COVID-19 in children: epidemic issues and candidate vaccines

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Abstract

A large-scale vaccination of coronavirus disease-19 (COVID-19) in adults has been conducted for nearly a year, and there is a growing recognition that immunization for children is also essential. It has been months since emergency use of pediatric COVID-19 vaccine was approved, we reviewed the prevalence and transmission of COVID-19 in children. The prevalence of COVID-19 in children is reduced due to vaccination even in a Delta prevalent period, so an increase in the vaccination rate is needed in children. Although the precise role of children in the transmission requires more research to uncover, they likely played a significant role, according to the available literature. We also described four candidate COVID-19 vaccines for children on their safety and immunogenicity and the impact of severe acute respiratory syndrome coronavirus 2 variants on childhood vaccination. Safety issues on pediatric vaccines post-approval, like adverse events following immunization and adverse events of special interest require studies on long-term and effective regulatory mechanisms.

Keywords: Adverse events; COVID-19; Children; COVID-19 vaccine; SARS-CoV-2 transmission; Vaccine safety

Introduction

In December 2019, a novel single-stranded, sense positive, and enveloped RNA beta-coronavirus emerged. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by The International Committee on Taxonomy of Viruses due to its evolutionary relationship with SARS-CoV-1. The related disease, officially named coronavirus disease-19 (COVID-19), spread worldwide at an overwhelming speed soon after. As of January 21, 2022, a cumulative number of confirmed COVID-19 cases surpassed 340 million, including over 5.6 million deaths according to the weekly reports of World Health Organization (WHO).[1]

SARS-CoV-2 is generally susceptible to all-age-range population worldwide and spread rapidly by human-to-human contact.[2] The epidemic characteristics of COVID-19 in children differ from adults, as the role of children in the transmission of the virus remains not that clear. It is now well established that taking vaccines could be an optimal strategy to curb the pandemic of SARS-CoV-2 since researchers failed to find a specific drug to cure COVID-19 patients.[3,4] To date, various COVID-19 vaccine candidates were showing an acceptable safety profile and good immunogenic tolerance for adults and the elders in the clinical trials. As of 21 January, 2022, WHO listed ten vaccine candidates that passed emergency use listing procedure in humans including BNT162b2 (BioNTech Manufacturing GmbH, Mainz, Germany), AZD1222 Vaxzevria (AstraZeneca AB, Sodertalje, Sweden), COVISHIELD™ (Serum Institute of India Pvt. Ltd, Pune, India), Ad26.COV2.S (Janssen–Cilag International NV, Beerse, Belgium), mRNA-1273 (Moderna Biotech, Cambridge/Massachusetts, America), BBIBP-CorV (Beijing Institute of Biological Products Co., Ltd., Beijing, China), CoronaVac (Sinovac Life Sciences Co., Ltd., Beijing, China), COVAXIN (Bharat Biotech International Limited, Shamirpet Mandal, India), COVOVAX (Serum Institute of India Pvt. Ltd, Pune, India) and NUVAXOVID (Novavax CZ a.s., Jevany, Czechia).[5] Unfortunately, for safety and vaccine priorities concerns, most of the COVID-19 vaccines did not include children as participants in clinical trials at the beginning. However, it turns out that many children were actually infected

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although a lower proportion of pediatric patients was reported.[6] The pandemic caused by SARS-CoV-2 is an ongoing public health challenge, immune barriers for populations of all age group are needed. Therefore, vaccination for children is necessary and significant.

Given the aforementioned situation, Canada was the first country to authorize the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in children 12 to 15 years of age on May, 2021,[7] followed by European Medicines Agency and the United States.[8,9] China has also expanded the target population of CoronaVac and BBIBP-CorV to children 3 to 17 years old after their approval for emergency use by WHO.

This review fills a gap in the literature by portraying vital epidemic issues that need to pay attention to COVID-19 in children and the COVID-19 vaccine candidates that were approved for emergency use approval (EUA) for children, and provides a reference for future clinical trials and vaccination regimens of COVID-19 vaccines in children and formulating and adjusting vaccine policy.

Literature Search

Two literature searches were performed through PubMed, Web of Science for publications in English. And we included literature available in refereed journals. The first search focused on the incidence and household or school cluster transmission of COVID-19 in children. Various search terms and their combinations were used including "COVID-19," "SARS-CoV-2, "children," "adolescent," "epidemic," "transmission," "school," and "household" form January 1, 2020 to October 1, 2021. The second search was mainly on the COVID-19 vaccine candidates for children, including clinical trial reports, observational study reports, adverse events after injection, and problems facing SARS-CoV-2 variants. To stay up-to-date on research through literature, search time was from January 1, 2020 to January 24, 2022, the date of the accomplishment of this manuscript. Search terms included "COVID-19," "SARS-CoV-2," "children," "adolescent," "vaccine," "variants," "efficacy," "clinical trial," "vaccine adverse event reporting system," "adverse events following immunization," and "adverse event of special concern." We also searched "gray" literature on official website of the United States, European countries, and WHO.

Epidemic and Transmission of COVID-19 in Children

Prevalence situation of COVID-19 in children

Early in the pandemic, infection of SARS-CoV-2 was not common in children. Though pediatric cases had been reported, they are valued little due to report of the high prevalence of serious adult cases.[10-12] As the global pandemic of COVID-19 constantly intensified, there had been an increasing realization that situation in children was not that optimistic.[13,14] Information from WHO suggested that over 8.8 million children under 14 years old were confirmed to be infected with SARS-CoV-2 worldwide from December 30, 2019 to October 25, 2021.[15]

The incidence trend of COVID-19 according to the age of onset in the United States showed that an increasing number of pediatric cases were confirmed before the U.S. Food and Drug Administration (FDA) issued an EUA for Moderna (mRNA-1273), Pfizer-BioNTech (BNT162b2), and Janssen (Ad26.COV2.S) COVID-19 vaccine in individuals 18 years of age and older (Moderna, Janssen) or 16 years of age and older (Pfizer-BioNTech).[16] The highest daily COVID-19 incidence of persons aged 0 to 17 years peaked in January 2021 at 34.3 cases per 100,000 persons and then decreased substantially in the following 3 months.[17] When the Delta variants became predominant, the incidence in children increased greatly since July 2021, even persons aged 12 to 15 years had already begun to take vaccination,[17] approximately 174.5 pediatric cases per 100, 000 individuals weekly from July 1, 2021 to October 28, 2021 *vs*. 87.9 cases per 100, 000 individuals weekly from January 1, 2021 to July 1, 2021.[18] Data in Europe is consistent with that in the United States.[19] With the emergence of Omicron variants in late November 2021,[20] a massive increase of confirmed pediatric cases was found during the past month in both American and European countries when the Omicron variant is dominant, which may be explained by a low rate of vaccination in those countries or changed transmission patterns of Omicron.[16,21,22] It is estimated that the United States weekly growth rate of pediatric cases in Omicron dominant time from December 1, 2021 to January 20, 2022 was about 13 times higher than that in Delta prevailing time from July 1, 2021 to November 1, 2021 [Figure 1].

Israel had a high vaccination rate previously in adults, and it might have already provided some indirect protection among the unvaccinated 0 to 15 age group.[23] With the start of vaccination for adolescents aged 12 to 15 years, the incidence of cases aged 12 to 15 years in Israel revealed a decrease and remained very low till the end of 2021.[24] And vaccination for children 5 to 11 years since November 11, 2021 also worked well, but still, a noticeable increase of pediatric cases was reported since the beginning of January 2022. Although vaccines for children 5 to 11 years were approved for emergency use several months ago, the rate of 5–11-year-old children who received at least one dose was low, with 3.4% in the United States and 19.64% in Israel as of January 24, 2022,[21,25] vaccination data of children under 10 years old were not reported in European countries. So, we recommend improving childhood immunization rates under the complex situation of the pandemic.

Role of children in the transmission of COVID-19

We summarized studies that referred to taking children as index cases or analyzed the spread of SARS-CoV-2 from children in Table 1. Data on the transmission of COVID-19 through children in selected papers were all collected especially before 2021 when the vaccines for humans were not broadly taken, which provided unbiased evidence for the interpretation of the role of children in the transmission of COVID-19.

The existing evidence indicated that children indeed had played a role in the transmission of COVID-19, especially in households. In Japan, between January 1 to October 2020, there were 9.8% (297/3042) of primary pediatric

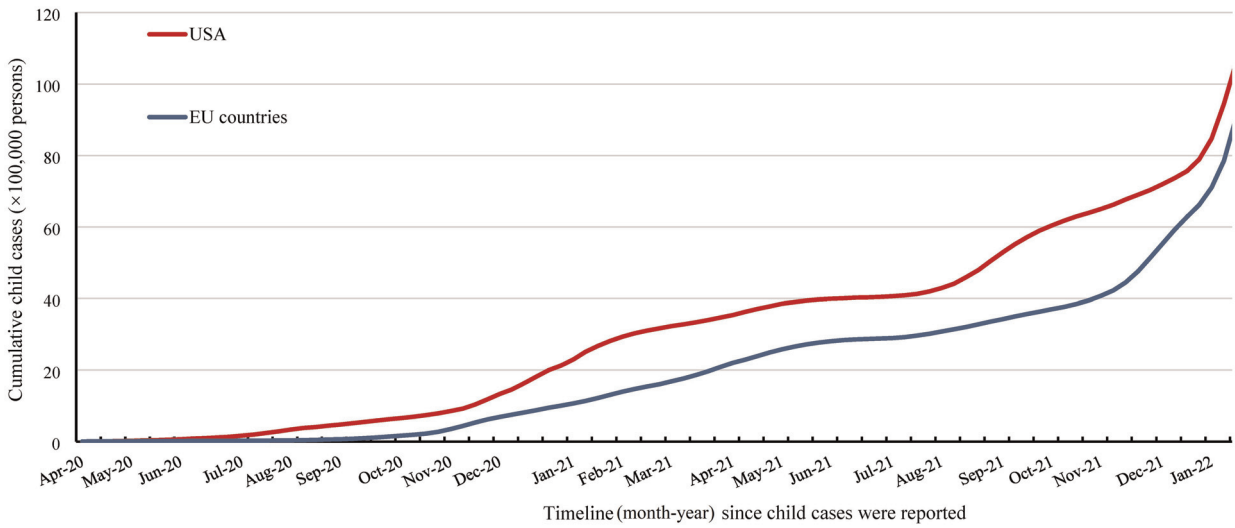

Figure 1: Cumulative child cases reported in Europe and the United States. Data were collected on web of American Academy of Pediatrics and European center for Disease Prevention and Control. Child cases were <15 years old in EU countries, and basically <18 years old in the United States. EU: European union.

Table 1: Summary of studies on the transmission of SARS-CoV-2 by children.

First author, reference	Type of study	Sample size	Rate of children as index case	Time and site of data collection	Main conclusions
Imamura *et al*[26]	Retrospective observational study	7758 cases	9.8%	15th Jan–31st Oct 2020, Japan	The most common place for children transmitting SARS-CoV-2 was in household School children aged 13–18 years had higher possibility to generate secondary case than children aged 7–12 years
Miller *et al*[27]	Prospective cohort study	181 index cases and 452 household contacts	50.8%	30th Mar–17th Nov 2020, England	Secondary attack rate was lower in children under 11 years old; there was a high risk for children to transmit SARS-CoV-2 in household
Li *et al*[28]	Retrospective cohort study	29,578 primary cases and 57,581 household contacts	1.4%	2nd Dec 2019–18th Apr 2020, Wuhan, China	Children and adolescents under 20 years old were more likely to transmit SARS-CoV-2 to others than people <60 years old (OR 1.58, 95% CI 1.28–1.95)
Laws *et al*[29]	Prospective observational study	188 contacts (120 adults; 68 children)	1.6%	Mar–May 2020 Utah and Wisconsin, USA	Transmission of SARS-CoV-2 from children was observed in about one-fifth households
Paul *et al*[30]	Prospective cohort study	9861 individuals from 6280 households	7.5%	1st Jun–31st Dec 2020 Ontario, Canada	Children aged 0–3 years were more likely to transmit SARS-CoV-2 infection compared with children aged 14–17 years; there were increased odds of transmission in children 4–13 years, as well
Telle *et al*[31]	Prospective cohort study	7548 index cases	34.2%	1st Mar 2020–1st Jan 2021, Norway	Adults and children >17 years old account for most part of index cases Young children and adults transmit the virus to the same extent within the household when infected
Kim *et al*[33]	Retrospective observational study	107 pediatric index cases and 248 household members	100%	20th Jan–6th Apr 2020, South Korea	Secondary attack rate from children was 0.5% under circumstances of social distancing in South Korea
Macartney *et al*[34]	Prospective cohort study	27 primary cases and 18 secondary cases	44.4%	25th Jan–10th Apr 2020, New South Wales, Australian	The rate of child-to-child transmission was 0.3%, child-to-adult transmission was 1.0% in educational settings. Effective measures contained the spread of SARS-CoV-2 in educational settings of Australian
Jordan *et al*[35]	Prospective observational study	39 cases and 253 contacts	23.1%	29th Jun–31st Jul 2020, Barcelona, Spain	A total reproduction number R_e was 0.3 in this study Little transmission of SARS-CoV-2 was found in preventive measures schools
Mossong *et al*[36]	Prospective observational study	424 COVID-19 cases	6.8%	4th May–25th Jul 2020, Luxembourg	A percentage of 84% of the secondary cases were transmitted by children. Precautionary measures like social distancing reduced transmission of SARS-CoV-2 in school settings
Merckx *et al*[38]	Review	NA	NA	Until 25th Jun 2020	Compared with adults, the rate of children transmitting SARS-CoV-2 was lower

Table 1
(continued).

First author, reference	Type of study	Sample size	Rate of children as index case	Time and site of data collection	Main conclusions
Li *et al*[39]	Review	16 unique studies	NA	Until 30th Apr 2020	Prolonged faecal shedding found in studies suggested the potentially increased risk of faeco-oral transmission in children.
Zhao *et al*[40]	Model study	1126 COVID-19 cases	NA	5th Jan–19th Feb 2020 Hunan, China	Children under 14 years had a lower rate to transmit SARS-CoV-2 compared with people >45 years old, but they did transmit SARS-CoV-2
Zhu*et al*[41]	Meta-analysis	57 articles	NA	Until 24th Aug 2020, multi-country	Children were less frequently classified as the index case of household SARS-CoV-2 clusters Insufficient case numbers were determined to figure out the transmissibility of COVID-19 from children

COVID-19: Coronavirus disease 2019; NA: Not available; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

cases generated secondary cases, and 77% (141/184) of secondary transmission was found at households.[26] In a cohort study in England, the secondary attack rate from children under 11 years was 25% (14/61) (95% CI, 12%–38%) in the family.[27] A study in Wuhan also found confirmed cases of children and adolescents under 20 years old had higher infectivity than other individuals (odds ratio [OR] = 1.58, 95% CI, 1.28–1.95).[28] In Utah and Wisconsin of America, the transmission of COVID-19 from children to others was observed in approximately one-fifth households.[29] It seems like children of different age groups may have varied contributions to the spread of COVID-19, and younger children under 5 years old had higher infectivity than older children aged 5 to 9 years. In 6280 households in Ontario, Canada, for pediatric cases transmitted COVID-19 to household contacts, the odds ratio of children aged 0 to 3 years to children aged 14 to 17 years was 1.43 (95% CI, 1.17–1.75), and a higher odds ratio was also found in children aged 4 to 8 years (OR = 1.40, 95% CI, 1.18–1.67) and 9 to 13 years (OR = 1.13, 95% CI, 0.97–1.32) .[30] Similar results were found in Norway, as well. Children of 0 to 6 years old generated more secondary cases (24%, 116/487, 95% CI, 20%–28%) than children of 7 to 12 (14%, 198/1455, 95% CI, 12%–15%) or 13 to 16 years old (14%, 304/2109, 95% CI, 13%–16%).[31]

With the timely implementation of effective preventive interventions like early testing of suspect cases, setting attendance and entry rules, keeping physical distancing, and use of medical masks, the transmission of COVID-19 from children was limited.[32] The transmission dynamics of 107 pediatric COVID-19 cases in Republic of Korea identified a secondary attack rate of 0.5% (95% CI, 0%–2.6%) from children under the social distance.[33] New South Wales of Australia issued hygiene measures in school settings in the early stage of the pandemic. The secondary attack rate from children to others was 0.4% (3/752) in educational settings during January 25 and April 10 in 2020.[34] A study on the transmission of COVID-19 among children in summer schools with stringent preventive measures in Barcelona of Spain did reverse transcription-polymerase chain reaction (RT-PCR) test in students of 22 summer schools, the effective reproduction number was 0.3 and no secondary cases were generated from child index cases.[35] Results were similar in a study in Luxembourg, although 84% of the secondary cases were from children, the effective reproduction number was only 0.27 in school settings.[36] Public health and social measures should be consistently and appropriately implemented for all ages in schools, especially when we are in a time of indelibility of mass vaccination in children under 12 years old.[37]

Although some studies suggest that the rate of children-to-children or children-to-adults transmission was lower than adult-to-adult transmission,[38-41] current evidence revealed children are indeed a part of the chain of COVID-19 spread. Recently, the highly transmissible variants of Omicron have already led to an increased hospitalization of children in America.[22,42] It is vital to have more research to determine whether children are more likely to transmit Omicron than other SARS-CoV-2 variants. We hope studies on the role of children in the transmission of COVID-19 inspired us to strengthen control measures in school settings and establish immune protection for school children.

COVID-19 Vaccine Candidates for Children

COVID-19 vaccine clinical trials in healthy children

As of January 24, 2022, there were 140 COVID-19 vaccine candidates undergoing clinical trials worldwide, and 33 of them had been emergently or fully approved by at least one country to prevent COVID-19 in the population aged ≥18 years.[5,43,44] Of all the COVID-19 vaccine clinical trials on the registry platform, there were 16 vaccine candidates designed to include people under 18 years old as a part or full sample as of January 20, 2022 [Table 2].[40] Published data were reported in seven studies among those vaccine clinical trials. Table 2 showed summarized results of trials in children, studies that classified people aged >16 years as the adult group were excluded in our table due to inaccessibility of relevant datasets.

The efficacy trials of two RNA based vaccines in adolescents aimed to expand its target population to people aged >12 years with the same regimen compared with that in adults.[45,46] It seems BNT162b2 was better than mRNA-1273 from efficacy and safety profile results

Table 2: Clinical trials of vaccine candidates in children as of January 20, 2022.

Vaccine name	Platform	Developer	Current phase	Age (years)	Dose
BBIBP-Corv	Inactivated	Beijing Institute of Biological Products Co., Ltd.	Phase 4	3–17	Normal dose with schedule exploring
CoronaVac	Inactivated	Sinovac Life Sciences Co., Ltd.	Phase 3	0.5–17	Same with that in adults
Covaxin	Inactivated	Bharat Biotech International Limited	Phase 2/3	2–18	NA
Inactivated SARS-CoV-2 vaccine (vero cell)	Inactivated	Shenzhen Kangtai Biological Products Co.	Phase 2	3–17	NA
Ad26.COV2.S	Non-replicating viral vector	Janssen–Cilag International NV	Phase 2/3	12–17	Exploring moderate doses
Ad5-ncov	Non replicating viral vector	CanSino Biologics Inc.	Phase 3	6–17	Normal dose with a nebulized inhalation subgroup
ChAdOx1 nCoV-19	Non-replicating viral vector	AstraZeneca AB	Phase 2	6–17	Normal dose
Gam-COVID-vac M	Non-replicating viral vector	Gamaleya Research Institute of Epidemiology and Microbiology	Phase 2/3	12–17	1/10 or 1/5 of full adult dose
Abdala	Protein subunit	Center for Genetic Engineering and Biotechnology	Phase 2	3–18	Same with that in adults
MVC-COV1901	Protein subunit	Medigen Vaccine Biologics Corp.	Phase 2	12–17	Same with that in adults
Covax-19	Protein subunit	CinnaGen Co.	NA	12–18	NA
Recombinant SARS-CoV-2 vaccine (CHO Cell)	Protein subunit	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	Phase 2/3	3–17	Same with that in adults
Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	Protein subunit	WestVac Biopharma Co., Ltd.	Phase 1/2	3–17	Exploring moderate doses
SCB-2019	Protein subunit	Clover Biopharmaceuticals AUS Pty Ltd.	Phase 2/3	0–17	Exploring moderate doses
BNT162b2	RNA based vaccine	BioNTech Manufacturing GmbH	Phase 3	0.5–17	Exploring dose from 3 mcg to 30 mcg
mRNA-1273	RNA based vaccine	ModernaTX, Inc.	Phase 2/3	0.5–11	Exploring moderate doses

NA: Not available; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

as shown in Table 3. Real world data on the effectiveness of BNT162b2 vaccine in adolescents in Republic of Korea was 99.1% (95% CI: 98.5%–99.5%) post-second dose against symptomatic or asymptomatic SARS-CoV-2 infection.[47] To further expand its immune population, Pfizer conducted a pivotal trial in children 5 to 11 years and revealed some results on September 20, 2021.[48,49] Overall, Pfizer reduced the dose of BNT162b2 to 10 μg in children >12 years old, a carefully chosen dosage which was one-third of that in people >16 years of age. The injection interval remained unchanged. The U.S. (FDA) authorized the Pfizer-BioNTech COVID-19 vaccine for emergency use in children 5 years through 11 years of age due to its favorable safety profile and robust neutralizing antibody responses on October 29, 2021.[50,51] Whereas the trial of Pfizer and BioNTech COVID-19 vaccine in children 6 months to under 5 years of age showed that compared to the 16 to 25-year-old population in which high efficacy was demonstrated, non-inferiority was not found for the 2 to 5-year-old population.[52] Moderna's RNA-1273 has only been authorized for emergency use in population 18 years and older in the United States so far, whereas it got EUA for children aged 12 to 17 years in the European Union and Canada.[53,54] The other two inactivated vaccines got approval for emergency use in children 3 to 17 years in China.[55-57] It is worth mentioning that different doses in a pediatric clinical trial of CoronaVac though the interval time remained the same as that in adults, results of two regimens of 1.5 and 3 μg with 3 weeks interval supported the use of 3 μg in phase 3 trials, which was the same regimen as that in adults. For BBIBP-CorV, they explored 2, 4, and 8 μg on a three-dose schedule with 3 weeks interval, and a 4 μg with two-dose regimen was recommended at last based on careful consideration of safety and immunogenicity. A group of subjects aged 6 to 17 years was recruited in a phase 2b trial of recombinant adenovirus type-5-vectored COVID-19 vaccine. The groups showed better immunogenicity but a higher rate of adverse events compared with adult groups.[58] Other vaccine trials that included people under 18 years as subjects were BBV152 (COVAXIN) from India, SARS-CoV-2 rS/Matrix-M1 adjuvant from the United States, SARS-CoV-2 recombinant spike protein nanoparticle from Vietnam, and COVAXIN from India with few data revealed. We hope more results from trials of varieties of COVID-19 vaccines in children will be available to facilitate increased kinds of pediatric COVID-19 vaccines that get emergency use approval.

Challenges for pediatric vaccination due to predominance of SARS-CoV-2 variants

An important consideration for the necessity of accelerating pediatric vaccination is the potential increased transferability and higher susceptibility, which might be brought by SARS-CoV-2 variants.[59-62] A retrospective cohort study on severity of COVID-19 caused by SARS-CoV-2 variants of concern (VOC) in children demonstrated there was an increased Delta COVID-19 incidence in children and Gamma (P.1 and sublineages) rather than Alpha (B.1.1.7 and sublineages) or Delta (B.1.617.2 and sublineages) increased severity of the disease.[63] In Israel,

Table 3: Results of candidate COVID-19 vaccine clinical trials in children.

Vaccine	Platform	Age	Dose and regimen	Phase	Safety	Immunogenicity (95% CI)	Efficacy (95% CI)
BNT162b2[45]	RNA	12–15	0–21 days, 30 μg	3	2.9% related adverse events within 30 days after dose 2	NT50 GMT: 1283.0 (1139.6–1444.5)	100% (75.3–100%)
BNT162b2[98]	RNA	3–11	0–21 days, 10 μg	2/3	3.0% related adverse events within 30 days after dose 2	NT50 GMT: 1197.6 (1106.1–1296.6)	90.7% (67.7–98.3%)
mRNA-1273[46]	RNA	12–17	0–28 days, 100 μg	2/3	84.6% solicited adverse reactions within 7 days after any dose	NT50 GMT: 1401.7 (1276.3–1539.4)	93.3% (47.9–99.9%)
CoronaVac[56]	Inactivated	3–17	0–28 days, 1.5/3.0 μg	1/2	25.2% solicited adverse reactions within 7 days after any dose	NAb GMT: 142.2 (124.7–162.1)	NA
BBIBP-CorV[57]	Inactivated	3–17	0–28–56 days, 2/4/8 μg	1/2	30.3% overall adverse reactions after whole vaccination	NAb GMT in 3–5-year-old group: 180.2 (163.7–198.5) NAb GMT in 6–12-year-old group: 168.6 (152.0–187.1) NAb GMT in 13–17-year-old group: 155.7 (137.4–176.5)	NA

CI: Confidence interval; GMT: Geometric mean titer; NT50: 50% neutralizing titer; NAb: Neutralizing antibodies; NA: Not available.

a doubled transmission rate of SARS-CoV-2 from children aged 0 to 9 years was found during the circulation of Alpha (B.1.1.7) variant.[64] These findings suggest that problems brought by SARS-CoV-2 variants deserve our attention and the importance of vaccination for children under 12 years old after a rigorous risk assessment and approval procedures.[65] Three clinical trials have already set a neutralizing antibody titer to SARS-CoV-2 VOC after full vaccination of relevant vaccine in people under 18 years old as immunogenicity endpoint.[66-68] Studies on vaccine efficacy against different SARS-CoV-2 variants in the real world showed reduced effectiveness.[69-71] And a case-control study in 16 states of America revealed 93% (95% CI: 83%–97%) effectiveness against adolescent hospitalization after two doses of BNT162b2 when Delta variant was predominant strain.[72] The trial of BNT162b2 in children 5 to 11 years of age mentioned above were also conducted during the Delta-dominant period, and vaccine efficacy was 90.7% (95% CI, 68.3%–98.3%) against COVID-19 at least 7 days after dose two vaccination, which demonstrated high protection from SARS-CoV-2 infection in the predominant time of Delta variant.[73] A study in Israel evaluated the short-term effectiveness of BNT162b2 among adolescents during Delta variant-dominant period. The estimated efficacy against SARS-CoV-2 infection was 90% (95% CI, 88%–92%) from 7 days through 21 days post the second dose.[74] Another retrospective cohort study in Israel demonstrated adjusted vaccine effectiveness for days 8 to 28 after the second dose was 91.5% (95% CI, 88.2%–93.9%) during Delta variant-dominant period.[75] As for the Omicron variant, a study showed that highly preserved omicron-specific functional humoral immunity was observed in children receiving 100 μg of BNT162b2 vaccine.[76] The latest research from Israel reported that children aged 5 to 11 years who received two doses of 30 μg BNT162b2 in the past 2 months got protection rates twice as those unvaccinated during the Omicron epidemic.[77] The efficacy of COVID-19 vaccines to SARS-CoV-2 variants still needs further confirmation in subsequent studies and clinical trials to acquire more helpful vaccination against emerging SARS-CoV-2 variants for children despite its high efficacy in the preliminary stage.

Safety issues on candidate vaccines in children

A few countries have started their COVID-19 vaccination campaigns in children of different ages with emergency use approved vaccine by their local authorities.[15] Advice from WHO's Strategic Advisory Group of Experts was Pfizer-BioNTech (BNT162b2) vaccine is suitable for use by people aged ≥12 years.[78] Tracking adverse events caused by relevant vaccines as pediatric vaccination campaigns are rolled out will be critical to providing adequate and safer protection for children. The occurrences of adverse events following immunization (AEFI) were reported with the progress of mass vaccination previously.[79] A study on the safety profile of COVID-19 vaccines concluded that pooled reporting rates of AEFIs from nationwide safety surveillance data in some countries were 3424.5 (95% CI, 2725.7–4123.3) per million-dose for BNT162b2 and 316.4 (95% CI, 285.8–347.0) per million-dose for BBIBP-CorV. AEFIs in children or adolescents were less common than adults in clinical trials of CoronaVac, yet the opposite results were shown with BNT162b2.[80]

Adverse event of special interest (AESI) is a pre-specified medically significant events that has the potential to be causally associated with a vaccine product, and it needs to be carefully monitored and confirmed by further special studies.[81] A licensed vaccine post-marketing should put more attention on AESI, especially in children and adolescents. Some of the AESIs are receiving more interest, such as rhabdomyolysis, Bell's palsy, Guillain-Barré Syndrome (GBS), coagulation disorder, myocarditis or pericarditis, and thrombocytopenia. It was found that BNT162b2 was associated with a higher risk of myocarditis,[82] according to some previous reports. After the authorization of vaccination for children and adolescents, myocarditis post-mRNA vaccine injection was more frequently reported in young males,[83-89] although no myocarditis cases were documented in phase 3 trials of BNT162b2 or mRNA-1273. Other AESIs like multisystem inflammatory syndrome, thrombocytopenia, and GBS have also been reported in young adolescents or children.[90-92] Myocarditis or pericarditis was found in adolescents post-mRNA COVID-19 vaccination. Although the incidence of myopericarditis or pericarditis increased,[93,94] the exited

data currently suggest the cases of myocarditis or pericarditis following vaccination tended to be mild and respond to conservative treatment and were less severe or self-limited with better outcomes than classical myocarditis or COVID-19.[95,96] Bell's palsy used to be suspected related to BNT162b2 vaccination, whereas a brief report from FDA on BNT162b2 clinical trials stated that Bell's palsy discovered in the vaccine group is comparable to the incidence observed in the general population.[97] Trials data of BNT162b2 in children aged 5 to 12 years also showed no cases of Bell's palsy.[98] These safety issues related to vaccination in children remind us to focus more not only on the safety profile in the clinical trials of COVID-19 vaccines for children but also on the strengthened surveillance of authorized pediatric vaccines during the post-marketing phase. Various vaccine safety monitoring platforms could provide passive or active surveillance, such as Vaccine Adverse Events Reporting System, World Health Organization Uppsala Monitoring Centre, Vaccine Safety Datalink, and MHRA's COVID-19 Yellow Card scheme. Active Vaccine Safety Surveillance (AVSS) systems collect relevant data from all individuals within a defined population beyond a passive surveillance system. We hope countries and areas that introduced COVID-19 vaccination could all establish or get access to passive surveillance systems and AVSS systems for COVID-19 vaccine-related AESIs.

Discussion

Several hypotheses might explain the low rate of severe pediatric COVID-19 patients and could be summarized as the unique immune mechanism in children, different from adults.[99] Angiotensin converting enzyme-2 (ACE2) is a functional receptor for SARS coronavirus, some experts believe that the ACE2 in children are less susceptible to SARS-CoV-2, or the maturity of ACE2 in children is not enough to bind with SARS-CoV-2.[100-102] A study by Yale University showed that the early immune response and the activation of the innate immune pathway in children's nasopharynx were more active than adults, indicating that they may generate a high antiviral response in the very early stages of infection.[103] A quicker response to the receptor-binding domain was observed in children with SARS-CoV-2 during the early stages of infection, so as the reaction of peripheral blood B cell transcriptomic signature.[104] Those more vigorous and rapid innate immune responses to SARS-CoV-2 found in children may play a substantial role in mild symptoms.

Although the current evidence suggested the possibilities of COVID-19 transmission by children is limited, schoolchildren may be at high risk when they contact their peers who may be in the incubation period of SARS-CoV-2 infection. Meanwhile, the emerging variants suggest it is ignorable to put attention on children, as the character of those variants is different on transmissibility, viral loads, and high risk of disease progression compared with the wild-type strain.[105,106] Research of data in the Global Initiative on Sharing All Influenza Data hCoV-19 database showed that compared with previously circulating lineages, there was an estimation of 29% (95% CI, 24%–33%), 25% (95% CI, 20%–30%), and 97% (95% CI, 76%–117%) increase on transmissibility for Alpha, Beta, and Delta variants, respectively.[107] Studies at the present stage are not adequate to fully describe the special effect SARS-CoV-2 VOCs have on children, and research on this topic needs to be further expanded.

There were debates about the actual benefit-risk profile in post-approval of COVID-19 vaccines in children,[108] and we suggest the benefits outweigh the risks. The published and reported results of relevant clinical trials of the COVID-19 vaccine in people under 18 years of age proved to be safe and well immunogenic. However, problems of waning immunity or reduction of neutralizing antibodies a few months after full dose vaccination because of antibodies decay over time or immune escape of mutation were found in adults.[69,109-111] The same problem will come for children soon as their prime vaccination begin. Some intervention strategies effectively cope with the waning immunity after vaccination, such as a third homologous or heterologous boost dose of COVID-19 vaccine.[112-115] There might be some novel approaches in vaccine designs later, FDA has already approved a booster of BNT162b2 for children 12 to 17 years of age.[116] And the third dose regimen was already implied in phase 1/2 clinical trials of BBIBP-CorV.[57] Meanwhile, safety issues post-COVID-19 vaccination especially in mRNA vaccines need more attention. Thromboembolic events after injection of adenovirus-vectored COVID-19 vaccines from AstraZeneca (AZD1222) and Janssen (Ad.26.COV2.S) brought to light an important lesson on preventing serious adverse events occurring in the vaccinated populations.[117,118] Therefore, ensuring high efficacy, and continuous safety monitoring of the COVID-19 vaccine for children is of great necessity.

Currently, the situation of the COVID-19 pandemic appears tense and volatile worldwide. There is a high demand for available vaccines globally. The vaccination rate remains low in some low- to middle-income countries (LMIC), which rely on imports or moral aid from developed countries. The immunization for children might be their last option because vaccination should be prioritized for a high-risk population. Although it was delightful that COVID-19 vaccination for children was accessible in some countries, the challenge is short for vaccine supply and heavy burden of logistics systems for LMIC. The success of the aforementioned vaccine clinical trials in children provided a rationale for testing other COVID-19 vaccines in pediatric clinical trials, and more alternative COVID-19 vaccines for children are needed for optimal benefits across childhood populations and providing broader protection against emerging variants often in the face of varying settings and provider preference. The advanced market commitment, launched by the global alliance for vaccines and immunization, aims to provide sufficient COVID-19 vaccines for LMIC, but not all LMIC will get enough vaccines. When countermeasures like reducing the price of COVID-19 vaccines are unable to work,[119] measures to give a fair distribution of COVID-19 vaccines are needed.

Conflicts of interest

None.

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