and wellbeing. The emergence of variants of concern (particularly Delta and Omicron) has raised new issues about transmissibility in children, as preliminary data suggest that children may be at increased risk of infection, especially if unvaccinated. Global national prevalence data show that SARS-CoV-2 infection in children and adolescents is rising due to COVID-19 vaccination among adults and increased circulation of Delta and Omicron variants. To mitigate this, childhood immunisation programmes are being implemented globally to prevent direct and indirect consequences of COVID-19 including severe complications (e.g., MIS-C), debilitating long-COVID symptoms, and the indirect impacts of prolonged community and school closures on childhood education, social and behavioural development and mental health. This review explores the current state of knowledge on COVID-19 in children including COVID-19 vaccination strategies.

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IMPACT:

- Provides an up-to-date account of SARS-CoV-2 infections in children.
- Discusses the direct and indirect effects of COVID-19 in children.
- Provides the latest information on the current state of global COVID-19 vaccination in children.

INTRODUCTION

The global pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for more than 500 million cases, with over 6 million recorded deaths by April 2022 according to the World Health Organisation (WHO).[1] The epidemiology and transmission characteristics from early COVID-19 outbreaks have been instrumental in providing insights for public health mitigation strategies (such as social distancing and stay at home regulations) to stem community transmission.[2–4] In initial phases of the pandemic, it was evident that children were less likely to become infected than adults, and typically experienced milder illness.[5–9] Consequently, those at highest risk of hospitalisation and death such as the elderly population, were prioritised for the early vaccine trials and subsequent national COVID-19 vaccination programmes.[10]

The global landscape of the pandemic has changed rapidly with the emergence of SARS-CoV-2 variants that are more infectious and potentially more virulent than the original Wuhan-Hu-1/2019 strain.[11] What we now know is that children and adolescents of all ages are susceptible to SARS-CoV-2 infection[6,7] and preliminary data indicate that they may be at increased risk of infection to particular SARS-CoV-2 variants such as Delta[12,13] and Omicron,[14,15] especially if unvaccinated. As global prevalence rises, in areas where the virus has not been contained by public health mitigation strategies (prior to vaccination), there have been increasing numbers of children requiring critical care (e.g., the United States of America (USA) and the United Kingdom (UK)).[8,16,17] In contrast, in low-to-middle income countries (LMICs) where there is often lower vaccine availability, lower critical care capacity and poor healthcare quality, there have been disproportionate fatalities.[18] This review provides a current state of the SARS-CoV-2 (COVID-19) literature in children at a critical time when children have become a major focus during this pandemic and to guide targeted future empirical research to improve the COVID-19 response in paediatric populations.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched for any peer-reviewed articles relating to SARS-CoV-2 infection and vaccination in children until April 2022 using PubMed, Scopus and Google Scholar databases and Search terms included 'COVID-19', 'SARS-CoV-2', 'Variants of Concern', 'Delta Variant', 'Omicron', 'Long-COVID', 'MIS-C', 'COVID-19 vaccination'. Articles were also identified through cross-referencing. References from English and non-English languages were reviewed.

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GLOBAL SARS-COV-2 EPIDEMIOLOGY

Between January and March 2020 early reports suggested that children represented 1–5% of total COVID-19 cases.[2,6,9,19] This was in contrast to other respiratory viruses, such as influenza or respiratory syncytial virus (RSV), which prior to the pandemic, had a higher burden of disease in young children.[20] However, the emergence of several variants of concern (VOC) and the use of COVID-19 vaccines in adults has seen SARS-CoV-2 cases increase among children. Table 1 shows estimates of age-specific SARS-CoV-2 cases per 100,000 people from national and WHO surveillance data over the 2 years of the COVID-19 pandemic from April 2020 to April 2022, highlighting the change in SARS-CoV-2 prevalence among children over this period. It is important to note the level of data and testing practices (including routine household testing) in children varies widely between countries, with some settings (e.g., Indonesia, China, India) likely to underestimate prevalence in children. As the global pandemic continues to evolve, children now represent between 10 and 23% of COVID-19 cases (Table 1).

SARS-COV-2 VARIANTS OF CONCERN

The WHO has identified five SARS-CoV-2 VOC—Alpha, Beta, Gamma, Delta, Omicron—that have emerged around the world since September 2020.[11] These variants are associated with one or more of the following—increased transmissibility, increased virulence or change in clinic disease caused, and/or decreased effectiveness of public health mitigations strategies, available diagnostics, vaccines or therapeutics.[11] In late 2020 and early 2021 during subsequent second and third waves of the pandemic, these VOC circulated in various frequencies in geographical regions until September 2021 where Delta rapidly replaced the Alpha variant globally to become the then predominant strain.[21] Delta is thought to be twice as contagious[13] and some studies suggest might cause more severe illness and hospitalisation in unvaccinated persons compared to the Alpha or original Wuhan variants.[22,23] Delta-specific data from the UK show a direct link between infection and hospitalisation among predominately unvaccinated children, where children (5–12 years) had a five-fold higher incidence of infection compared to those over 65 years (most of who have been fully vaccinated with a COVID-19 vaccine).[12] This in part is due to restriction easing and increased social interaction and school attendance in young people.[12] Similarly, CDC data from the USA reported a five-fold increase in child and adolescent hospitalisations, a ten-fold increase in young children (0–4 years) and a ten-fold increase in unvaccinated compared to vaccinated adolescents (12–17 years).[24] Hospital admissions requiring ICU admission have remained similar to the pre-Delta period (~20%).[17]

As of April 2022, the newest circulating variant Omicron represents >99% of total variant frequency globally.[21] First identified in November 2021, Omicron rapidly spread through South Africa where childhood cases were higher than in all three previous pandemic waves, with hospitalisation increasing uncharacteristically ahead of adult populations.[15] Similarly in early 2022, US CDC data have indicated that children aged 0–4 years old not yet eligible for COVID-19 vaccination are being hospitalised at five times the rate previously seen during Delta predominance.[14] However, despite higher case incidence, multiple studies suggest children infected with Omicron are likely to be younger and less likely to experience severe disease.[25–27]

In addition, during the transitional phases of Delta to Omicron, some countries have begun to vaccinate younger age groups (i.e., 3 or 5 up to 11 years), although significant vaccine inequity still exists in settings such as South and Central Africa where less than 10% of the population were vaccinated. Vaccines developed during the pre-Omicron phase are now being re-evaluated, where a two-dose mRNA vaccine regimen has been shown to still protect against

Table 1. Age-specific SARS-CoV-2 prevalence data per 100,000 and percentage (%) of total COVID-19 cases from National Surveillance Data during the period April 2020 to April 2022.

	April 2020				April 2021				April 2022			
Age	**0–9**	**10–19**	**(0–19)**	**70–79**	**0–9**	**10–19**	**(0–19)**	**70–79**	**0–9**	**10–19**	**(0–19)**	**70–79**
Australia[44]	1 (0.6%)	7 (3.3%)	4 (3.9%)	38 (10.7%)	49 (5.5%)	78 (8.4%)	64 (13.9%)	89 (5.7%)	8970 (6.0%)	12,554 (8.1%)	10,719 (14.1%)	4917 (1.9%)
Brazil[19]	14 (1.3%)	50 (5.0%)	33 (6.3%)	199 (5.9%)	1136 (3.6%)	1919 (6.4%)	1539 (10.0%)	4880 (4.9%)	1195 (3.6%)	2027 (6.5%)	1623 (10.1%)	5007 (4.8%)
England[47]	13 (0.7%)	21 (1.1%)	17 (1.7%)	309 (12.2%)	2249 (4.7%)	5239 (10.5%)	3721 (15.2%)	2934 (6.1%)	19338 (5.3%)	37,340 (10.0%)	28,205 (15.3%)	11,279 (2.3%)
EU/EAA[a] (Europe)[46]	18 (2.0%)	36 (3.8%)	27 (5.8%)	117 (9.8%)	1086 (5.3%)	2278 (11.1%)	1681 (16.4%)	1553 (5.9%)				
Indonesia[b] [19,49]			2[c] (7.3%)		124 (5.1%)	231 (9.1%)	177 (14.2%)	380 (2.6%)	527 (5.3%)	1010 (9.8%)	765 (15.1%)	1665 (2.7%)
Italy[19]	32 (0.7%)	50 (1.3%)	42 (2.1%)	518 (14.8%)	4390 (5.3%)	7609 (10.7%)	6130 (16.0%)	5412 (8.1%)	27,964 (9.6%)	33,013 (13.4%)	30,693 (23.0%)	13,294 (5.7%)
USA[45]	15 (1.0%)	36 (2.7%)	26 (3.7%)	199 (8.9%)	2643 (4.5%)	6030 (11.0%)	4392 (15.5%)	5225 (5.6%)	11,879 (7.5%)	18,882 (12.6%)	15,494 (20.1%)	12,392 (4.9%)

Age-specific prevalence per 100,000 reported in the table was calculated from cumulative prevalence SARS-CoV-2 data from either National or WHO surveillance data and national population numbers.[111] Percentages (%) report percentage cases of total COVID-19 cases from this cumulative prevalence data.
[a]European data reported in columns April 2020 and April 2021 represent intervals July 2020 and July 2021 due to the availability of data from the European Centre for Disease Prevention and Control (ECDC). There are no current data available for the year 2022.
[b]Indonesia's testing rate per million population ranks low regionally, and likely underestimates the true age-specific prevalence of age groups listed above.[49]
[c]Indonesia data reported in April 20 represent children 0–18 years rather than 0–19 years.[49]

hospitalisation and severe disease in children, although less effectively than against Delta.[28,29] A booster dose in 16–17-year-old adolescents can restore vaccine effectiveness up to 81%.[28]

In children, it is not currently clear whether Omicron[14,15,25–27] causes a higher severity of illness compared to earlier variants or if rising hospital admissions reflect increases in transmission in susceptible unvaccinated child cohorts. Further research is needed to determine the virulence and transmission characteristics of SARS-CoV-2 variants and implications for unvaccinated children.

SARS-COV-2 TRANSMISSION IN CHILDREN

Early studies into transmissibility and susceptibility of the Wuhan strain in children provide useful insights into the mode of transmission of VOC. Transmission of SARS-CoV-2 predominantly occurs through the direct person-to-person spread of respiratory droplets and indirectly via fomite transmission (contaminated surfaces).[3,4] In addition, airborne transmission (infectious agent suspended as aerosol) can occur in specific circumstances (i.e., during oral medical procedures and airway management).[3] Prolonged viral shedding in the faeces of children has also been identified, even when children are asymptomatic,[30,31] although the significance of faecal-oral/faecal-aerosol transmission in children is not fully understood. The primary setting for viral transmission is during close proximity when indoors with contact with infected individuals (e.g., the household, workplaces and educational settings).[3]

Determining the relative infectiousness of children has been difficult as children are infrequently reported as the index case in household studies due to confounding factors such as shared sources of infection, increased exposure during caring for an unwell child, and asymptomatic cases in children being under-recognised.[32] Data from national South Korean contact tracing of over 10,592 household participants found that transmission of the Wuhan variant was high if the index patient was 10–19 years old, but low in households with 0–9-year-old children.[2] A meta-analysis of 54 household studies since the beginning of the pandemic found a significantly lower secondary attack rate in children compared to adults (16.8% vs 28.3%)[32] and an increasing SARS-CoV-2 household prevalence with age, from 23% in those <5 years old and up to 68% in those >65 years.[33] Furthermore, transmissibility is more likely with symptomatic compared to asymptomatic or pre-symptomatic index cases,[32] where asymptomatic children have been shown to have lower SARS-CoV-2 viral RNA levels.[34] This supports the notion that children, who are more likely to be asymptomatic,[5,9,35] are less likely to transmit the virus.

Educational settings such as Early Childhood Education Care (ECEC), primary and secondary schools are also important transmission sites for seasonal respiratory viral infections such as influenza and RSV.[20,36] In response to the COVID-19 pandemic, 107 countries had implemented school closures as early as March 2020.[20] Many studies have shown that school closures during the pandemic reduce viral transmission; how effective this mitigation strategy is for SARS-CoV-2 remains still uncertain. A technical report from the Murdoch Children's Research Institute in Australia analysing the global literature on pandemic school closures (pre-Delta variant) concluded schools were not a primary driver of SARS-CoV-2 transmission and pose no greater risk with mitigation strategies compared to other public places.[37] The evidence-based recommendations from this report, weighing up the indirect effects of school closures, advocated for the prioritisation of school reopening.[37] In returning to in-person teaching, multi-layered mitigation strategies have been introduced around the world to reduce the incidence of SARS-CoV-2 infections in school-age children (many of whom are still unvaccinated), as well as teachers and other staff. Strategies include hand hygiene, social distancing, masks, cohorting (a system for grouping students in classes), regular surveillance with rapid antigen tests, mandatory vaccination in staff and supply of air-purification systems.[38]

Transmission rates of the Wuhan strain during late 2020 across 25 Australian educational settings (15 schools and 10 ECEC services) found the secondary attack rate to be low at 2.8%.[39] Child-to-child transmission (0.3%) was lower than child-to-staff (1.0%) and staff-to-staff (4.4%) secondary transmission[39] and transmission was higher during sports, particularly indoors.[40] A report from the National Centre of Immunisation Research and Surveillance in Australia in mid-2021 recorded a five-fold higher transmissibility with the Delta variant in educational settings compared to the ancestral Wuhan strain in 2020.[41] Across 51 similar educational settings (19 schools and 32 ECEC services) the secondary attack rate for Delta was 4.7% with transmission remaining highest in staff-to-staff (11.2%) and lowest in child-to-child (1.6%).[41] In addition, tertiary transmission to household contacts from secondary cases acquired in educational settings was 70.7% (73.4% from children and 66.3% from staff) for the Delta variant, considerably higher than the 16.5% tertiary attack rate seen in the ancestral Wuhan strain.[41] Overall, only 2% of children were hospitalised in this study, with most infections being asymptomatic or mild.[41]

In the later part of 2021, a report found at the beginning of the transition to Omicron predominance, the Omicron variant was 1.5 times more transmissible than Delta in Australia.[42] In schools affected by Omicron outbreaks, the child-to-child spread was high (4%) and more than eight-fold higher in primary school children compared to high school children (0% vs 8.4%),[42] likely reflecting high uptake of vaccination in adolescents >12 years in Australia. Importantly, school outbreaks appear to occur during high rates of community transmission, poor compliance with mitigation strategies or when staff are the primary drivers of transmission.[36,37,39,41] These findings highlight that with the implementation of multi-layered mitigation strategies, a return to face-to-face teaching is unlikely to contribute to community transmission of COVID-19.[42] This is supported by further evidence that school closures alone are conversely insufficient to stem community transmission and should be used as a last resort.[37,41,43]

ACUTE CLINICAL FEATURES OF COVID-19 DISEASE IN CHILDREN

One of the first landmark retrospective studies from China, and a smaller study in Italy (using the same descriptive categories of severity) found that up to 90%[7] and 98%[35] of confirmed paediatric cases, respectively, were either asymptomatic, mild or moderate. The highest incidence of SARS-CoV-2 infection occurs in those 10–19 years of age[19,44–47] with varied estimates of mean age between 5 and 11 years.[5–8] The exact proportion of infected children who are asymptomatic is currently unclear, with variable estimates between 4.4%[7] and 16%[5] but can be as high as 68% depending on the setting.[6]

The most common symptoms in older children are fever and cough (50%).[5,6,8,9] For very young children <6 months, many COVID-19 disease symptoms (such as loss of smell and taste) are unable to be reported. Children can also present with gastrointestinal symptoms like nausea, vomiting and diarrhoea, sometimes as the sole presenting feature.[5,6] While critical illness in children is rare,[8,9,35] it can and does occur. In areas where SARS-CoV-2 was not initially contained by public health measures, for example in the USA, UK (prior to vaccination) and LMICs like Indonesia, there have been large numbers of children requiring hospitalisation and critical care.[8,16–18] Age (infants <1 month and adolescents 10–14 years), health status and co-morbidities (e.g., pulmonary disease, obesity, oncological, neurological and congenital heart disease) all increase the risk of severe disease and death (although rare) among children.[5,8,48] In Indonesia, UNICEF

reported that malnutrition was a factor in children experiencing severe COVID-19.[49]

COMPLICATIONS AND SEQUELAE OF COVID-19 IN CHILDREN—MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) AND LONG-COVID

The harms experienced by children were not a major focus of health system efforts early in this pandemic given the milder form of acute COVID-19 illness compared to adults.[6,7,9] There is however the potential risk for severe complications or prolonged and recurrent symptoms that can impact long-term health in children. Multisystem inflammatory syndrome in children (MIS-C), otherwise known as Paediatric Multisystem Inflammatory Syndrome – Temporally Associated with SARS-CoV-2 (PIMS-TS) is a rare but serious hyperinflammatory condition that occurs approximately 1 month after exposure to SARS-CoV-2.[8,50,51] MIS-C shares similar clinical features to Kawasaki disease and toxic shock syndrome. Primary treatment for these illnesses is with intravenous immunoglobulin (IVIG) or systemic corticosteroids in addition to supportive care.[52] Recent conditional recommendations from the WHO suggest using corticosteroids in place of IVIG; however, there remains limited evidence of direct comparison between these therapies, and other factors such as global availability need to be taken into account.[52] Other biological immunosuppressive agents have been trialled, although no randomised trials, nor data are available to evaluate their benefits.[53]

There have been multiple studies from the UK and USA characterising MIS-C using criteria outlined by WHO and CDC.[8,50,51] One study of 456 COVID-19-positive children admitted to UK hospitals found 54 cases (11%) met MIS-C criteria at or during hospitalisation and were up to five times more likely to be admitted to critical care.[8] Incidence data from the USA show 316 MIS-C cases per 1,000,000 SARS-CoV-2 infections in those aged <21 years.[50,53] Multiple studies estimate the median age of MIS-C onset is between 8 and 9 years old and more likely to affect males and children from Hispanic, Latino or black backgrounds compared with children from white backgrounds.[8,50,51,54] In one global review, most children with MIS-C were previously healthy (80%) and had gastrointestinal (71%) and cardiovascular (82%) system involvement, requiring invasive treatment in critical care units including mechanical ventilation (18%).[55] MIS-C also presents a significant risk of acute illness and an unknown risk of long-term complications for children. CDC data from the US show that 17% of children suffer from coronary-artery aneurysms,[55] and up to 0.8% die.[54]

There are also increasing reports of prolonged or recurrent symptoms following the recovery of COVID-19, referred to as 'long-COVID' or 'post-COVID syndrome'.[56–62] Mechanisms including immune dysregulation, autoimmunity or potential viral persistence have been suggested to explain long-COVID;[62] however, data to test these hypotheses are needed. Long-COVID syndrome has mainly been characterised in adults[59,62] with less data available in children and adolescents[58,59] and all of these data pre-date Omicron predominance. A national UK analysis consistently found that long-COVID syndrome was lower in children, highest among females aged 50–69 years and occurred in those with higher viral loads during infection.[60]

A number of important limitations have been highlighted in studies of long-COVID.[58,59] These include the lack of a clear definition of long-COVID, reliance on self-reporting and the uncertainty of symptom identification without clinical assessment.[58,59] Furthermore, control groups are vital for any inference of symptoms attributable to long-COVID, especially given the non-specific nature and high natural prevalence of symptoms as well as the confounding impact of indirect health effects attributable to the pandemic itself and associated public health restrictions such as school closures.[58] A critical review from Zimmermann et al. in 2022 highlighted the variability among 27 long-COVID studies where only 9 of 27 studies included an uninfected control group.[61] The difference in reported persisting symptoms between confirmed SARS-CoV-2 cases and the control group ranged from −1 and 13%, where all but one study was <3%.[61] The most commonly reported symptoms of long-COVID are headache (3–80%), fatigue (3–87%), sleep disturbance (2–63%), concentration difficulties (2–81%), abdominal pain (1–76%), muscle aches and pain (1–61%), respiratory symptoms (1–30%), loss of smell (3–26%), and loss of appetite (2–50%).[58]

Furthermore, with implications for the long-term health of children, there is also emerging literature showing high expression of angiotensin-converting enzyme 2 (ACE2), a host cell receptor required for SARS-CoV-2 viral entry, in male sperm and female reproductive tissues.[63] Both the consequences of long-COVID and urogenital concerns of SARS-CoV-2 have serious potential for lasting impacts on the health and wellbeing of children and are yet to be fully characterised. Large longitudinal studies that assess the sequelae of SARS-CoV-2 on health and development as well as how this impacts school absenteeism and educational performance in children will provide more robust data on this issue.[57]

SARS-COV-2 IMMUNE RESPONSES

There is still much unknown regarding the nature and persistence of immunity following infection with SARS-CoV-2 in children. Limited lines of evidence characterising the humoral and cellular response to the virus show a more robust innate immune response during early infection, which is suggested to limit the infection and lead to the favourable clinical outcomes seen in children.[64–66]

Cellular and humoral antibody-mediated responses are vital components of viral defence.[67] Antibodies play a critical role in the neutralisation of the receptor-binding domain (RBD) on the Spike (S) protein of SARS-CoV-2 binding to the ACE2 receptor, which is responsible for viral cell entry and is the highly divergent component compared to other human coronaviruses.[68] The rapid rise of Omicron predominance can also be explained by numerous mutations in the Spike protein allowing this variant to partially escape immune recognition from a number of pre-existing vaccines developed for previous ancestral strains of SARS-CoV-2.[69] CD4+ T cells are also critical in generating the neutralising antibody response and development of adaptive immunity and memory.[67] Antibodies targeting the S protein are therefore the basis of protection from infection and current COVID-19 vaccines.[67]

In adults, a range of studies has reported an association between a higher neutralising antibody titre in severe compared to mild COVID-19 disease.[70] However, children are able to mount an effective and specific IgG antibody response against SARS-CoV-2 following infection that persists for at least 8 months.[71] The exact duration of these antibodies remains to be determined and is estimated to persist for between 1 and 2 years based on the sustained IgG response of closely related SARS (which shares ~69% homology with SARS-CoV-2).[70] An early study in adults investigating reinfection following recovery from the wild-type Wuhan-Hu-1 strain of SARS-CoV-2 found natural immunity appears to confer protection for at least 1 year.[72] While some evidence suggests slightly lower protection from reinfection is inferred from the Beta variant,[73] it remains unclear for other prevalent variants such as Delta and Omicron. Studies comparing the strength of the antibody response in children following SARS-CoV-2 infection and duration of protection against reinfection are needed.

Pre-existing cross-immunity from endemic coronavirus infections may provide some protection from novel SARS-CoV-2.[74] Despite this, higher cross-reactive IgA and IgG SARS-CoV-2 antibodies have been observed in older adults compared to

children who have mostly IgM, indicating a less experienced but more polyreactive response due to less endemic coronavirus exposure.[75] Currently, it remains unclear whether cross-immunity contributes to lower disease severity in children.[74] With the divergence in infection rates of school-aged children (10–19 years), age-stratified data are needed to understand differences in the immunological response to SARS-CoV-2 and how this may inform strategies to protect children.

COVID-19 VACCINATION IN CHILDREN

A number of countries with an adequate supply of COVID-19 vaccines have successfully immunised high proportions of their adult population and have now begun to vaccinate adolescents <18 years of age including children as young as 2 years old, as shown in Table 2. Recommendations on which vaccine and age group differ between countries due to the consideration of safety concerns of COVID-19 vaccines in younger children and the benefit of protecting at-risk children from SARS-CoV-2 based on their epidemiological situation. Figure 1 illustrates the global COVID-19 vaccination programmes in children.

Currently, the SARS-CoV-2 mRNA vaccines 'Comirnaty' (Pfizer-BioNTech's BNT162b2) and 'Spikevax' (Moderna's mRNA-1273) are by far the most common globally approved vaccines in adolescent age groups (12–17 years of age) and Comirnaty the most common in children 5–11 years of age (see Table 2). The immunogenicity of COVID-19 mRNA vaccines has shown non-inferior immune responses in children and adolescents when compared to adults.[76–79] Specifically, following two doses of the Pfizer-BioNTech's Comirnaty vaccine the geometric mean ratio of SARS-CoV-2 50% neutralising titres of 5–11-year olds[78] (receiving a smaller dose of the vaccine comparable to young adults, 10 µg compared to 30 µg) and 12–15-year olds[76] relative to young adults 16–25 years was 1.04 and 1.76, respectively. Similarly, the Spikevax vaccine elicited an 8% higher neutralising antibody titre in 12–17-year olds compared to those aged 18–25 years.[77] Preliminary data submitted to regulators show that Spikevax also generates a robust neutralising antibody response in 6–11-year and 6-month to 6-year-old cohorts given smaller doses of the vaccine comparable to young adults (50 and 25 µg compared to 100 µg, respectively).[79] Vaccination programmes in children differ between countries, where many have begun immunisation of children aged 5–11 years with Comirnaty and 6–11 years with Spikevax, while others including Finland, Germany, Sweden as well as Pakistan and Ukraine have not begun vaccination of children <12 years of age due to risk of adverse effects (Table 2).

A direct comparison between the two mRNA vaccines is difficult due to study design differences and variations in the assays used to measure neutralising antibodies[77] and there is currently no head-to-head studies comparing these vaccines in children. In adults, Comirnaty produces a slightly lower antibody response compared to the Spikevax vaccine.[71] The efficacy of Pfizer-BioNTech's Comirnaty reported by negative SARS-CoV-2 PCR nasal swabs in those aged 12–15 years at 7 days after two doses was 100% in those aged 12–15 years[76] and 90.7% in those aged 5–11 years with a reduced dosage.[78] In comparison, the efficacy of Spikevax vaccine reported by positive SARS-CoV-2 PCR nasal swab was 100% in preventing COVID-19 disease (i.e., displaying symptoms) and 56% in preventing any SARS-CoV-2 infection (i.e., symptomatic and asymptomatic) at 14 days following the second dose in those 12–17 years of age.[77] However in the setting of Omicron predominance, recent Spikevax Phase 3 trials showed reduced vaccine efficacy in 6 months to 2 years (43.7%) and those 2–6 years (37.5%) of age, although similar to trends observed in adult data.[79] A recent study also showed that both vaccines reduce viral load in front-line healthcare workers by up to 40%.[80] There is yet to be a similar study for viral load in children.

Table 2. Nationally active COVID-19 vaccination programmes in child age groups <18 years of age (as of April 2022).

Country	Age (years)	
Africa		
Egypt;[112] South Africa;[113] Morocco[112]	12–17	Comirnaty
Jordan[112]	12–17	Comirnaty and Covilo
Guinea[112]	12–17	Comirnaty and Spikevax
Namibia[a] [112]	12–17	–
Zimbabwe[114]	14–17	CoronaVac
Americas		
Cuba;[85] Venezuela[115]	2–17	Soberana 02
Chile[94]	3–17	CoronaVac
	5–17	Comirnaty
United States (USA);[116] Uruguay[117]	5–17	Comirnaty
Brazil[118]	5–17	Comirnaty
	6–17	CoronaVac
Canada;[119] Colombia[120]	5–17	Comirnaty
	6–17	Spikevax
Argentina[121]	5–17	Covilo
	12–17	Comirnaty and Spikevax
Costa Rica[a] [112]	5–17	–
Mexico[122]	12–17	Comirnaty
Asian-pacific/Asia		
China[123]	3–17	Coronavac and Covilo
	5–17	Comirnaty
Cambodia[124]	3–17	Coronavac
Australia;[125] Vietnam[112]	5–17	Comirnaty
	6–17	Spikevax
Japan;[126] Malaysia;[127] Singapore;[128] South Korea;[129] New Zealand[130]	5–17	Comirnaty
Thailand[131,132]	5–17	Comirnaty
	6–17	CoronaVac and Covilo
Indonesia[133]	6–17	CoronaVac
	12–17	Comirnaty
Mongolia[134]	12–17	Comirnaty
India[89]	12–17	Corbevax
	15–17	Covaxin
Europe/UK		
Europe[b] [135] and UK[136] (exc. Switzerland, Netherlands, Finland, Sweden, Russia, Germany)	5–17	Comirnaty
Switzerland;[137] Netherlands[138]	5–17	Comirnaty
	12–17	Spikevax
Finland[c];[139] Sweden[140]	12–17	Comirnaty
Russia[141]	12–17	Sputnik V
Germany[c] [142]	16–17	Comirnaty

Table 2. continued

Country	Age (years)	
Middle-East		
Israel[143]	5–17	Comirnaty
Iran[144]	5–17	Comirnaty
Pakistan[145]	12–17	Comirnaty
	12–17	Covilo and Coronavac
Saudi Arabia[146]	5–17	Comirnaty
	12–17	Spikevax
United Arab Emirates (UAE)[d] [147]	3–11	Covilo
	5–17	Comirnaty
Ukraine[148]	12–17	Comirnaty

[a]It is unclear from references what vaccine is currently used in national vaccination programs in Namibia and Costa Rica.
[b]Europe (EU) inclusive of Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, France, Greece, Greenland, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain are all approved for Comirnaty (Pfizer-BioNTech) and Spikevax (moderna), with predominant use of Comirnaty in those 5-11 years of age.
[c]Vaccination of high risk children and young people (i.e. those who are at greater risk of infection or severe disease due to serious conditions such as oncological, neurological, heart or pulmonary disease, immunocompromised and congenital syndrome) is occuring in 5-11 year olds in Finland and 12-15 year olds in Germany.
[d]United Arab Emirates (UAE) inclusive of Abu Dhabi, Ajman, Dubai, Fujairah, Ras Al Khaimah, Sharjah and Umm Al Quwain.

Phase 1/2 trials of the inactivated SARS-CoV-2 vaccines, 'CoronaVac' (Sinovac Biotech) and 'Covilo' (Sinopharm's BBIBP-CorV), have also been tested for safety and immunogenicity in children 3–17 years of age.[81,82] CoronaVac shows a higher neutralising antibody response at all ages receiving two smaller 1.5 µg doses than that elicited in adults receiving two full doses (3 µg).[81] Similarly, Covilo induced a robust neutralising antibody response in all ages comparable to convalescent serum and adult participants by 56 days following two doses of 4 µg.[82] However, a lower seroconversion rate and corresponding lower neutralising antibody titre was reported at 28 days in the 3–5 years age group, similar to those >60 years, believed to be due to the less developed/weakened immune system in these age groups.[82] Phase 3 efficacy trials and long-term follow-ups are still required to evaluate the protection against SARS-CoV-2 infection and persistence of antibodies elicited by these inactivated vaccines. Currently, the WHO does not recommend the use of CoronaVac or Covilo for the vaccination of children <18 years of age.[83,84] However approval has been granted for one or both of these inactivated vaccines in children as young as 3 years old in Chile, China, Cambodia and The United Arab Emirates as well as in those >6 years in Argentina, Indonesia, Thailand and Brazil (see Table 2).

Furthermore, Cuba and Venezuela are the first countries to begin vaccination of children as young as 2 years old with a single dose of Finlay Institutes anti-RBD FINLAY-FR-2 vaccine 'Soberana 02'.[85] There is yet to be published large-scale trial data; however, a Phase I/II trial of 350 children aged 3–18 years in Cuba showed no severe adverse events and induction of neutralising antibody titres as high as convalescent children following two doses.[86]

India has also approved three vaccines for use in children. The world's first DNA vaccine, 'ZyCOV-D' produced by India's Cadila,[87] found to be safe and well tolerated in 935 adolescents (12–17 years) with efficacy in preventing symptomatic PCR positive cases in those aged 12–18 years by 66.6%.[88] Also a protein subunit vaccine 'Corbevax' (Biological E Limited) in 12–17-year olds and an inactivated vaccine 'Covaxin' (Bharat Biotech) in 15–17-year olds.[89] There are currently no published data on these vaccines and the WHO does not recommend the use of Covaxin in children <18 years.[90]

The 'Vaxzevria' (AstraZeneca-Oxford University's ChAdOx1 nCoV-19) and Ad26.COV2.S (Johnson and Johnson) vaccines are currently not approved for use in children.

IMPLICATIONS FOR COVID-19 VACCINATION IN CHILDREN

The global vaccine rollout in children has been slow and inequitable in many parts of the world (see Fig. 1). In the setting of limited vaccine supply, the WHO recommends vaccination in populations at high risk of severe disease (i.e., elderly and healthcare workers).[10] For many LMICs, there is insufficient access to COVID-19 vaccines to immunise high-priority groups.[91] Since severe disease in children is rare, they have not been initially prioritised for COVID-19 vaccination, in contrast to prior pandemics such as the 2009 H1N1 Influenza outbreak.[92] As the proportion of SARS-CoV-2 infections in children and adolescents rises around the world,[19,44–47,49] an increasing argument to prioritise childhood vaccination can be made to prevent severe disease,[5,6,8] MIS-C,[8,50,51,93] the debilitating effects of long-COVID[56–60] and the indirect impacts of prolonged community and school closures.[37,41,43] A number of countries have now approved and begun immunising children >2 years of age, although global vaccination rates in children are poorly reported and inconsistent compared to adults. By April of 2022, Australia has fully vaccinated 34% of 5–11-year olds and 80% of 12–15-year olds,[44] while Chile has fully vaccinated greater than 82% of 3–17-year olds.[94] Still, many nations have not yet begun vaccination programmes <12 years of age (see Table 2).

The indirect effects of unprecedented and prolonged closure of schools, direct and indirect insults to personal health, loss of support networks and community access present ongoing challenges for children, adolescents and their families (see Fig. 2). For some LMICs, like Indonesia, the lack of remote learning hardware has led to unprecedented school drop-out rates.[49] In-person participation in education provides an essential safe and supportive learning environment that fosters social, behavioural, cognitive and physical development as well as access to healthcare.[37,41,95] During this pandemic, children have been reported to experience loneliness, isolation, disruption to routines and coping mechanisms as well as stress related to remote learning.[96] According to a Royal Children's Hospital survey of over 2000 parents of 3400 children in Melbourne (a setting of prolonged lockdowns), over 36% stated COVID-19 has negatively affected their child's mental health, and up to one-in-ten children were either struggling or unable to cope with life.[97] School closures also impact school vaccination programmes. During the pandemic, routine vaccination has been delayed in 20% of children in western settings and over 60% in LMIC settings,[98,99] putting them at increased risk and susceptibility to vaccine-preventable disease.

There is also a significant risk for unvaccinated children once public health restrictions are eased and international travel restarts. This includes children travelling overseas with families, for educational placements, as well as local susceptibility to SARS-CoV-2 community transmission. Recently, as the Omicron variant spreads globally there has been a disproportionate number of child cohorts infected with the virus in settings where the elderly population, most at risk of hospitalisation and death, have been prioritised in early vaccine trials and subsequent national COVID-19 vaccination programmes.[10] For example, in some LMIC settings yet to vaccinate children <12 years old, childhood cases are higher than in all three previous pandemic waves, and hospitalisation has increased uncharacteristically ahead of adult populations.[15]

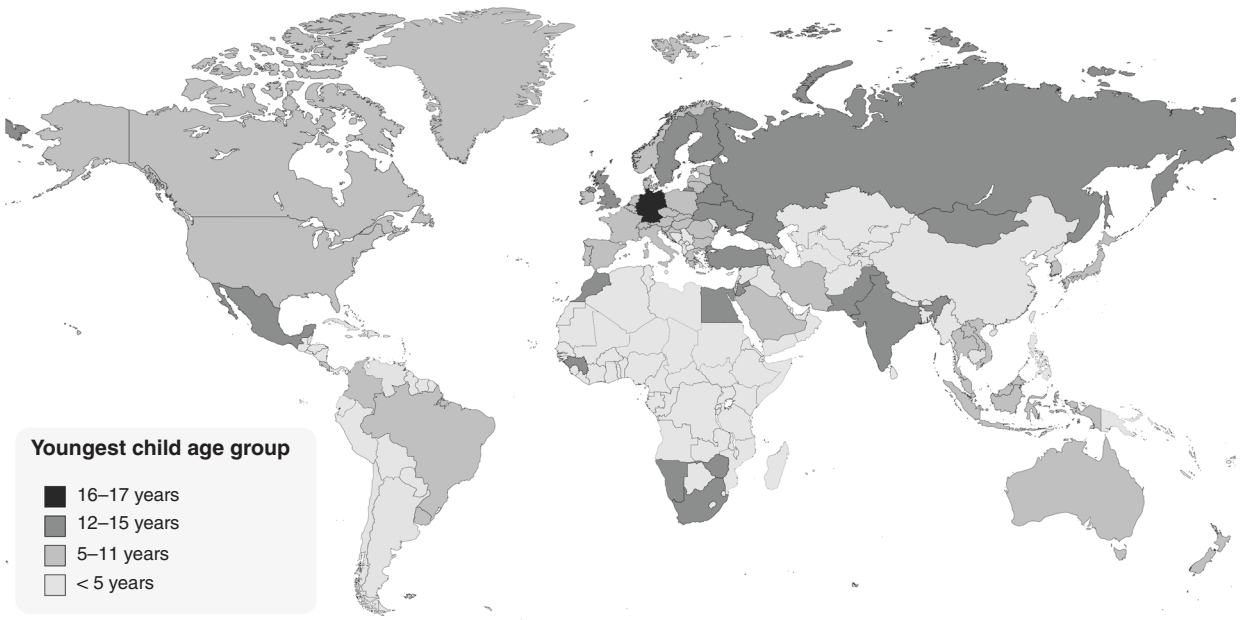

Fig. 1 Global COVID-19 vaccination programmes in children. World map showing where COVID-19 vaccines have been approved and/or used in national rollout programmes in children 3–17 years of age (as of April 2022).

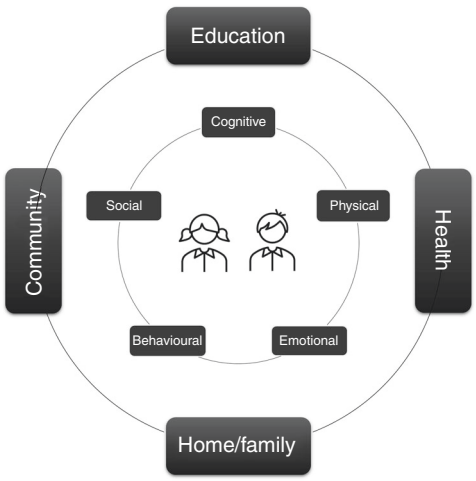

Fig. 2 Indirect effects of the COVID-19 pandemic on children. Social and health determinants of COVID-19 in children—altering any of education, health, home-life or access to the community is likely to impact one or more developmental areas whether social, behavioural, emotional or otherwise.

Similarly, in some developing settings the very young 0–4 years old not eligible for COVID-19 vaccination (due to concerns of vaccine safety) are also affected.[14]

The safety of COVID-19 vaccines in children is an important consideration. Serious heart conditions (myocarditis and pericarditis) have been reported during community surveillance with mRNA vaccines Comirnaty and Spikevax in Canada,[100] USA[101] and Israel[102] showing a predominance for male patients in adolescent age groups (15–24 years).[101] For this reason, the use of the Spikevax vaccine in Sweden and Norway has been temporarily suspended for those <30 years in Sweden and those <18 years in Norway (with Comirnaty recommended for men <30 years) due to the potential of an increased incidence in heart inflammation compared to Comirnaty.[103,104] While both mRNA vaccines are associated with an increased risk of myocarditis/pericarditis, head-to-head comparison data in the US among 18–39-year olds shows Spikevax has a significantly higher rate of myocarditis/pericarditis compared to Comirnaty.[105] A direct comparison in the 12–18-year age group is still not possible given the different age groups authorised to receive each vaccine.[105] Ongoing surveillance will be crucial to detect any rare side effects even with reduced dosages in younger age groups. Until recently, vaccine safety in very young (<12 years of age) was unclear.

Comirnaty has shown a favourable safety and immunogenicity profile in a smaller cohort of 2268 children aged 5–11 years of age who received a smaller dose of the vaccine (10 µg compared to 30 µg).[78] In addition, safety and efficacy trials are also underway for Spikevax in children 6 months to 12 years where interim results indicate similar safety and tolerability to older age groups, with no severe adverse events including cases of myocarditis/pericarditis or MIS-C reported in 6700 children.[79] While these sample sizes are too small to make definitive conclusions about rare adverse events including heart inflammation, surveillance data from CDC following administration of 8.7 million doses of Pfizer's Comirnaty vaccine in children aged 5–11 years found of 4249 adverse events 97.6% were non-serious.[106] Overall, the risk of vaccine-induced heart disease is thought to be smaller than that attributable to COVID-19 infection itself. A large study in Israel found COVID-19 is associated with an increased risk of myocarditis (11 events per 100,000 cases; 95% CI 3.95–25.12) compared to mRNA vaccination (2.7 events per 100,000 people; 95% CI 1.55–12.44).[107] Emerging data from the USA also suggest that patients with COVID-19 are 16 times more likely to develop myocarditis compared to those not diagnosed with COVID-19, with a disproportionate incidence in males and those <16 years old.[108] In the USA, hospital-based myocarditis has risen over 40% in 2020 alone,[108] presenting serious implications for the long-term health and wellbeing of at-risk children.

Covilo[82] and CoronaVac[81] vaccines have also shown to be well tolerated in children aged 3–17 years, with one case of systemic acute allergic reaction (later diagnosed with food allergy) reported for Covilo[82] and one case of pneumonia reported for CoronaVac.[81] Both systemic adverse reactions were considered unrelated to vaccination. Currently, no additional severe adverse reactions have been reported; however, community surveillance outside of China has been limited to date. AstraZeneca's 'Vaxzevria' Phase 3 trials in

children (6–17 years) ceased recruiting on the potential of a higher risk of thrombosis and thrombocytopenia syndrome. Trials are continuing for those 16 years and older,[109] and current recommendations for use are for those >18 years only.[110] Careful surveillance for safety signals following COVID-19 vaccination in children will be critical to ensure public confidence in the vaccines themselves as well as to ensure we adequately protect children.

CONCLUSION

The international landscape of the COVID-19 pandemic is rapidly changing. As the proportion of SARS-CoV-2 infections in children and adolescents rises globally, an increasing argument to prioritise childhood vaccination can be made to prevent direct and indirect consequences of COVID-19 disease including complications from severe disease, debilitating long-COVID symptoms, and the indirect impacts of prolonged community and school closures on childhood education, social and behavioural development. It is important for policymakers to consider the safety concerns of COVID-19 vaccines in young children to guide their use as communities re-open. Moreover, ensuring equitable vaccine supply to LMICs will be critical to prevent severe disease and death in high-risk child and adult populations.

Research gaps

Significant progress has been made in our understanding of how COVID-19 has affected children and their role in the pandemic over the past 2 years. However, considerable gaps in our knowledge remain where research should be prioritised. This includes a better grasp of why children are less susceptible to severe disease and the immunological characteristics that may underpin this. Moreover, we are only beginning to understand the indirect effects of the pandemic and how this may have affected their mental health as well as their educational progress. Greater precision around long-COVID diagnoses in children is also urgently needed. Finally, the safety and efficacy of COVID-19 vaccines in children, particularly those 5–11 years of age (and younger), will need to be investigated in detail given their relatively low risk of developing severe COVID-19 disease in these age groups.

REFERENCES

1. World Health Organization (WHO). *WHO Coronavirus (COVID-19) – Global Situation* (accessed 30 March 2022); https://covid19.who.int/ (2021).
2. Park, Y. J. et al. Contact tracing during Coronavirus Disease outbreak, South Korea, 2020. *Emerg. Infect. Dis.* **26**, 2465–2468 (2020).
3. World Health Organization (WHO). *Transmission of SARS-CoV-2: Implications for Infection Prevention Precautions* (accessed 30 March 2022); https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions (2020).
4. Chan, J. F. et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* **395**, 514–523 (2020).
5. Götzinger, F. et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc. Health* **4**, 653–661 (2020).
6. Bialek, S. et al. Coronavirus disease 2019 in children — United States, February 12–April 2, 2020. *MMWR Morb. Mortal. Wkly Rep.* **69**, 422–426 (2020).
7. Dong, Y. et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* **145**, e20200702 (2020).
8. Swann, O. V. et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ* **370**, m3249 (2020).
9. Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* **109**, 1088–1095 (2020).
10. SAGE Working Group. *WHO SAGE Roadmap for Prioritizing Uses of COVID-19 Vaccines in the Context of Limited Supply* (World Health Organisation (WHO), 2020).
11. World Health Organisation (WHO). *Tracking SARS-CoV-2 Variants* (accessed 16 April 2022); https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (2022).
12. Riley, S. et al. REACT-1 round 12 report: resurgence of SARS-CoV-2 infections in England associated with increased frequency of the Delta variant. Preprint at *medRxiv* 2021.06.17.21259103 (2021).
13. Centre for Disease Control and Prevention (CDC). *Delta Variant: What We Know About The Science* (accessed 22 October 2021); https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html (2021).
14. Marks, K. J. et al. Hospitalization of infants and children aged 0–4 years with laboratory-confirmed COVID-19 — COVID-NET, 14 states, March 2020–February 2022. *MMWR Morb. Mortal. Wkly Rep.* **71**, 429–436 (*2022*).
15. Cloete, J. et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. *Lancet Child Adolesc. Health* **6**, 294–302 (2022).
16. Preston, L. E. et al. Characteristics and disease severity of US children and adolescents diagnosed with COVID-19. *JAMA Netw. Open* **4**, e215298 (2021).
17. Siegel, D. A. et al. Trends in COVID-19 cases, emergency department visits, and hospital admissions among children and adolescents aged 0-17 years – United States, August 2020-August 2021. *MMWR Morb. Mortal. Wkly Rep.* **70**, 1249–1254 (2021).
18. Kitano, T. et al. The differential impact of pediatric COVID-19 between high-income countries and low- and middle-income countries: a systematic review of fatality and ICU admission in children worldwide. *PLoS ONE* **16**, e0246326 (2021).
19. World Health Organization (WHO). *Who COVID-19 Dashboard – Cases and Deaths with Age and Sex Reported* (World Health Organization (WHO), Geneva, 2022).
20. Viner, R. M. et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *Lancet Child Adolesc. Health* **4**, 397–404 (2020).
21. GISAID and Nextstrain. *Genomic Epidemiology of Novel Coronavirus – Global Subsampling* (accessed 16 April 2022); https://nextstrain.org/ncov/gisaid/global (2022).
22. Fisman, D. N. & Tuite, A. R. Progressive increase in virulence of novel SARS-CoV-2 variants in Ontario, Canada. *CMAJ* **193**, E1619–E1625 (2021).
23. Sheikh, A., McMenamin, J., Taylor, B. & Robertson, C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* **397**, 2461–2462 (2021).
24. Delahoy, M. J., Ujamaa, D. & Whitaker, M. Hospitalizations associated with COVID-19 among children and adolescents—COVID-NET, 14 states, March 1, 2020–August 14, 2021. *MMWR Morb. Mortal. Wkly Rep.* **70**, 1255–1260 (2021).
25. Martin, B. et al. Acute upper airway disease in children with the Omicron (B.1.1.529) variant of SARS-CoV-2—a report from the US National COVID Cohort Collaborative. *JAMA Pediatr.* **176**, 819–821 (2022).
26. Butt, A. A. et al. COVID-19 disease severity in children infected with the Omicron variant. *Clin. Infect. Dis.* ciac275 (2022).
27. Wang, L. et al. Incidence rates and clinical outcomes of SARS-CoV-2 infection with the Omicron and Delta variants in children younger than 5 years in the US. *JAMA Pediatr.* **176**, 811–813 (2022).
28. Klein, N. P. et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated emergency department and urgent care encounters and hospitalizations among nonimmunocompromised children and adolescents aged 5-17 years - VISION Network, 10 states, April 2021-January 2022. *MMWR Morb. Mortal. Wkly. Rep.* **71**, 352–358 (2022).
29. Price, A. M. et al. BNT162b2 protection against the Omicron variant in children and adolescents. *N. Engl. J. Med.* **386**, 1899–1909 (2022).
30. Xu, Y. et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat. Med.* **26**, 502–505 (2020).
31. Han, M. S. et al. Viral RNA load in mildly symptomatic and asymptomatic children with COVID-19, Seoul, South Korea. *Emerg. Infect. Dis.* **26**, 2497–2499 (2020).
32. Madewell, Z. J., Yang, Y., Longini, I. M. Jr, Halloran, M. E. & Dean, N. E. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. *JAMA Netw. Open* **3**, e2031756 (2020).
33. Rosenberg, E. S. et al. COVID-19 testing, epidemic features, hospital outcomes, and household prevalence, New York State—March 2020. *Clin. Infect. Dis.* **71**, 1953–1959 (2020).
34. Chung, E. et al. Comparison of symptoms and RNA levels in children and adults with SARS-CoV-2 infection in the community setting. *JAMA Pediatr.* **175**, e212025 (2021).
35. Parri, N., Lenge, M. & Buonsenso, D. Children with COVID-19 in pediatric emergency departments in Italy. *N. Engl. J. Med.* **383**, 187–190 (2020).
36. Haapanen, M., Renko, M., Artama, M. & Kuitunen, I. The impact of the lockdown and the re-opening of schools and day cares on the epidemiology of SARS-CoV-2 and other respiratory infections in children – a nationwide register study in Finland. *EClinicalMedicine* **34**, 100807 (2021).
37. Russell, F. et al. *COVID-19 in Victorian Schools: an Analysis of Child-care and School Outbreak Data and Evidence-based Recommendations for Opening Schools and*

Keeping Them Open (Murdoch Children's Research Institute and the University of Melbourne, Melbourne, Australia, 2020).
38. Murdoch Children's Research Institute. *COVID-19 and Children's Surveillance Report: Number 13, Compiled: 21 March 2022* (MCRI, Melbourne, 2022).
39. Macartney, K. et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. *Lancet Child Adolesc. Health* **4**, 807–816 (2020).
40. Gettings, J. R. et al. Severe Acute Respiratory Syndrome Coronavirus 2 transmission in a Georgia School District—United States, December 2020–January 2021. *Clin. Infect. Dis.* **74**, 319–326 (2022).
41. National Centre of Immunisation Research and Surveillance (NCIRS). *COVID-19 in Schools and Early Childhood Education and Care Services – The Experience in NSW: 16 June to 31 July 2021* (NSW Government, Canberra, 2021).
42. National Centre of Immunisation Research and Surveillance (NCIRS). *COVID-19 in Schools – The Experience in NSW: 18 October 2021 to 17 December 2021* (NSW, 2022).
43. European Centre for Disease Prevention and Control (ECDC). *COVID-19 in Children and the Role of School Settings in Transmission – Second Update* (ECDC, Stockholm, 2021).
44. Australian Department of Health. *Coronavirus (COVID-19) at a Glance Infographic Collection: April 2020–April 2022* (Australian Department of Health, 2021).
45. Centers for Disease Control and Prevention (CDC). *Demographic Trends of COVID-19 Cases and Deaths in the US Reported to CDC* (U.S. Department of Health & Human Services, 2022).
46. European Centre for Disease Prevention and Control (ECDC). *COVID-19 Surveillance Report: Week 43, 2022 – Age-sex Distribution of Cases at Different Levels of Severity and by Time Period, Pooled Data for EU/EEA Countries* (ECDC, Stockholm, 2022).
47. Public Health England. *Coronavirus (COVID) in the UK: Age Demographic of Cases by Specimen Date* (GOV.UK, 2022).
48. Tsankov, B. K. et al. Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. *Int J. Infect. Dis.* **103**, 246–256 (2021).
49. UNICEF. *UNICEF Indonesia COVID-19 Response Situation Reports: May 2020* (accessed 16 April 2022); https://reliefweb.int/report/indonesia/unicef-indonesia-covid-19-response-situation-report-may-7-2020 (2020).
50. Payne, A. B. et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw. Open* **4**, e2116420 (2021).
51. Abrams, J. Y. et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc. Health* **5**, 323–331 (2021).
52. World Health Organisation (WHO). *Living Guidance for Clinical Management of COVID-19: Living Guidance, 23 November 2021* (WHO, Geneva, 2021).
53. Dionne, A., Son, M. B. F. & Randolph, A. G. An update on multisystem inflammatory syndrome in children related to SARS-CoV-2. *Pediatr. Infect. Dis. J.* **41**, e6–e9 (2022).
54. Centers for Disease Control and Prevention (CDC). *Health Department-reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States* (accessed 16 April 2022); https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (2021).
55. Radia, T. et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr. Respir. Rev.* **38**, 51–57 (2021).
56. Buonsenso, D. et al. Preliminary evidence on long COVID in children. *Acta Paediatr.* **110**, 2208–2211 (2021).
57. Munblit, D., Sigfrid, L. & Warner, J. O. Setting priorities to address research gaps in long-term COVID-19 outcomes in children. *JAMA Pediatr.* **175**, 1095–1096 (2021).
58. Zimmermann, P., Pittet, L. F. & Curtis, N. How common is long COVID in children and adolescents? *Pediatr. Infect. Dis. J.* **40**, e482–e487 (2021).
59. Amin-Chowdhury, Z. & Ladhani, S. N. Causation or confounding: why controls are critical for characterizing long COVID. *Nat. Med.* **27**, 1129–1130 (2021).
60. Office for National Statistics. *Technical Article: Updated Estimates of the Prevalence of Post-acute Symptoms among People with Coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021* (UK Government, London, 2021).
61. Zimmermann, P., Pittet, L. F. & Curtis, N. The challenge of studying long COVID: an updated review. *Pediatr. Infect. Dis. J.* **41**, 424–426 (2022).
62. Brodin, P. et al. Studying severe long COVID to understand post-infectious disorders beyond COVID-19. *Nat. Med.* **28**, 879–882 (2022).
63. Mali, A. S., Magdum, M. & Novotny, J. COVID-19 impact on reproduction and fertility. *JBRA Assist Reprod.* **25**, 310–313 (2021).
64. Neeland, M. R. et al. Innate cell profiles during the acute and convalescent phase of SARS-CoV-2 infection in children. *Nat. Commun.* **12**, 1084 (2021).
65. Pierce, C. A. et al. Natural mucosal barriers and COVID-19 in children. *JCI Insight* **6**, e148694 (2021).
66. Tosif, S. et al. Immune responses to SARS-CoV-2 in three children of parents with symptomatic COVID-19. *Nat. Commun.* **11**, 5703 (2020).
67. Rydyznski Moderbacher, C. et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell* **183**, 996–1012.e19 (2020).
68. Jeyanathan, M. et al. Immunological considerations for COVID-19 vaccine strategies. *Nat. Rev. Immunol.* **20**, 615–632 (2020).
69. Kannan, S., Shaik Syed Ali, P. & Sheeza, A. Omicron (B.1.1.529) – variant of concern – molecular profile and epidemiology: a mini review. *Eur. Rev. Med Pharm. Sci.* **25**, 8019–8022 (2021).
70. Murchu, E. O. et al. Immune response following infection with SARS-CoV-2 and other coronaviruses: a rapid review. *Rev. Med. Virol.* **31**, 2 (2021).
71. Chen, Y. et al. Differential antibody dynamics to SARS-CoV-2 infection and vaccination. Preprint at *bioRxiv* 2021.09.09.459504 (2021).
72. Vitale, J. et al. Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy. *JAMA Intern. Med.* **181**, 1407–1408 (2021).
73. Chemaitelly, H., Bertollini, R. & Abu-Raddad, L. J. Efficacy of natural immunity against SARS-CoV-2 reinfection with the Beta variant. *N. Engl. J. Med.* **385**, 2585–2586 (2021).
74. Huang, A. T. et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. *Nat. Commun.* **11**, 4704 (2020).
75. Selva, K. J. et al. Systems serology detects functionally distinct coronavirus antibody features in children and elderly. *Nat. Commun.* **12**, 2037 (2021).
76. Frenck, R. W. et al. Safety, immunogenicity, and efficacy of the BNT162b2 COVID-19 vaccine in adolescents. *N. Engl. J. Med.* **385**, 239–250 (2021).
77. Ali, K. et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N. Engl. J. Med.* **385**, 2241–2251 (2021).
78. Walter, E. B. et al. Evaluation of the BNT162b2 COVID-19 vaccine in children 5 to 11 years of age. *N. Engl. J. Med.* **386**, 35–46 (2021).
79. Moderna Inc. *Moderna Accounces its COVID-19 Vaccine Phase 2/3 Study in Children 6 Months to under 6 Years has Successfully Met its Primary Endpoint* (accessed 20 April 2022); https://investors.modernatx.com/news/news-details/2022/Moderna-Announces-its-COVID-19-Vaccine-Phase-23-Study-in-Children-6-Months-to-Under-6-Years-Has-Successfully-Met-Its-Primary-Endpoint/default.aspx (2022).
80. Thompson, M. G. et al. Prevention and attenuation of COVID-19 with the BNT162b2 and mRNA-1273 vaccines. *N. Engl. J. Med.* **385**, 320–329 (2021).
81. Han, B. et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect. Dis.* **21**, 1645–1653 (2021).
82. Xia, S. et al. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial. *Lancet Infect. Dis.* **22**, 196–208 (2022).
83. World Health Organisation (WHO). *The Sinovac-CoronaVac COVID-19 Vaccine: What You Need to Know – Updated 2 September 2021* (accessed 16 April 2022); https://www.who.int/news-room/feature-stories/detail/the-sinovac-covid-19-vaccine-what-you-need-to-know (2021).
84. World Health Organisation (WHO). *The Sinopharm COVID-19 Vaccine: What You Need to Know – Updated 2 September 2021* (accessed 26 October 2021); https://www.who.int/news-room/feature-stories/detail/the-sinopharm-covid-19-vaccine-what-you-need-to-know (2021).
85. National Center for Medical Sciences Information. *Press Release 29 September 2021: How is Immunization against COVID-19 Working in Cuba?* (accessed 25 October 2021); https://actualidad.sld.cu/ (2021).
86. Puga-Gómez, R. et al. Open label phase I/II clinical trial and predicted efficacy of SARS-CoV-2 RBD protein vaccines SOBERANA 02 and SOBERANA Plus in children. Preprint at *medRxiv* 2022.03.03.22271313 (2022).
87. Ministry of Science & Technology (India). *DBT-BIRAC Supported ZyCoV-D Developed by Zydus Cadila Receives Emergency Use Authorization: 20 August 2021* (accessed 20 April 2022); https://www.pib.gov.in/PressReleasePage.aspx?PRID=1747669 (2021).
88. Khobragade, A. et al. Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): the interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India. *Lancet* **399**, 1313–1321 (2022).
89. Ministry of Health and Family Welfare (India). *Children Vaccination* (accessed 12 April 2022); https://www.cowin.gov.in/ (2022).
90. The World Health Organisation (WHO). *The Bharat Biotech BBV152 COVAXIN Vaccine against COVID-19: What You Need to Know* (accessed 20 April 2022); https://www.who.int/news-room/feature-stories/detail/the-bharat-biotech-bbv152-covaxin-vaccine-against-covid-19-what-you-need-to-know (2022).
91. Figueroa, J. P. et al. Urgent needs of low-income and middle-income countries for COVID-19 vaccines and therapeutics. *Lancet* **397**, 562–564 (2021).
92. Weintraub, R. L., Subramanian, L., Karlage, A., Ahmad, I. & Rosenberg, J. COVID-19 vaccine to vaccination: why leaders must invest in delivery strategies now. *Health Aff. (Millwood)* **40**, 33–41 (2021).

93. Levy, M. et al. Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. *JAMA* **327**, 281–283 (2022).
94. Ministry of Health (Chile). *COVID-19: More than 80% of Children between 3 and 17 Years Old Have Completed their Vaccination Schedule: 8 March 2022* (accessed 12 April 2022); https://www.minsal.cl/covid-19-mas-del-80-de-los-ninos-entre-3-y-17-anos-ha-completado-su-esquema-de-vacunacion/ (2022).
95. UNESCO. *COVID-19 Impact on Education* (accessed 31 August 2021); https://en.unesco.org/covid19/educationresponse#schoolclosures (2021).
96. Commision for Children and Young People. *Impact of COVID-19 on Children and Young People: Mental Health* (CCYP, Victoria, 2020).
97. The Royal Children's Hospital National Child Health Poll. *Poll 18 – COVID-19 Pandemic: Effects on the Lives of Australian Children and Families* (accessed 16 April 2022); https://www.rchpoll.org.au/wp-content/uploads/2020/07/nchp-poll18-report-covid.pdf (2020).
98. The Royal Children's Hospital National Child Health Poll. *Routine Childhood Vaccinations: Effects of the COVID-19 Pandemic. Poll Number 18 Supplementary Report* (accessed 31 August 2021); https://www.rchpoll.org.au/wp-content/uploads/2020/08/nchp-immunisation-embargoed.pdf (2020).
99. Causey, K. et al. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. *Lancet* **398**, 522–534 (2021).
100. Health Canada. *Health Canada Updates Pfizer-BioNTech and Moderna COVID-19 Vaccine Labels to Include Information on Myocarditis and Pericarditis* (accessed 31 August 2021); https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75959a-eng.php (2021).
101. Vaccine Safety Team CDC COVID-19 Vaccine Task Force. *COVID-19 Vaccine Safety Updates from Vaccines and Related Biological Products Advisory Committee (VRBPAC): 10 June 2021* (accessed 31 July 2021); https://www.fda.gov/media/150054/download (2021).
102. Pharmacovigilance Risk Assessment Commitee (PRAC). *Safety News Update: Comirnaty and Spikevax: Possible Link to Very Rare Cases of Myocarditis and Pericarditis: 9 July 2021* (accessed 21 October 2021); https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis (2021).
103. Public Health Agency (Sweden). *Moderna's COVID-19 Vaccine Spikevax Halted for Young People* (accessed 11 October 2021); https://www.krisinformation.se/en/news/2021/october/moderna-vaccine-spikevax-halted-for-young-people (2021).
104. Norwegian Institute of Public Health (NIPH). *Myocarditis in Boys and Young Men Can Occur More Often after the Spikevax Vaccine from Moderna* (accessed 11 October 2021); https://www.fhi.no/en/news/2021/myocarditis-in-boys-and-young-men-can-occur-more-often-after-the-spikevax-v/ (2021).
105. Advisory Committee on Immunization Practices (ACIP). *Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons*. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf (2021).
106. Hause, A. M. et al. COVID-19 vaccine safety in children aged 5–11 years—United States, November 3–December 19, 2021. *MMWR Morb. Mortal. Wkly Rep.* **70**, 1755–1760 (2021).
107. Barda, N. et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. *N. Engl. J. Med.* **385**, 1078–1090 (2021).
108. Boehmer, T. K. et al. Association between COVID-19 and myocarditis using hospital-based administrative data—United States, March 2020–January 2021. *MMWR Morb. Mortal. Wkly Rep.* **70**, 1228–1232 (2021).
109. AstraZeneca and University of Oxford. *Oxford/AstraZeneca COVID-19 Vaccine Effectiveness in England (RAVEN): NCT05047822* (accessed 27 October 2021); https://clinicaltrials.gov/ct2/show/NCT05047822?term=oxford&cond=COVID-19&age=0&draw=2&rank=1 (2021).
110. Buntsma, D., Cheng, D., Machingaifa, F. & McGuire, R. *COVID-19 Vaccination in Children: Immunisation References* (accessed 20 April 2022); https://mvec.mcri.edu.au/immunisation-references/#n (2022).
111. Population Pyramid. *National Population by Sex and Age* (accessed 31 August 2021); https://www.populationpyramid.net/sources (2021).
112. Reuters. *Factbox: Countries Vaccinating Children against COVID-19: 2 December 2021* (accessed 17 April 2022); https://www.reuters.com/business/healthcare-pharmaceuticals/countries-vaccinating-children-against-covid-19-2021-06-29/ (2021).
113. Department of Health (Republic of South Africa). *Vaccine Information Portal* (accessed 17 April 2022); https://sacoronavirus.co.za/vaccine-updates/ (2022).
114. Ministry of Health and Child Care (Zimbabwe). *Teenagers now Eligible for Vaccination: 1 September 2021* (accessed 17 April 2022); http://www.mohcc.gov.zw/index.php?option=com_content&view=article&id=403:teenagers-now-eligible-for-vaccination&catid=84&Itemid=435 (2021).
115. Reuters. *Venezuela Begins Vaccinating 2-Year-Old Children with Cuban Doses—Vice President* (accessed 17 April 2022); https://www.reuters.com/business/healthcare-pharmaceuticals/venezuela-begins-vaccinating-2-year-old-children-with-cuban-doses-vice-president-2021-11-08/ (2021).
116. U.S Food & Drug Administration. *Comirnaty and Pfizer-BioNTech COVID-19 Vaccine: Updated 29 March 2022* (accessed 12 April 2022); https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine (2022).
117. Ministry of Public Health (Uruguay). *Technical Report: Vaccination against COVID-19 in the Pediatric Population Aged 5 to 11 Years: 29 November 2021* (accessed 12th Apr 2022); https://www.gub.uy/ministerio-salud-publica/comunicacion/publicaciones/informe-tecnico-vacunacion-contra-covid-19-poblacion-pediatrica-5-11 (2021).
118. Agencia Brasil. *Institute Requestes Recommendation to Vaccinate Children Aged 3 to 5: Published 14 March 2022* (accessed 12 April 2022); https://agenciabrasil.ebc.com.br/en/saude/noticia/2022-03/institute-requestes-recommendation-vaccinate-children-aged-3-5 (2022).
119. Public Health Agency (Canada). *Vaccines for Children: COVID-19: Updated 17 March 2022* (accessed 12 April 2022); https://www.canada.ca/en/public-health/services/vaccination-children/covid-19.html (2022).
120. Department of Health (Columbia). *COVID-19 Vaccines for Children 5 to 11* (accessed 17 April 2022); https://www2.gov.bc.ca/gov/content/covid-19/vaccine/children (2022).
121. Ministry of Health (Argentina). *What Vaccines Are We Applying in the Country? Updated 21 September 2021* (accessed 12 April 2022); https://www.argentina.gob.ar/coronavirus/vacuna/cuales (2021).
122. Secretariat of Health (Mexico). *Summary of the Main Characteristics of the Vaccines Available in Mexico* (accessed 12 April 2022); http://vacunacovid.gob.mx/wordpress/informacion-de-la-vacuna/ (2022).
123. National Medical Products Administration. *Vaccination of Young Children Begins around Country: Updated 26 October 2021* (accessed 12 April 2022); http://subsites.chinadaily.com.cn/nmpa/2021-10/26/c_671254.htm (2021).
124. Reuters. *Cambodia Vaccinates Children Aged Three to Five against COVID* (accessed 17 April 2022); https://www.reuters.com/business/healthcare-pharmaceuticals/cambodia-vaccinates-children-aged-three-five-against-covid-2022-02-23/ (2022).
125. Therapeutic Goods Administration (TGA). *COVID-19 Vaccine: Provisional Registrations* (accessed 12 April 2022); https://www.tga.gov.au/covid-19-vaccine-provisional-registrations (2022).
126. Ministry of Health Labour and Welfare (Japan). *The Vaccination: Available COVID-19 Vaccines* (accessed 12 April 2022); https://v-sys.mhlw.go.jp/en/about/ (2022).
127. Ministry of Health (Malaysia). *PICkids COVID Vaccination Program: Children Aged 5 to under 12* (accessed 12 April 2022); https://covid-19.moh.gov.my/vaksin-covid-19/pickids (2022).
128. Ministry of Health (Singapore). *COVID-19 Vaccinating Your Child: Who is Eligble?* (accessed 12 April 2022); https://www.moh.gov.sg/covid-19/vaccination/faqs---children-related-vaccination-matters (2022).
129. Smith, J. S. *Korea Approves Pfizer COVID-19 Vaccine for Children Aged 5-11* (Reuters, 2022).
130. MedSafe New Zealand Medicines and Medical Devices Safety Authority. *Approval Status of COVID Vaccines Applications Received by Medsafe: 20 March 2022* (accessed 12 April 2022); https://www.medsafe.govt.nz/COVID-19/status-of-applications.asp (2021).
131. Food and Drug Administration Ministry of Public Health (Thailand). *FDA Press Release: FDA Approves Pfizer in Children 5 to 11 years: 20 December 2021* (accessed 12 April 2022); https://www.fda.moph.go.th/SitePages/News.aspx?IDitem=1427 (2021).
132. Food and Drug Administration Ministry of Public Health (Thailand). *FDA Press Release: FDA Approves Sinovac and Sinopharm for Use in Children 6 and Older: 4 February 2022*. https://www.fda.moph.go.th/SitePages/News.aspx?IDitem=1457 (2022).
133. Ministry of Health (Indonesia). *The Government Holds a Kick off for COVID-19 Vaccinations for Children Age 6-11 Years Simultaneously in 3 Provinces: 14 December 2021* (accessed 16 April 2022); https://www.kemkes.go.id/article/view/21121400001/pemerintah-gelar-kick-off-vaksinasi-covid-19-anak-usia-6-11-tahun-serentak-di-3-provinsi.html (2021).
134. Baljma, T. *Children Aged 12-15 to be Offered COVID-19 Vaccine: 23 July 2021* (accessed 12 April 2022); https://montsame.mn/en/read/268007 (2021).
135. European Medicines Agency. *COVID-19 Vaccines: Authorised* (accessed 12 April 2022); https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised (2022).
136. Public Health England. *A Guide for Parents of Children Aged 5 to 11 Years: updated 28 March 2022* (accessed 12 April 2022); https://www.gov.uk/government/publications/covid-19-vaccination-resources-for-children-aged-5-to-11-years/a-guide-for-parents-of-children-aged-5-to-11-years (2021).

137. Federal Office of Public Health (FOPH). *Coronavirus: Vaccination. Updated 31 March 2022* (accessed 12 April 2022); https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen.html (2022).
138. Ministry of Health (Netherlands). *Coronavirus Vaccination for Children Aged 5 to 11* (accessed 17 April 2022); https://www.government.nl/topics/coronavirus-covid-19/dutch-vaccination-programme/vaccination-of-children-aged-5-to-11 (2022).
139. Finish Institue for Health and Welfare. *Coronavirus Vaccinations for Children and Young People* (accessed 17 April 2022); https://thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronavirus-covid-19-latest-updates/vaccines-and-coronavirus/coronavirus-vaccinations-for-children-and-young-people#:~:text=Coronavirus%20vaccinations%20are%20currently%20offered,be%20vaccinated%20from%20now%20on (2022).
140. Public Health Agency of (Sweden). *Children and Adolescents – Vaccination against COVID-19* (accessed 17 April 2022); https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/covid-19/vaccination-against-covid-19/children-and-adolescents--information-about-vaccination-against-covid-19/ (2021).
141. Russian News Agency. *Russia Approves COVID-19 Vaccine for Teenagers, Developer Says* (accessed 17 April 2022); https://tass.com/society/1365751 (2021).
142. Ministry of Health (Germany). *Vaccines against COVID-19: Comirnaty® by BioNTech/Pfizer: 14 October 2021* (accessed 17 April 2022); https://www.zusammengegencorona.de/en/vaccines-against-covid-19-comirnaty-r-by-biontech-pfizer/ (2021).
143. Ministry of Health (Israel). *COVID-19 Vaccine for Children* (accessed 12 April 2022); https://corona.health.gov.il/en/vaccine-for-covid/under-12/ (2021).
144. Mehdi, S. Z. *Iran Approves Vaccination of Children Aged 5-11: 22 January 2022* (Anadolu Agency, 2022).
145. Ministry of National Health Services Regulation & Cordination (Pakistan). *Pfizer COVID Vaccine Guidelines: 19 November 2021* (accessed 12 April 2022); https://storage.covid.gov.pk/new_guidelines/19November2021_20211119_Interim_Guidelines_for_Pfizer_Vaccine_for_COVID_19_7307_(1).pdf (2021).
146. Ministry of Health (Saudi Arabia). *COVID-19 & Vaccine FAQs* (accessed 12 April 2022); https://www.moh.gov.sa/en/Ministry/HotTopics/Pages/COVID-19-Vaccine.aspx (2022).
147. Ministry of Health (UAE). *Vaccines against COVID-10 in the UAE*. https://u.ae/en/information-and-services/justice-safety-and-the-law/handling-the-covid-19-outbreak/vaccines-against-covid-19-in-the-uae (2022).
148. Ministry of Health (Ukraine). *The Ministry of Health Recommends in Some Cases to Vaccinate Children 12+ against COVID-19: 30 July 2021* (accessed 12 April 2022); https://vaccination.covid19.gov.ua/news/childrenvaccination (2021).

AUTHOR CONTRIBUTIONS

J.N. wrote the first draft of the manuscript, provided intellectual input into the content and revised the manuscript. P.V.L. and Z.Q.T. conceived the idea for the manuscript, provided intellectual input into the content and edited the manuscript. L.A.H.D. provided intellectual input into the content and edited the manuscript. K.M. provided important intellectual input into the manuscript and edited the manuscript. All authors approved the final version of the manuscript to be submitted.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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