

## REVIEW ARTICLE

# Providing children with COVID-19 vaccinations is challenging due to lack of data and wide-ranging parental acceptance

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## Abstract

**Aim:** Vaccines are vital to ending the COVID-19 pandemic and we reviewed the data on vaccinating children, and including them in clinical trials, as most of the activity has focused on adults.

**Methods:** English and Chinese databases, including PubMed, Elsevier Scopus, Web of Science, CNKI and CQVIP were searched, along with websites such as the World Health Organization and the University of Oxford.

**Results:** We identified 44 papers and 16 news items about vaccinating children against the virus, published from 10 February 2020 to 14 July 2021. Child vaccination has been slow and only a few countries have included children in Phase II or III clinical trials. The data on children were much more limited than on adults, but most children were asymptomatic or had mild symptoms and some deaths had been recorded. More clinical trials are needed to assess the safety and efficacy of vaccinating children, as higher vaccination levels can help to build up herd immunity. The percentage of parents willing to vaccinate their children against the virus ranged from 48.2% to 72.6%, with much lower rates for letting them participate in clinical trials.

**Conclusion:** Vaccines should be offered to children as soon as their safety and efficacy are established.

## KEYWORDS

efficacy, herd immunity, parents, safety, vaccine

## 1 | INTRODUCTION

The COVID-19 pandemic has caused unprecedented health and socioeconomic challenges. The number of children infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gradually increased since the start of the pandemic.<sup>1</sup> Going back to school after lockdown, continuing to get routine vaccinations and going outdoors have all been severely affected. Jones et al. showed that the viral load of asymptomatic children with COVID-19 was the same, or higher, than that of symptomatic children or adults.<sup>2</sup> The load was closely related to their infectivity, which suggested that

children and adults were equally infectious. COVID-19 measures, such as quarantining, timely nucleic acid testing and wearing masks, have been implemented in many countries. These include China, which has now entered a period of normalised prevention, control and management of the COVID-19 pandemic.

Although relevant basic and clinical research has been gradually increased, awareness of the aetiological, epidemiological and clinical characteristics of SARS-CoV-2 has also continuously improved. Meanwhile, relevant prevention and control plans and diagnosis and treatment recommendations have been continuously revised and improved. However, preventing and controlling the SARS-CoV-2

**Abbreviations:** MIS-C, Multisystem inflammatory syndrome in children; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

infection is still a matter of global concern.<sup>1,3</sup> This is due to huge differences in factors such as people's values, cultures, traditions, mobility and disease control measures, and how intensely they are implemented. In general, diagnoses, fatalities and immunity levels have been low in children, but they have proved highly infectious and the transmission route has been relatively wide. SARS-CoV-2 endangers public health safety, damages the physical health of infected children and affects their psychological and spiritual health.<sup>4</sup> Measures such as nucleic acid testing, quarantining and wearing masks can effectively curb the spread of the virus in the short term. However, in the long run, vaccination is the way for the population to obtain specific immunity to the virus and is the most effective way to prevent the spread of the virus.<sup>3</sup> The World Health Organization (WHO) established the COVID-19 Vaccines Global Access Facility on 15 July 2020 and 187 countries were members by 16 April 2020. On 16 November 2020, the WHO published interim guidelines to help governments formulate and update national deployment and vaccination plans.<sup>5</sup> However, due to uncertainties about the safety and efficacy, parents remained neutral about whether children should be vaccinated and children had not begun to receive the COVID-19 vaccine widely by 16 April 2021.<sup>6</sup> This paper reviews the challenges of providing children with COVID-19 vaccines, covering aspects such as epidemiology, vaccine development, the current status of children vaccination at the time of writing and the benefits and disadvantages of vaccination to children, parents and society.

## 2 | METHODS

We searched English and Chinese medical databases for relevant papers published between 10 February 2020 and 14 July 2021. The English databases included PubMed, Elsevier Scopus, Web of Science, Embase, Google Scholar and Science Direct. The Chinese databases included CNKI, WanFangData, CQVIP and CBM. The keywords that were used were: coronavirus disease 2019, COVID-19, 2019-nCoV, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, mutant, vaccine, COVID-19 vaccine, vaccine coverage, vaccination, vaccinate, safety, efficacy, children, epidemiological characteristics, clinical characteristics, multisystem inflammatory syndrome in children, MIS-C, long-term symptoms of COVID-19, long COVID, parental acceptance and herd immunity. Relevant papers published in English or Chinese on routine immunisation regimens during the COVID-19 pandemic were included. We also researched a range of key websites, including the WHO, American Academy of Pediatrics, Gavi, the United States Centers for Disease Control and Prevention, the Bloomberg COVID-19 vaccine tracker and the University of Oxford. These provided information on the epidemiological characteristics of COVID-19 in children from different countries, progress on vaccine research, including paediatric participants, where children were actually being vaccinated and the transmissibility of the virus and the severity of different mutations. EndNoteX9 (Clarivate Analytics, Philadelphia, USA) was used

### Key notes

- This review focused on the challenges of vaccinating children to reduce COVID-19, as most of the activity has focused on adults.
- We identified 60 papers and news item from leading databases and websites up to 14 July 2021 and these showed limited paediatric involvement in clinical trials and wide variations in parental support for vaccinations.
- Child vaccination should be offered as soon as its safety and efficacy are established.

to manage the references, and bibliometrics and various statistical descriptions. Other methods were used to analyse the distribution of the basic clinical elements of the study. Keyword analysis and abstract subject analysis were used to describe research and vaccination progress, including the clinical status of children who had received the vaccine or participated in vaccine trials and the challenges they faced. Bibliometrics were used to analyse the country or region of the study and the characteristics of the study subjects. Statistical descriptions and distribution charts were used to evaluate, and demonstrate, the children's epidemiological characteristics and the safety, efficacy and parental acceptance of vaccine. This process enabled us to summarise the key findings of 44 academic papers and 16 news items.

## 3 | RESULTS

### 3.1 | Prevalence and challenges of COVID-19 in children

SARS-CoV-2 is a universally susceptible global virus and children of all ages are affected, with no obvious gender differences. Since the outbreak started there have been many reports about paediatric cases.<sup>1,3</sup> State-level data from the American Academy of Pediatrics showed that by 8 April 2021, children in the United States accounted for 5.30%–32.30% of virus positive cases in the country and 0.10%–1.90% of infected children were hospitalised. Children also accounted for 0.00%–0.19% of COVID-19 deaths<sup>4</sup> (Table 1).

A study from Wuhan reported that infants up to 1 year of age were 2.20 times more likely to be infected with SARS-CoV-2 than children aged 2–5 years and 1.53 times more likely than children aged 6–12 years. In addition, individuals under the age of 20 were 1.58 times more likely to spread the virus to others than adults over 60.<sup>7</sup> Children with COVID-19 tended to be characterised by cluster infections. For example, Yoon et al. identified the percentage of children with COVID-19 who had been infected by family members in Korea. It was 78.3% of children aged 0–9 years and 23.8% of children aged 10–19 years.<sup>8</sup>

TABLE 1 COVID-19 pandemic status of children in different countries

Country (2021 end date)	Children as a percentage of total cases (%)	Children as a percentage of total hospital admissions (%)	Children as a percentage of total deaths (%)
USA <sup>4</sup> (8 April)	13.50	1.30–3.00	0.00–0.03
Canada <sup>50</sup> (9 April)	17.70	1.70	0.00
Sweden <sup>50</sup> (15 April)	14.08	1.06	0.00–0.10
Spain <sup>50</sup> (14 April)	12.70	3.40	0.00
New Zealand <sup>51</sup> (18 April)	13.50	3.12	0.00
Italy <sup>50</sup> (7 April)	14.10	/	0.00
China <sup>52</sup> (16 April)	2.10	/	0.10

Studies have also showed that, although most children have had mild COVID-19, there have also been many severe cases. According to an American study by Feldstein et al., about one-third of children who were nucleic acid-positive for SARS-CoV-2 were admitted to intensive care units. So were up to 80% of children with multisystem inflammatory syndrome in children (MIS-C), which is a clinical syndrome related to COVID-19.<sup>9</sup> The United States Centers for Disease Control and Prevention found that many of the children with MIS-C had serious complications, including heart inflammation and kidney damage. Nearly two-thirds of those children were admitted to intensive care units for an average of 5 days. By 29 March 2021, 3,185 children in the USA had been diagnosed with MIS-C and 36 had died.<sup>10</sup> Buonsenso et al. studied 129 Italian children with COVID-19, at an average of  $162.5 \pm 113.7$  days after diagnosis. They found that 41.8% of diagnosed children fully recovered, 35.7% had one or two symptoms and 22.5% had three or more symptoms. The most commonly reported symptoms were: insomnia (18.6%), respiratory symptoms, including pain and chest tightness (14.7%), nasal congestion (12.4%), fatigue (10.8%), muscle and joint pain (6.9%) and difficulty concentrating (10.1%).<sup>11</sup> Swedish case studies of children with long COVID-19 showed fatigue, dyspnoea, palpitations or chest pain 60 days after their initial diagnosis and all five had persistent symptoms six months later.<sup>12</sup>

Ng et al. found that 5.3% of 302 adults who were not infected with SARS-CoV-2 carried immunoglobulin G antibodies that could bind to the virus. However, protein reactive immunoglobulin G antibodies could not be detected in 43.8% of the 48 who were virus free.<sup>13</sup> A Canadian study that analysed data from more than 200,000 COVID-19 cases, and was published in July 2021, reported that the Alpha, Beta and Gamma variants were associated with a greater surge in virulence and transmissibility than non-variants of concern.<sup>14</sup> These variants also increased the risk of hospitalisation, intensive care admissions and death by 59%, 105% and 61% respectively. They also increased the probability of children being infected.<sup>14</sup>

The COVID-19 pandemic has had a negative impact on children's education, emotional health and social development. Anderson et al. showed that rotavirus, varicella and other conventional vaccines significantly reduced the mortality rate of children with those diseases in the United States. The authors added that the number of deaths of children with COVID-19 in 1 year was rapidly approaching that level

and would surpass the number of child deaths related to influenza from 2016 to 2020.<sup>15</sup>

Therefore, children should be vaccinated against COVID-19 to prevent the pandemic from harming children, families and society.

### 3.2 | The COVID-19 vaccine and child vaccination

The global COVID-19 vaccine development is based on seven key technical vaccine routes: inactivated, virus-like particle, protein subunit, virus-vectored, deoxyribonucleic acid, messenger ribonucleic acid and live-attenuated. Most of the current vaccines target the spike protein, glycoprotein S, and its variants.<sup>16</sup> The structure and function of SARS-CoV-2 glycoprotein S are similar to highly pathogenic Beta coronaviruses, such as Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus. Glycoprotein S comprises two subunits. S1 contains a receptor binding domain that interacts with the angiotensin-converting enzyme 2 receptor on the cell surface. S2 mediates the fusion of the virus membrane and cell membrane by forming a six-helix bundle fusion core. In order to prevent SARS-CoV-2 infections, it is very important to form neutralising antibodies against the S1 receptor binding domain and the S1 N-terminal domain. These antibodies can block the binding of the receptor binding domain to the angiotensin-converting enzyme 2 receptor and prevent S2-mediated membrane fusion or entry into the host cells, thereby inhibiting the virus infection.<sup>17</sup>

By 16 April 2021, 14 COVID-19 vaccines had been approved worldwide: five from China, three from Russia, two from India, two from the United States, one from Germany and one from the UK. Of those, two are messenger ribonucleic acid vaccines, five are inactivated virus vaccines, five are non-replicating virus vector vaccines and two are protein subunit vaccines. In addition, 102 vaccines were already undergoing clinical trials: 30 phase I, 42 phase II and 30 phase III.<sup>18</sup> State-level data from the American Academy of Pediatrics showed that by 14 July 2021, 6.8 million children in the USA were fully vaccinated: 38% aged 16–17 years and 25% aged 12–15 years. Meanwhile, 8.8 million American children under the age of 18 had received at least one dose of the COVID-19 vaccine: 46% aged 16–17 years and 34% aged 12–15 years.<sup>19</sup>

The development of children's COVID-19 vaccines has been slow, but the non-replicating nature of the Astra Zeneca vaccine makes it

TABLE 2 Research progress, efficacy and safety of the approved COVID-19 vaccines

Type <sup>18</sup>	Basic information on vaccines <sup>18</sup>		Progress <sup>18</sup>	Dosing and overall vaccine efficacy (%)	Dosing and vaccine efficacy (moderate or severe cases) (%)	Total incidence of adverse events (%)	Serious incidence of adverse events (%)	Most common adverse reactions	
	Developer/coconut/age range	Developer/coconut/age range						Local (%)	Systemic (%)
Protein subunit	FBRI	2 doses 21 days	Approved in 2 countries and 3 trials in 1 country	95.00 <sup>53</sup>	/	/	/	/	/
	EpiVacCorona Russia ≥ 18	2 doses 21 days apart:	Approved in 2 countries and 6 trials in 5 countries	94.00 <sup>53</sup>	/	3 doses 30 days apart: 48.00 <sup>54</sup>	3 doses 30 days apart: 3.00 <sup>54</sup>	3 doses 7 days apart: 30.00 <sup>54</sup>	3 doses 7 days apart: 10.00 <sup>54</sup>
	Anhui Zhifei Longcom receptor binding domain-Dimer China ≥ 18	/	Approved in 82 countries and 17 trials in 12 countries	95.00 <sup>53,57</sup>	/	2 doses 21 days apart: 1.95 <sup>55</sup>	2 doses 21 days apart: 0.027 <sup>55</sup>	2 doses 21 days apart: 68.60 <sup>56</sup>	2 doses 21 days apart: 64.20 <sup>a,56</sup>
RNA	Moderna mRNA-1273 USA ≥ 18	2 doses 21 days apart:	Approved in 46 countries and 14 trials in 3 countries	94.00 <sup>53</sup>	2 doses 21 days apart: 100.00 <sup>53</sup>	2 doses 21 days apart: 2.20 <sup>55</sup>	2 doses 21 days apart: 0.023 <sup>55</sup>	2 doses 21 days apart: 81.90 <sup>56</sup>	2 doses 21 days apart: 74.80 <sup>a,56</sup>
	BioNTech/Pfizer BNT162b2 Germany ≥ 16	2 doses 21 days apart:	Approved in 82 countries and 17 trials in 12 countries	95.00 <sup>53,57</sup>	/	2 doses 21 days apart: 1.95 <sup>55</sup>	2 doses 21 days apart: 0.027 <sup>55</sup>	2 doses 21 days apart: 68.60 <sup>56</sup>	2 doses 21 days apart: 64.20 <sup>a,56</sup>
	CanSino Ad5-nCoV China ≥ 18	1 dose 28 days apart:	Approved in 5 countries and 6 trials in 6 countries	65.28 <sup>58</sup>	1 dose 28 days apart: 90.07 <sup>58</sup>	1 dose 28 days apart: 76.00 <sup>29</sup>	1 dose 28 days apart: 1.00 <sup>58</sup>	/	/
Non replicating viral vector	Gamaleya Sputnik V Russia ≥ 18	2 doses 21 days apart:	Approved in 62 countries and 19 trials in 6 countries	85.60-95.20 <sup>17</sup>	2 doses 21 days apart: 94.40-100.00 <sup>17,53</sup>	2 doses 21 days apart: 94.00 <sup>17</sup>	2 doses 21 days apart: 0.30 <sup>17</sup>	/	/
	Oxford/AstraZeneca AZD1222 UK ≥ 16	2 doses 21 days apart:	Approved in 91 countries and 24 trials in 15 countries	70.40 <sup>59</sup>	2 doses 21 days apart: 100.00 <sup>53,57</sup>	2 doses 21 days apart: 0.70 <sup>59</sup>	2 doses 21 days apart: 0.15 <sup>28</sup>	/	/
	Serum Institute of India Covishield India ≥ 18	/	Approved in 33 countries 2 trials in 1 country	/	/	/	/	/	/
Inactivated	Janssen (Johnson & Johnson) Ad26.COV2.S USA ≥ 18	1 dose 28 days apart:	Approved in 40 countries and 7 trials in 17 countries	72.00 <sup>57</sup>	1 dose 28 days apart: 100.00 <sup>57</sup>	/	/	/	/
	Bharat Biotech Covaxin India 12-65	/	Approved in 6 countries and 5 trials in 1 country	/	/	/	/	/	/
	Sinopharm (Beijing) BBIBP-CorV China ≥ 18	2 doses 28 days apart:	Approved in 35 countries and 6 trials in 7 countries	79.34 <sup>58</sup>	2 doses 28 days apart: 79.34 <sup>58</sup>	2 doses 7 days apart: 1.02 <sup>29</sup>	2 doses 7 days apart: 0.36 <sup>29</sup>	2 doses 7 days apart: 0.66 <sup>29</sup>	2 doses 7 days apart: 0.66 <sup>29</sup>

(Continues)

TABLE 2 (Continued)

Type <sup>18</sup>	Basic information on vaccines <sup>18</sup> Developer/coconut/ age range	Progress <sup>18</sup>	Dosing and overall vaccine efficacy (%)	Dosing and vaccine efficacy (moderate or severe cases) (%)	Total incidence of adverse events (%)	Serious incidence of adverse events (%)	Most common adverse reactions	
							Local (%)	Systemic (%)
	Sinopharm (Wuhan) Inactivated (Vero Cells) China ≥ 18	Approved in 2 countries and 6 trials in 7 countries	2 doses 28 days apart: 72.51 <sup>58</sup>	2 doses 28 days apart: 100.00 <sup>57</sup>	2 doses 7 days apart: 1.02 <sup>29</sup>	/	2 doses 7 days apart: 0.46 <sup>29</sup>	2 doses 7 days apart: 0.31 <sup>29</sup>
	Sinovac CoronaVac China ≥ 18	Approved in 22 countries and 14 trials in 7 countries	2 doses 14 days apart: 50.70% <sup>60</sup>	2 doses 14 days apart: 100.00 <sup>60</sup>	2 doses 21 days apart: 15.00 <sup>28</sup>	2 doses 21 days apart: 0.00 <sup>28</sup>	2 doses 21 days apart: 15.50 <sup>28</sup>	2 doses 21 days apart: 4.80 <sup>28</sup>
	Chumakov Center KoviVac Russia ≥ 18	Approved in 1 country and 2 trials in 1 country	/	/	2 doses 28 days apart: 26.60 <sup>28</sup>	2 doses 28 days apart: 1.04 <sup>28</sup>	2 doses 28 days apart: 61.50 <sup>28</sup>	2 doses 28 days apart: 48.40 <sup>28</sup>

Note: Data available at: <sup>17</sup>02/02/21, <sup>18</sup>16/04/21, <sup>27</sup>01/04/21, <sup>28</sup>24/02/21, <sup>29</sup>21/04/21, <sup>53</sup>54/24/03/21, <sup>55</sup>09/03/21, <sup>56</sup>06/04/21, <sup>57</sup>14/04/21, <sup>58</sup>02/03/21, <sup>59</sup>09/01/21, <sup>60</sup>16/04/21.

<sup>a</sup>Systemic reactions do not include allergic reactions or anaphylaxis.

relatively safe for children. The manufacturers included children up to 12 years of age in the second phase of its clinical trials.<sup>20</sup> On 23 January 2021, Israel began to vaccinate children aged 16–18 years with the Astra Zeneca vaccine and by 10 March approximately 600 children under 16 with underlying diseases had also been vaccinated.<sup>21</sup> Previous Astra Zeneca vaccine trials in adults had indicated that it was safe, could produce a strong immune system response and had high efficacy. A UK study was launched on 12 February 2021 to assess if healthy children aged 6–17 years had a good immune response to the Astra Zeneca vaccine. It is being carried out by the University of Oxford and three partner sites in London, Southampton and Bristol. The study has recruited 300 children aged 6–17 years. They gave 240 children the same vaccine dose as the adults and the other 60 formed the control group and received the meningitis vaccine group.<sup>22</sup> The results had not been published at the time of writing. By 16 January 2021, the manufacturers of the Chinese Sinopharm CNBG COVID-19 vaccine had already finished Phase I and II clinical trials on children aged 3–5, 5–12 and 12–17 years, having completed previous clinical trials on those aged 17–59 and 60 plus. The safety data for children aged 3–17 years showed good results and immunogenicity data. This vaccine is expected to cover all patients over the age of 3 years.<sup>23</sup> In June 2021, Sinovac and Hebei Provincial Center for Disease Control and Prevention jointly published the results of a clinical trial that evaluated the clinical results of the CoronaVac in healthy children aged 3–17 years.<sup>24</sup> This was the first study to report the results of an inactivated SARS-CoV-2 vaccine in children. The results showed that CoronaVac was well tolerated and safe and induced humoral responses in children and adolescents aged 3–17 years. In addition, it indicated that children had a higher immune response after vaccination than adults, but this also meant that they were more likely than adults to develop immune overreactions, such as fever and allergies. This highlights the need to balance the protective immune response and side effects when children are vaccinated. In addition, the children under 12 years of age were at a critical stage of their growth and development and the long-term impact of vaccines on children's development should be carefully evaluated.<sup>24</sup>

The American Academy of Pediatrics has recommended that children aged 16 plus who meet priority group criteria are vaccinated and the organisation has continued to encourage vaccine manufacturers to include young children in their trials to determine safety and efficacy. By February 2021, Pfizer had included children under the age of 12 in clinical trials and Moderna had included adolescents aged 12–17 years.<sup>25</sup> Another study stated that Pfizer had provided two doses, 21 days apart, for individuals aged 16 plus, while Moderna had trialled two doses, 28 days apart, for those aged 18 plus.<sup>26</sup> In April 2021, Mahase published the results of a phase III trial of 2260 children aged 12–15 years in the USA and reported that the preliminary results indicated that the Pfizer vaccine had shown 100% efficacy. The vaccine elicited robust antibody responses and was well tolerated and the side effects were consistent with those observed in participants aged 16–25 years. They have also launched a vaccine trial that will assess the safety, tolerability and immunogenicity of the vaccine in three age groups: 6 months to 2 years and 2–5 and 5–11 years.<sup>27</sup>

TABLE 3 Parents' acceptability of COVID-19 vaccination for their children in different studies

Region	Methods	Sample size	Willing to vaccinate children (%)	Unsure/no answer (%)	Not willing to vaccinate Children (%)
UK <sup>36</sup>	Online cross-sectional survey and semi-structured interviews	1252 parents and guardians	48.2	48.3	3.4
16 paediatric EDs across the USA, Canada, Israel, Japan, Spain and Switzerland <sup>37</sup>	International cross-sectional survey	1541 caregivers and parents	65.2	1.8	33.0
China <sup>38</sup>	Cross-sectional and closed online survey	1052 parents	72.6	21.3	6.1
New Zealand <sup>39</sup>	Self-administered questionnaire	1191 parents and caregivers	69.6	1.5	28.9
Ankara City Hospital <sup>40</sup>	Face-to-face or online questionnaire	428 parents	56.8 <sup>a</sup>	0	43.2 <sup>a</sup>
17 EDs across the USA, Canada, Israel, Japan, Spain and Switzerland <sup>41</sup>	International cross-sectional survey	2768 parents and caregivers	18.4 <sup>b</sup>	0	81.6 <sup>c</sup>

Note: ED: Emergency Departments, Data available at: <sup>36</sup>17/11/20, <sup>37</sup>10/11/20, <sup>38</sup>12/20, <sup>39</sup>03/21, <sup>40</sup>01/04/21, <sup>41</sup>23/11/20.

<sup>a</sup>Data on national vaccines.

<sup>b</sup>Parents were willing to involve their children in COVID-19 vaccine clinical trials.

<sup>c</sup>Parents were not willing to involve their children in COVID-19 vaccine clinical trials.

### 3.3 | Safety and efficacy of vaccinating children

Children have not yet been universally vaccinated, as the vaccine development and testing time has been relatively short. However, the results of phase III clinical trials of various vaccines are now available, as well as details of adverse reactions in adults and smaller numbers of children. The question remains: is it safe for children to be vaccinated against the virus?

Studies have shown that most of the adverse events from vaccines against SARS-CoV-2 have been mild to moderate and resolved within 24 h. The immune response to vaccines, and the incidence of adverse reactions, have positively correlated with the dose of vaccine. The most common local adverse reactions that have been reported have been pain, redness and swelling or itching at the injection site. The most common systemic adverse reactions have been fatigue, fever, headache, cough, myalgia, chills, nausea, vomiting and diarrhoea. This shows that most vaccines provide good effectiveness and safety and double-dose vaccinations have been recommended.<sup>28</sup> In April 2021, reports on the Chinese Sinopharm CNBG COVID-19 vaccine trial of people aged 12 plus showed that the incidence of adverse reactions were highest among adolescents aged 12–18 years (11.31%). These were predominantly fatigue and pain at the injection site. In short, the long-term efficacy, safety and dosage, age and process differences of the various COVID-19 vaccines need to be confirmed by more studies<sup>29</sup> (Table 2). Myocarditis has been referred to be a rare complication of COVID-19 mRNA vaccination, particularly in young adults and adolescent males after the second dose of COVID-19 mRNA vaccination. Symptoms of myocarditis always appeared chest pain, elevated cardiac troponin levels, a forceful heartbeat that may be irregular, shortness of breath, abnormal Electrocardiograph with ST elevations.<sup>30,31</sup> In the United States, as of 11 June 2021, the crude reporting rates of myocarditis or pericarditis cases per million doses after COVID-19 mRNA vaccination for children aged 12–17 years was 4.2 in females and 32.4 in males.<sup>31</sup> Meanwhile, the US Vaccine Adverse Event Reporting System received 1226 initial reports of myocarditis and pericarditis after administering approximately 300 million doses of Pfizer and Moderna vaccines.<sup>30</sup> Between December 2020 and May 2021, 275 cases of myocarditis were reported among more than five million vaccinated people in Israel, most cases in males aged 16–19 years after the second dose of vaccine. It was unclear why myocarditis was predominantly male. However possible explanations were related to differences in immune response and sex hormones in myocarditis.<sup>31</sup> Although there were cases of myocarditis being reported after COVID-19 mRNA vaccination, most cases have been mild.<sup>30</sup> Not only would the COVID-19 vaccine prevent COVID-19-related hospitalisations and deaths (mortality remains 0.1–1 per 100,000 for people aged 12–29 years), it would also prevent COVID-19-related complications, such as myocarditis, MIS-C and post-acute sequelae of long COVID-19.<sup>31</sup> For the vast majority of people, myocarditis is a benign, self-limiting condition that can be easily treated with non-steroidal anti-inflammatory drugs. Only



a few people were left with impaired heart muscle, so the benefits of vaccination clearly outweigh the risks.<sup>30</sup>

Some adults have experienced adverse events or even serious adverse events after vaccination and more clinical safety assessments are needed before children are fully vaccinated.

On 20 April 2021, the WHO stated that three main variants of SARS-CoV-2 had emerged. The Alpha variant had been reported in 125 countries by that date. There was no difference in the neutral response of the recovered plasma in this strain and the initial SARS-CoV-2 strain, so it did not affect the efficacy of the existing vaccine.<sup>32</sup> The Beta variant had been found in 67 countries by that date and has been associated with a higher viral load that might increase infectivity.<sup>32</sup> Wang et al. showed that the Beta variant can escape the effect of neutralising antibodies, so the protective ability of the vaccine might be reduced. The antibodies induced by the Moderna and Pfizer vaccines have been shown to slightly decrease the neutralising activity of the Beta variant, indicating that these vaccines might need to be updated regularly to prevent loss of clinical efficacy.<sup>33</sup> The Gamma variant had circulated in 43 countries by that date and the efficacy of the vaccine was still being evaluated.<sup>32</sup>

A systematic review by Xing et al. showed that the 28d seroconversion rate in COVID-19 subjects was more than 80% in 10 studies. In two clinical trials each with a 10,000-scale, the vaccine efficacy was 95% and 70.4% respectively.<sup>28</sup> Huang et al. reported that more than three-quarters of 1733 COVID-19 inpatients in Wuhan Jinyintan Hospital still had at least one persistent symptom 6 months after discharge. The authors also reported that 52.5% of the 94 patients who had undergone an immune response test during the peak of infection only had half the neutralising antibody titres after 6 months, which might make re-infection possible.<sup>34</sup>

Liu et al. analysed eight children with COVID-19 and found that three of them had neutralising antibodies in their serum during the acute phase, with all eight demonstrating them during the recovery period. This indicates that humoral immunity might play a more critical role in the rehabilitation of children than adults. However, the children continued to shed the virus after producing neutralising antibodies, indicating that the neutralising antibodies produced in the acute phase were not enough to clear SARS-CoV-2 quickly. Clearing the virus might require the production of high-titre neutralising antibodies. The children's specific antibody response to SARS-CoV-2 was mainly limited to the immunoglobulin G anti-S antibody and the overall level of neutralising activity was lower than adults.<sup>35</sup>

The efficacy of existing vaccines needs to be further studied, as variants have been discovered in many countries, leading to a further increase in the number of infections.

### 3.4 | Parental acceptance of the SARS-CoV-2 vaccine

Parents usually make decisions about vaccinating children under the age of 18. A study by Bell et al. from 19 April to 11 May 2020 showed that 48.2% of UK parents wanted their children to be vaccinated against

COVID-19, 48.3% were uncertain and 3.4% would refuse.<sup>36</sup> Goldman et al. surveyed 16 paediatric emergency departments across the USA, Canada, Israel, Japan, Spain and Switzerland from 26 March to 31 May 2020. They found that 65% of parents planned to vaccinate their children against the virus, 33% did not and 2% did not answer. The main reason for vaccination was to protect their children (62%) and the main reason for refusing vaccination was that it would be a new vaccine (52%).<sup>37</sup> The fact that most of the parents wanted their children to be vaccinated might have been related to specific factors, such as the demographics and the vaccination histories of the children and parents.<sup>37</sup> An online survey by Zhang et al., carried out between 1 September 2020 and 7 September 2020 found that 72.6% of Chinese parents would let their child be vaccinated.<sup>38</sup> A study by Jeffs et al. in New Zealand, from 8 May 2020 to 18 May 2020, showed that 60.5% of parents expressed some degree of concern that their child would catch the virus at school and 14.5% of them were very worried. The majority (79.0%) believed that if community transmission was widespread, children were likely to be infected with the virus at school. Most of them (69.6%) said they would let their child be vaccinated and 28.9% would refuse.<sup>39</sup> Yigit et al. carried out a study in Ankara City Hospital, Turkey, and stated that 28.9% of parents would let their child receive foreign vaccines, but 56.8% would agree to domestic vaccines.<sup>40</sup> Goldman et al. studied 17 paediatric emergency departments across the USA, Canada, Israel, Japan, Spain and Switzerland from 27 March 2020 to 30 June 2020 and found that only 18.4% of parents were willing to let children participate in clinical vaccine trials and the rest were unwilling. However, only 78.3% of those 18.4% parents would agree if it was a randomised controlled trial (Table 3). The most common reasons for refusal were uncertainties about the safety, efficacy and benefits. They were concerned about the side effects and their trust in vaccines from other countries was low. Parents from low-income families were more likely to refuse vaccination. Frequent interactions with medical institutions, such as chronic diseases or regular medication, did not increase parents' willingness to let children participate in vaccination trials. However, parents were more likely to agree if they trusted the medical system, had a medical or scientific background and their children were already receiving other vaccines in line with their country's immunisation programmes. These parents felt that vaccine trials were safe and would protect their children. Randomised designs reduced parental agreement.<sup>41</sup>

A paper by Whibley on the global upsurge in measles in 2018, and a major survey of 140 countries carried out in the same year, showed breath-taking variations in vaccine hesitancy.<sup>42</sup> In order to increase parental acceptance, it is necessary to highlight the risks and consequences of the virus and the safety and efficacy of the vaccines, including the transparency of the development process and safety testing. Any parental education and guidance should also deal with misinformation in a timely manner.<sup>36,40</sup>

### 3.5 | The direct and potential benefits of child vaccination

Savulescu et al. reported that the fatality rate for influenza in the UK and USA was more than one per 1,000,000 if children were not

vaccinated and less than one per 25,000,000 if they were.<sup>20</sup> Li et al. found that vaccinations had reduced deaths from 10 pathogens by 57% in children under 5 years of age: hepatitis B virus, Haemophilus influenzae type B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, Streptococcus pneumoniae, rotavirus, rubella and yellow fever. This figure was expected to increase to 77% from 2020 to 2030, which would prevent 120 million deaths among under-fives born during that 10-year period.<sup>43</sup> COVID-19 is similar to flu in this respect and children need to be vaccinated as it is not clear which children have a higher risk of serious and potentially life-threatening diseases.

In addition to direct medical benefits, being vaccinated against the virus could provide children with better life and learning benefits. The pandemic may have caused over a million child deaths due to significantly reduced access to food, interrupted basic health services, missed growth monitoring, and lack of preventive care and timely management of acute diseases and injuries.<sup>44</sup> During the pandemic, the most vulnerable children have included those separated from their caregivers.<sup>45</sup> Statistics on previous health-related disasters showed that as many as 30% of children met the criteria for post-traumatic stress disorder.<sup>45</sup> In addition schools had closed in more than 190 countries around the world by 13 April 2020 and 40 countries were still affected by those restrictions on 31 July 2020. This affected 1.57 billion children, which equated to 90% of the world's students.<sup>8</sup> School closures have exacerbated the learning gap, due to inequalities in digital access, with poor children falling further behind.<sup>45</sup> In addition, social distancing and lack of extra-curricular activities, such as sport, drama, music, art and social activities, have also affected children's emotional and psychological development.<sup>15</sup> Ludvigsson found that children with COVID-19 exhibited characteristics of family-aggregated infections, which was same as children with influenza. But this did not mean that school closures would reduce the transmission of SARS-CoV-2. The author also pointed out that school closures had an impact on the daily lives of children, including lack of education, and had an even more severe impact on vulnerable and disadvantaged children.<sup>46</sup> These findings indicate that child vaccination might have a positive and profound impact on health and equal education.<sup>15</sup> Vaccines are cost-effective health interventions. They provide direct protection for individuals and have a significant impact on public health safety when high coverage rates are achieved. They can also provide herd immunity for unvaccinated individuals.<sup>43</sup>

Vaccinating children against *Streptococcus pneumoniae*, rubella, influenza, rotavirus and hepatitis A has been clearly proven to provide community protection.<sup>47</sup> Similarly, although children are less likely to suffer severe COVID-19, they may spread the virus to more vulnerable adults at home or in schools. Vaccination would protect them and help to reduce community transmission.<sup>2</sup> Anderson et al. found that American school closures were temporarily linked to an overall decline in COVID-19 morbidity and mortality.

The pandemic has had a major impact on employment and caused a decline in the global economy. School closures and children's health have been closely related to whether parents can

work. For example, one study found that children's health was of great significance to economic recovery and reducing family pressure or burden.<sup>15</sup> Anderson et al.'s review of vaccine trials found that it was difficult to achieve 100% efficacy. They stated that if the R number was 2.5–3.5, and vaccine efficacy was 80%, about 75%–90% of people would need to be vaccinated to achieve herd immunity.<sup>48</sup> On 7 February 2021, the head of the Israeli Public Health Service stated that one-third of the 9.3 million people in Israel had received at least one vaccine dose and one in five had received two doses. However, there were 2.5 million children in Israel who could not be vaccinated and that, even if all the adults were vaccinated, Israel might not be able to achieve herd immunity.<sup>49</sup> Since children account for nearly a quarter of the world's population, effective herd immunity requires children to be vaccinated against the SARS-CoV-2 virus.

## 4 | CONCLUSION

The key findings of this review were that data on children COVID-19 vaccination were limited, as most of the activity has focused on adults. More clinical trials are needed to assess the safety and efficacy of vaccinating children, as higher vaccination levels can help to build up herd immunity. However, there are wide variations in the percentage of parents who would be willing to have their children vaccinated. Furthermore, we still do not know the full impact that the COVID-19 pandemic will have on children's lives and learning, public health safety and their parents' ability to work and support the economy. However, there is no doubt that the consequences will be felt many years to come. Therefore, protecting children from the SARS-CoV-2 infection is both a moral obligation and a practical need. If the vaccine is safe and effective for children, then it should be provided as soon as possible.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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