

Global COVID-19 vaccination in infants and children: Effectiveness, safety, and challenges

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Abstract

COVID-19 Vaccines, which include mRNA and inactivated vaccines, have been proven effective and safe for infants and children aged more than six months in reducing the severity of the disease, hospitalization, multisystem inflammatory syndrome in children, and death. Nonetheless, the real-world effectiveness of these vaccines in preventing infection is generally lower than in clinical trials due to the emergence of variants of concern, especially the Omicron strains. Despite the availability of vaccines for children, their uptake remains low globally, particularly among parents who are hesitant to vaccinate their children. This review article aims to provide a comprehensive overview of COVID-19 vaccine safety and efficacy from clinical trials and the current COVID-19 vaccine recommendations for infants and children aged 6 months to < 12 years for 2023-2024, discuss the progress made in vaccine implementation and real-world effectiveness, and address the knowledge gap and future directions.

Key words: COVID-19 vaccines, SARS-CoV-2, infants, children, pediatrics

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Introduction

As of September 2023, all age groups have been impacted by the SARS-CoV-2 infection and COVID-19-related illnesses, resulting in nearly 7 million deaths.¹ Children with SARS-CoV-2 infection tend to present with milder symptoms compared to adults. However, children remain at risk of developing severe disease and complications, including respiratory failure, myocarditis,

multisystem inflammatory syndrome in children (MIS-C), and long-COVID.^{2,3} Moreover, SARS-CoV-2 infection has negatively impacted children's psychosocial, emotional, and intellectual development.⁴ Prevention of SARS-CoV-2 infection, including COVID-19 vaccines, aims to ameliorate these effects.

Several COVID-19 vaccine platforms have been widely used in adult populations, including mRNA vaccines, viral vectors, protein-based vaccines, and inactivating vaccines. They aim to prevent SARS-CoV-2 infection, severe disease, hospitalization, death, and long COVID-19.⁵ Currently, there is solid evidence to support the use of mRNA vaccines, and they are widely available for children and adolescents, whereas other vaccines remain available for limited use. Inactivated vaccines have received conditional approval for mass vaccinations in the younger population in some countries; for example, CoronaVac (Sinovac) and Covilo (Sinopharm) were approved for children 3-11 or 6-11 years old in China, Thailand, Chile, and Brazil. Covaxin (Bharat Biotech) was approved for children aged 6-12 years in India. However, viral vector vaccines such as ChAdOx-nCoV have not undergone further evaluation in young children due to concerns arising from reports of thrombosis and thrombocytopenia syndrome among female adults.⁶ Protein-based vaccines such as NVX-CoV2373 (Novavax) are still undergoing trials to evaluate efficacy and safety in children younger than 12; however, Biological E's Corbevax has been approved for emergency use in children aged 5-12 years in India.

Recommendations for COVID-19 vaccines in children aged 6 months to < 12 years are varied. The Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) released an interim statement that countries should consider the individual and population-level benefits of vaccinating children. In March 2023, SAGE recommended considering the primary series and booster dose for healthy children and adolescents within the country-specific context only, including the disease burden in the age group, cost-effectiveness, other health or programmatic priorities, and opportunity costs.⁷ The United States Advisory Committee on Immunization Practices (ACIP) suggests vaccinating all children aged > 6 months. In comparison, the Joint Committee on Vaccination and Immunisation of the United Kingdom (JCVI-UK) advises the primary course and booster only in a clinical risk group aged > 6 months.⁸⁻⁹ In real-world practice, the uptake of mRNA vaccines in children is lower than in adults and older people due to several issues. These include lower severity of disease, parental concern about long-term safety, vaccine availability as the pandemic matures, and lower vaccine effectiveness as the virus evolves towards new variants.

This review article aims to summarize COVID-19 vaccine recommendations for infants and children aged 6 months to < 12 years, discuss the progress in vaccine implementation and real-world effectiveness, and address the knowledge gap and future directions.

I. Evolution of SARS-CoV-2 variants and immune evasion

SARS-CoV-2 was first identified in 2020. Viruses mutate over time, resulting in a survival advantage for the virus. Variants of Concern (VOCs) exhibit mutations that produce effects such as increased transmissibility, disease severity or immune evasion, and decreased performance of therapeutic drugs or diagnostic tests. The notable VOCs of SARS CoV-2 as classified by the WHO include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) and its sublineages.¹⁰ Unlike other VOCs, the Omicron variant contains over 30 mutations within the spike protein, continuously changes into sublineage, and increases the ability to escape immune responses elicited by vaccination or previous infection, thereby impacting vaccine efficacy and effectiveness. This led to the global wave seen from the end of 2021 to 2023.^{11,12} (**Figure 1**)

Immune evasion of viruses occurs over time due to the impairment of the humoral immune response, interruption of the cellular immune response, and impairment of immune effectors such as cytokines and apoptosis-related proteins.¹³ The mutations of viruses impair the binding affinity of antibodies. Neutralizing antibodies (nAbs) provide protection against the antigenic epitopes of the S-glycoprotein of SARS-CoV-2 and are evoked through vaccination.¹⁴ There are three classes of neutralizing antibodies for COVID-19 vaccines. Class I neutralizing antibodies primarily target the receptor binding domain (RBD) of the spike protein on the SARS-CoV-2 virus, thereby preventing the virus from

binding to the angiotensin-converting enzyme 2 (ACE2) receptor and infecting human cells. Class II neutralizing antibodies target other parts of the spike protein beyond the RBD, namely the N-terminal domain (NTD) and the S2 subunit, thus preventing entry into cells. Class III neutralizing antibodies also target other viral proteins, such as the nucleocapsid protein, to prevent the virus from replicating and spreading within the body.¹⁵ Most COVID-19 vaccines primarily induce class I neutralizing antibodies. However, VOCs have generated mutations within the antibody binding regions of S-glycoprotein which influence antibody escape events. The K417N/T mutation in Gamma (P.1) and Delta (B.1.351) is accountable for class I antibody escape, while the E484K and L452R mutations are accountable for class II and class III antibody escape, respectively.^{16,17} In addition, the neutralization activity against the Omicron (B.1.1.529) by mRNA vaccines was reduced compared with the Delta variants and ancestral strain due to S371L, N440K, G446S, and Q493R substitutions.^{12,13,18} When viruses escape neutralization, they can successfully enter host cells by binding to ACE2 receptors. This reduces mRNA vaccine efficacy in preventing infection, requiring an additional booster dose or a new variant-containing vaccine that protects against new strains.

SARS-CoV-2 mutations affecting the role of the T cell response remain poorly understood. Functional T cell responses are directed against multiple viral proteins, including spike protein, N protein, and M protein. The footprints of T cell escape are more broadly distributed than antibody-driven changes, which are concentrated within dominant epitopes of the spike protein.^{19,20} Several mutations within ORF3a and N protein result in a complete loss of recognition by CD8+T cell epitopes, such as N protein P13L in Omicron, L452R in Delta, and BA.4/BA.5 variant.^{21,22} In addition, L18F, D80A, and D215G in Beta, and D118H in Alpha have been associated with the loss of specific CD4+ responses.^{23,24} However, several studies demonstrate that T-cell responses from first-generation vaccines are sustained against the majority of VOCs, despite the loss of these particular responses, resulting in less than 30% overall CD4+ and CD8+ response reduction to Omicron.²⁴⁻²⁶ It appears that increased transmissibility and antibody evasion are more important contributors to the emergence of VOCs than T-cell escape.

Overall COVID-19 vaccines

The development of COVID-19 vaccines has taken place on a variety of platforms. As of March 2023, 382 COVID-19 vaccine candidates have been in development, with 11 vaccines approved for wider use and granted by the WHO and 4 vaccines approved for children 6 months to < 12 years.^{5,27} According to UNICEF, the global supply of a billion doses of SARS-CoV-2 vaccines includes 50% mRNA, 25% viral-vector, 14% inactivated, and 11% protein-based.²⁸ The COVID-19 mRNA vaccines consist of mRNA-encoding target genes, e.g., BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), and SYS6006 vaccine (CSPC Pharmaceutical Group from China). The COVID-19 non-replicating vector virus vaccines infect cells,

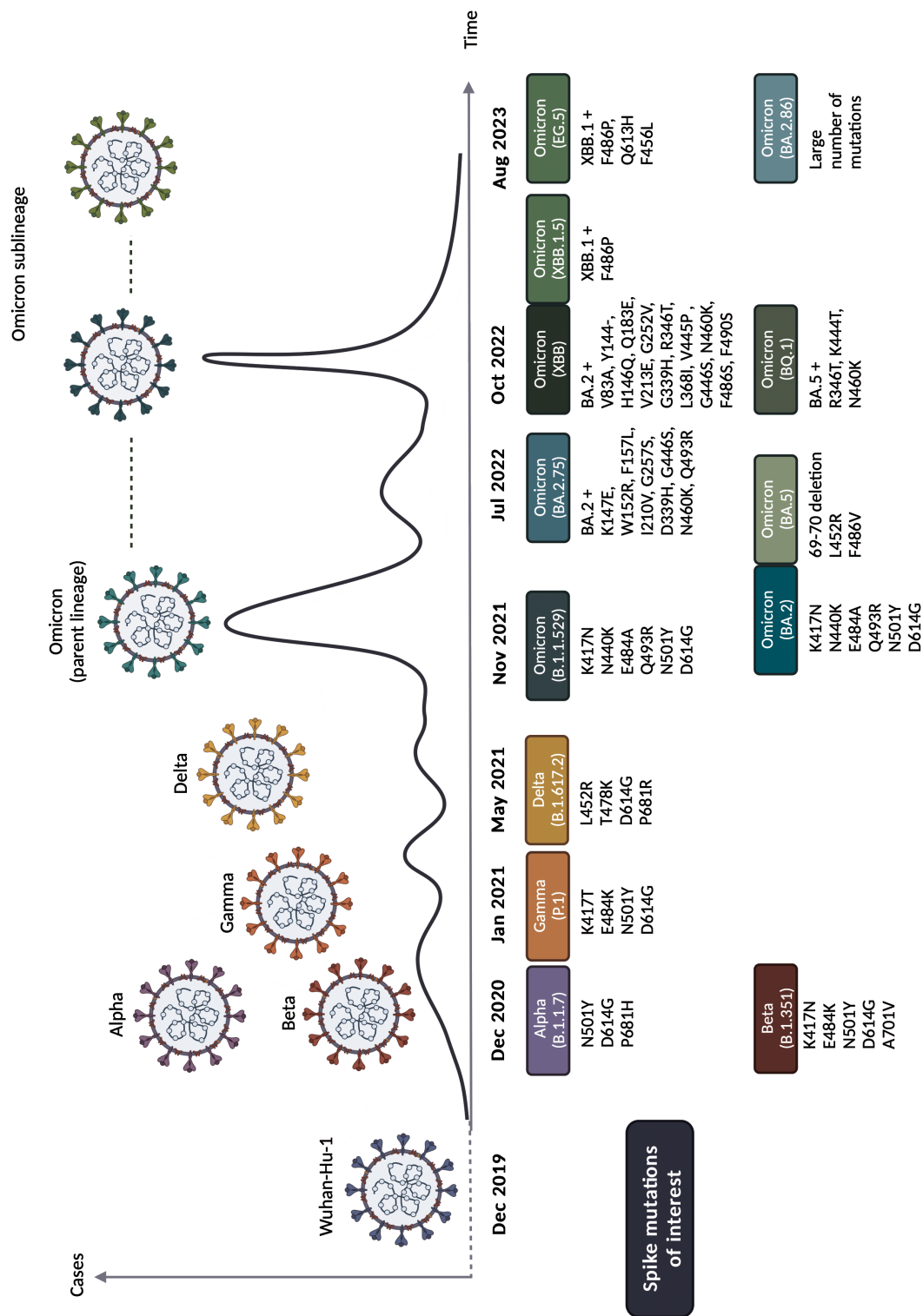


Figure 1. Evolution of SARS-CoV-2 variants of concern and mutations of interest.

producing the vaccine antigen to elicit an immune response; however, the viral vector cannot reproduce, e.g., Ad26.COV2.S (Janssen/Johnson&Johnson), ChAdOx1 nCoV-19/AZD1222 (AstraZeneca) and Gam-COVID-Vac Sputnik V (Gamaleya Institute). The COVID-19 inactivated vaccines are produced by growing SARS-CoV-2 in cell culture, chemically inactivating the virus, and combining it with an adjuvant to stimulate immune responses, e.g., CoronaVac (Sinovac), Covilo (Sinopharm) and Covaxin (Bharat Biotech). Protein-based vaccines consist of a protein purified from the virus or virus-infected cells, recombinant protein, or virus-like particles. The COVID-19 recombinant protein vaccines contain purified viral proteins, e.g., NVX-CoV2373 (Novavax). Comparisons of the relationship between efficacy and neutralizing and binding antibody titers in vitro across various vaccine platforms have been conducted. This data suggests higher antibody responses to the mRNA and the protein subunit vaccine than the viral-vectored and inactivated vaccines.^{29,30} Due to viral evolution and the decreasing effectiveness of the monovalent vaccine against the Omicron variant, bivalent mRNA vaccines, including the original strain and BA.1 or BA.4/BA.5, were created to counter the new strain as a booster dose.³¹ In May 2023, regarding the ongoing evolution of SARS-CoV-2, the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) announced the recommendations for COVID-19 vaccine antigen composition for the next vaccine that should induce an immune response against the Omicron XBB lineages and its descendances.³² COVID-19 vaccine manufacturers, Pfizer-BioNTech, Moderna, and Novavax, have been updating their target to the Omicron XBB. As of September 2023, XBB.1.5 adapted monovalent COVID-19 vaccines from 2 manufacturers, Pfizer-BioNTech and Moderna, have been authorized by the US- Food and Drug Administration (FDA) and European Medicine Agency and recommended by the US-ACIP to be used in persons aged 6 months and above to protect against the latest lineages.³³ The interim report on the use of XBB.1.5 monovalent vaccines (Moderna) as a booster showed that the vaccine elicited neutralizing antibodies against emerging variants, including EG.5.1, FL.1.5.1, and BA.2.86. Meanwhile, the Pfizer-BioNTech mRNA vaccine reported that the updated COVID-19 vaccine elicited neutralizing antibodies against emerging sublineages of EG.5.1 and BA.2.86.

Pediatric COVID-19 vaccines

This review article will focus on children stratified to school age (5-11 years), young children (6 months to 5 years), and passive maternal antibody transfer for infants < 6 months of age. (Table 1)³⁴

COVID-19 vaccines for children aged 5-11 years old

The COVID-19 vaccine platforms that have been authorized for children aged 5-11 years are mRNA and inactivated vaccines (Table 1). The mRNA vaccines, including BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), are used worldwide, while inactivated vaccines, CoronaVac (Sinovac) and Covilo (Sinopharm), are widely used in the Asia Pacific region and Latin America. A pivotal study conducted during the Delta predominant period showed that the vaccine efficacy against COVID-19 was 91% after two doses of BNT162b2 and 88% after a 2-dose regimen of 50 mcg of mRNA-1273.^{35,36} However, the mRNA vaccines were rolled out during the Omicron surge in October 2021, and the real-world vaccine effectiveness (RVE) was lower than that reported during the clinical trial phase. Studies have shown that the effectiveness against infection of the BNT162b2 primary series was 20-58%,³⁷⁻³⁹ and CoronaVac, against sublineage BA.2, was 41%,⁴⁰ lower than that reported during the Delta predominant period.⁴¹ The effectiveness was higher among previously infected children compared to naive children.⁴² However, hospitalization from COVID-19 was higher in unvaccinated children than in vaccinated children.⁴³ RVE against hospitalization on both platforms was 41-83%.^{38,43-45} In addition to preventing acute COVID-19, vaccination in children was associated with a lower probability of getting MIS-C.⁴⁶

The adverse events of mRNA vaccines in children are generally lower than in adults. The most common reaction reported was pain at the injection site after 70-95% of injections. The second and third most common reactions reported were fatigue (34-65%) and headache (22-54%).^{35,36,47} Myocarditis is a concern in young adult males, especially following the second dose. However, reports in children are much lower, within the range of 0.1-2.2 per million doses, and more prevalent in boys than girls.⁴⁸ Adverse reactions following a booster dose of the original or bivalent vaccines were similar to those described after the primary series, without any reports of myocarditis or death after the booster.^{48,49}

The heterologous vaccine regimen has been used in countries that used inactivated vaccines. In mid-2022, at the beginning of the Omicron period, a booster dose with an original monovalent mRNA vaccine was recommended five months after the primary series. Meanwhile, many children in certain countries, including Thailand, that had used an inactivated vaccine as the primary series were recommended an mRNA booster at least two months after the second dose of their primary series. The neutralizing antibodies against the Omicron variants (BA.1) in children were higher in participants who received an mRNA booster dose following an inactivated vaccine compared to two-dose of mRNA vaccines.⁵⁰ Omicron was evolving into immune escape variants e.g, BA.2.75, XBB, BQ.1.

Table 1. COVID-19 Vaccines Approval and Recommendation for Infants and Children aged < 12 years during 2021-2023.

Name (Manufacture)	Type	Recommendation	
		Primary series	Booster
Comirnaty (Pfizer/BioNTech) Examples of countries with approved vaccines: the United States, the United Kingdom, Europe, Australia, Singapore, Thailand	mRNA	5–11 years: Immunocompetent: Two intramuscular doses of 10 mcg of monovalent, 3–8 weeks apart Immunocompromise: The third primary series dose at least 28 days after the second 6 months – 4 years: Three intramuscular doses. The first two doses of 3 mcg of monovalent vaccine, 3–8 weeks apart. The third dose of 3 mcg of monovalent or bivalent, at least 8 weeks after the second	5–11 years: A single intramuscular 10 mcg booster dose of the bivalent vaccine at least 8 weeks after the second 6 months – 4 years: A single intramuscular 3 mcg booster dose of the bivalent vaccine at least two months after completing the primary series, if the monovalent vaccine was used for all three doses of the primary series A booster dose (ie, a second bivalent vaccine dose) has not been authorized and is not recommended, if the bivalent vaccine is used for the third dose of the primary series
Spikevax (Moderna) Examples of countries with approved vaccines: the United States, the United Kingdom, Europe, Australia, Singapore, Malaysia, the Philippines, Thailand	mRNA	6–11 years: Immunocompetent: Two intramuscular doses of 50 mcg of monovalent, 4–8 weeks apart Immunocompromise: The third primary series dose, given at least 4 weeks after the second 6 months – 5 years: Immunocompetent: Two intramuscular doses of 25 mcg of monovalent, 4–8 weeks apart. Immunocompromise: a third primary series dose, given at least 4 weeks after the second	6–11 years: A single intramuscular 25 mcg booster dose of the bivalent vaccine at least 8 weeks after the second 6 months – 5 years: A single intramuscular 10 mcg booster dose of the bivalent vaccine at least 8 weeks after the second
CoronaVac (Sinovac) Examples of countries with approved vaccines: Thailand, China, Chile, Brazil	Inactivated	3–12 years: Two intramuscular doses, 2–4 weeks apart	A booster with mRNA vaccines or a third dose of inactivated vaccines
Covilo (Sinopharm-Beijing) Examples of countries with approved vaccines: Thailand, China, Chile, Brazil	Inactivated	3–12 years: Two intramuscular doses, 3–4 weeks apart	A booster with mRNA vaccines or a third dose of inactivated vaccines
Covaxin (Bharat Biotech) Examples of countries with approved vaccines: India	Inactivated	6–12 years: Two intramuscular doses, 4 weeks apart	A booster with mRNA vaccines or a third dose of inactivated vaccines

At the end of 2022, the US- ACIP recommended a booster dose with a bivalent vaccine (BA.4/5) at least two months after the last dose of vaccination, regardless of the number of vaccines.⁵¹ As of 12 September 2023, the US-ACIP recommendations for a 2023-2024 (monovalent, XBB containing) mRNA COVID-19 vaccines for children is shown in **Table 2**.³³ According to high seroprevalence in children aged > 5 years, US-ACIP recommend only 1 dose of mRNA COVID-19 vaccines (PfizerBioNTech 10 mcg or Moderna 25 mcg) regardless of history of vaccination or infection. While the JCVI-UK statement on the COVID-19 vaccination program for autumn 2023 advises the booster program should offer a single dose of XBB-containing vaccine for children with a clinical risk group aged over 5 years, irrespective of prior vaccination status and at least three months from the previous dose.

COVID-19 vaccines for infants and children aged 6 months to less than 5 years old

For children aged 6 months to under 5 years, the currently authorized vaccines are mRNA and inactivated vaccines, similar to the 5-11 year age group.^{33,34,52,53} The BNT162b2 vaccine was authorized for emergency use by the US- FDA in children aged 6 months to under 5 years in June 2022, during the Omicron-predominant period.⁵² Simultaneously, mRNA-1273 was also authorized for emergency use in children aged 6 months to 5 years.⁵² The monovalent BNT162b2 vaccine was authorized as a 3-dose primary series, 3 mcg per dose at 3 and 8 weeks apart.^{52,53} The monovalent mRNA-1273 vaccine was approved as a 2-dose primary series, 25 mcg per dose at 4 weeks apart.⁵² In Europe, the European Medicines Agency also authorized mRNA vaccines, BNT162b2 and mRNA-1273,

Table 2. US-ACIP Recommendation of updated mRNA COVID vaccines for season 2023-2024 (monovalent, XBB containing) for Infants and Children aged < 12 years³³

COVID-19 vaccination history	Age 5–11 years	Age 6 months – 4 years
Not moderately or severely immunocompromised		
Unvaccinated	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna	3 doses of 3 mcg of Pfizer-BioNTech, 3–8 weeks apart for the first two doses and at least 8 weeks after the second dose 2 doses of 25 mcg of Moderna, 4–8 weeks apart
1 dose of any Moderna	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	1 dose of 25 mcg Moderna at least 4–8 weeks after the last dose
2 or more doses of any Moderna	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	1 dose of 25 mcg Moderna at least 8 weeks after the last dose
1 dose of any Pfizer-BioNTech	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	2 doses of 3 mcg of Pfizer-BioNTech, at least 3–8 weeks after the last dose and at least 8 weeks between the first and second vaccine doses
≥ 2 doses of any Pfizer-BioNTech	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	1 dose of 3 mcg of Pfizer-BioNTech, at least 8 weeks after the last dose
Moderately or severely immunocompromised*		
Unvaccinated	3 doses of 10 mcg Pfizer-BioNTech, 3 weeks apart for the first two doses and at least 8 weeks after the second dose or 3 doses of 25 mcg Moderna, 4 weeks apart for the first two doses and at least 4 weeks after the second dose	3 doses of 3 mcg Pfizer-BioNTech, 3 weeks apart for the first two doses and at least 8 weeks after the second dose or 3 doses of 25 mcg Moderna, 4 weeks apart for the first two doses and at least 4 weeks after the second dose
1 dose of any Moderna	2 doses of 25 mcg Moderna at least 4 weeks after the last dose and at least 4 weeks apart between the first and second vaccine doses	2 doses of 25 mcg Moderna at least 4 weeks after the last dose and at least 4 weeks between the first and second vaccine doses
2 doses of any Moderna	1 dose of 25 mcg Moderna at least 4 weeks after the last dose	1 dose of 25 mcg Moderna at least 4 weeks after the last dose
3 or more doses of any Moderna	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	1 dose of 25 mcg Moderna at least 8 weeks after the last dose
1 dose of any Pfizer-BioNTech	2 doses of 10 mcg Pfizer-BioNTech at least 3 weeks after the last dose and at least 4 weeks apart between the first and second vaccine doses	2 doses of 3 mcg of Pfizer-BioNTech, at least 3 weeks after the last dose and at least 8 weeks between the first and second vaccine doses
2 doses of any Pfizer-BioNTech	1 dose of 10 mcg Pfizer-BioNTech at least 4 weeks after the last dose	1 dose of 3 mcg of Pfizer-BioNTech, at least 8 weeks after the last dose
3 or more doses of any Pfizer-BioNTech	1 dose of 10 mcg Pfizer-BioNTech or 1 dose of 25 mcg Moderna at least 8 weeks after the last dose	1 dose of 3 mcg of Pfizer-BioNTech, at least 8 weeks after the last dose

*may receive 1 or more additional 2023–2024 mRNA COVID-19 vaccine doses, informed by the clinical judgment of a healthcare provider and personal preference and circumstances, and an additional dose should be administered at least 2 months after the last 2023–2024 COVID-19 vaccine dose.

**if recently had SARS-CoV-2 infection may consider delaying a COVID-19 vaccine dose by 3 months

in children of this age.⁵⁴ In Asia, these mRNA vaccines are authorized in many countries, e.g., Thailand, Singapore, and Australia. Apart from mRNA vaccine platform, inactivated vaccines were approved in children over 3 years of age in China.

The vaccine efficacy against COVID-19 in the phase 2–3 trial of BNT162b2 was 73% (95%CI 44–88) from 1 week to 2 months after the third dose.⁵³ The phase 2–3 trial of mRNA-1273 reported a vaccine efficacy against COVID-19 of 37% (95%CI 13–54) in children aged 2–5 years and 51%

(95%CI 21–69) in children aged 6 months to under 2 years, from 2 weeks to 3 months after the second dose.⁵⁵ However, the RVE against symptomatic infection was lower than in clinical trials. For BNT162b2 was 31% (95%CI 7–49) in children aged 3–4 years, from 2 weeks to 4 months after the third dose.⁵⁶ For mRNA-1273, the RVE was 60% (95%CI 49–68) from 2 weeks to 2 months and 36% (95%CI 15–52) 3–4 months after the second dose.⁵⁶ Common adverse reactions following vaccination included local pain/tenderness (15–73%), fatigue (24–48%),

and irritability (44–67%). These generally occurred at a lower rate than children aged 5–11. No cases of myocarditis/pericarditis were reported.^{53,55}

In December 2022, a bivalent mRNA-1273 vaccine was authorized under emergency use as a booster at least 2 months after the primary series.⁵² The bivalent BNT162b2 vaccine was approved for emergency use as the third dose in a primary series in December 2022 and a booster dose at least 2 months after the primary series in March 2023.⁵² In September 2023, the US-ACIP recommended using a 2022–2023 (monovalent, XBB containing) mRNA COVID-19 vaccines instead of bivalent COVID-19 vaccine.³³ Initial series of 2 Moderna vaccine doses or 3 Pfizer-BioNTech vaccine doses are recommended for the unvaccinated group while at least 1 dose of 2023–2024 COVID-19 vaccine is recommended for the vaccinated group. (Table 2)³³ Meanwhile, JCVI-UK suggests offering one XBB-containing booster in infants and children aged 6 months and over in a clinical risk group.

COVID-19 vaccines for infants aged younger than 6 months old

Infants under six months of age receive maternal antibodies via transplacental transfer and/or lactation. This follows the concept of maternal immunization, for example, with influenza, pertussis, and recently respiratory syncytial virus (RSV) vaccines.^{57,58} Several studies reported that vaccination during pregnancy reduced the risk of SARS-CoV-2 infection and hospitalization in infants during their first six months.^{59,60} This risk reduction declined as infants aged. The mean titer of maternally derived antibodies peaked at 2 months and decreased by 6 months.⁶¹ Maternal booster doses of BNT162b2 reported the effectiveness of 53% (95%CI 36–65%) and reduced infant hospitalization. A shorter time between immunization and delivery was linked to better protection.⁶² During lactation, antibodies (mostly IgA and IgG) are present in breast milk, particularly 1–8 weeks after the second dose.⁶³ The vaccine induces spike-reactive CD4+ T cells in breast milk, especially after the second dose of the BNT162b2 vaccine. These spike-reactive CD4+ T cells may have a protective function in the upper respiratory tract of infants.⁶⁴ Although the antibodies in breast milk only last hours to days after the cessation of breastfeeding, they may serve a complex immune function in the neonate and infant by helping to establish and maintain the gut microbiome and training the immune system to tolerate antigens at the mucosal surface.⁶⁵

The American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention, and other health organizations currently recommend pregnant and lactating women should receive the COVID-19 vaccine and stay up-to-date with booster doses, including the bivalent COVID-19 booster.⁶⁶ As SARS-CoV2 variants change, we forecast that similar to recommendations for pertussis and influenza prevention, future guidelines will embrace recommendations for routine COVID-19 booster vaccinations throughout the third trimester to reduce early infant morbidity.

Consideration of COVID-19 Vaccines in special populations *Children with a previous history of SARS-CoV-2 infection*

Immunity from natural infection wanes over time. Therefore, children with a history of SARS-CoV-2 infection should receive a COVID-19 vaccine. Moreover, hybrid immunity - defined as an immune response in individuals who have had one or more doses of a COVID-19 vaccine and experienced at least one SARS-CoV-2 infection before or after vaccination - provides higher immunity than vaccination alone or infection alone.^{67,68} The previous US-ACIP recommended that these children should receive primary series and booster doses according to their age. The recommendation in 2023 suggests the total dose of vaccine depends on their age and history of vaccination, regardless of history of infection and were given at least 3 months after infection.³³ (Table 2) However, several studies reported only 1 dose of mRNA vaccine could boost the neutralizing antibody among children with a history of SARS-CoV2 infection.^{69,70} Jarupan et al. reported the immunogenicity against Omicron infection among children aged > 6 years with a history of SARS-CoV-2 infection (Delta variant) and followed by monovalent BNT162b2 vaccination did not show a significant difference between 1- and 2-dose of vaccination.⁶⁹ In addition, a study in children aged 6 months to < 5 years with a history of SARS-CoV-2 infection during the Omicron-predominant period reported robust neutralizing antibody response after a single dose of BNT162b2.⁷⁰ A delayed interval of 3–6 months between infection and vaccination may be considered following several studies showing that a longer duration may enhance the immune response. Re-infection usually occurs after weeks or months of the previous infection.⁷¹ The actual timing of vaccination depends on individual factors such as the risk of severe disease, the likelihood of spreading COVID-19 within the community, and changes in the SARS-CoV-2 strain.

History of MIS-C

MIS-C is a serious complication of SARS-CoV-2 infection in children with dysregulated immune responses to SARS-CoV-2 infection. The risk of recurrence of a dysregulated immune response and the safety of the COVID-19 vaccine, particularly the risk of myocarditis, are concerns. However, Elias MD et al. reported that children aged 5 years and older with a history of MIS-C had no increased risk of serious adverse effects after receiving the COVID-19 vaccine, including myocarditis or the recurrence of MIS-C.⁷² Of those who received a COVID vaccination following MIS-C, mild adverse reactions (mainly injection site pain and fatigue) are similar to those of the general population. Immunization should be considered at least 3 months after MIS-C diagnosis, with expected clinical recovery to baseline cardiac function.

Immunocompromised children

Immunocompromised children - those with suppressed humoral or cellular immunity resulting in primary or secondary immunodeficiency - should get vaccinated against COVID-19. The immunogenicity and efficacy of COVID-19 vaccinations appear to be lower in this population compared to the general population.⁷³ A review of 26 reports of 1439 primary immunodeficiency patients vaccinated with COVID-19 vaccines revealed a serologic response rate of 72% and T cell responses in most patients with acceptable safety profiles.⁷⁴ The cellular and/or humoral immune responses were probably diminished in patients with combined immunodeficiency, common variable immunodeficiency, or other primary antibody deficiency.⁷⁴ However, the COVID-19-related hospitalization and ICU admission were lower than unvaccinated patients, with tending lower mortality rate.⁷⁵ Among secondary immunodeficiency patients, studies revealed a lower humoral immune response among immunocompromised adolescents compared to adolescents with other chronic diseases, especially in those post-solid organ transplantations and cancer patients receiving chemotherapy.^{76,77}

Although primary and secondary immunodeficiency patients have different immune response patterns, the recommendation of the COVID-19 vaccine is similar to immunocompromised condition patients. Previously, the US-ACIP recommended that children aged 6 months to 11 years old with certain immunocompromising conditions should receive 3 doses of a primary series and at least 1 bivalent booster dose at least 2 months later, depending on the history of vaccination. However, the additional dose of a bivalent mRNA is optional. As of September 2023, the US-ACIP recommends a series of 3 homologous mRNA COVID-19 vaccine doses at a time of initial vaccination and at least 1 2023–2024 COVID-19 vaccine dose. The further additional dose(s) may be administered, informed by the clinical judgment of a healthcare provider and personal preference and circumstances, for at least 2 months following the last 2023–2024 COVID-19 vaccine dose.³³ While the JCVI-UK recommended a 2-dose-primary series with an additional dose.⁹ In observational studies of immunocompromised individuals, receipt of three doses of mRNA vaccine is associated with higher vaccine effectiveness than two doses.⁷⁸ The timing of COVID-19 vaccination should consider current or planned immunosuppressive therapies, optimization of the underlying medical condition, anticipated response to immunization, and individual benefits and risks. In general, the administration of COVID-19 vaccines should not be delayed; whenever possible, COVID-19 vaccines should be administered at least 2 weeks before initiation or resumption of immunosuppressive therapies. For patients who receive B-cell-depleting therapies, COVID-19 vaccines should be administered 4 weeks before the subsequent scheduled treatment.

However, patients with immunocompromising conditions should be advised to continue other protective measures regardless of the number of vaccine doses received, as an immune response may be suboptimal despite three doses. Households and other close contacts of immunocompromised patients should be vaccinated. The other method of pre-exposure prophylaxis for immunocompromised individuals is a monoclonal antibody. However, the combination of tixagevimab-cilgavimab, which had previously been an effective option for age > 12 years and body weight more than 40 kg, is not expected to be effective against certain Omicron subvariants (BQ.1/BQ.1.1, XBB.1 and XBB.1.5).^{79,80} Therefore, the data of circulating strain in each country should be taken into account for the recommendation of monoclonal antibodies.

II. Vaccine hesitancy regarding pediatric COVID-19 immunization

Overall, the uptake of COVID-19 vaccines in infants and children has been very low. In the US, as of March 2023, 33% of 5–11-year-olds and 5% under 5 years had completed the primary series of COVID-19. Only 14% of children aged 5–9 years in EU/EEA countries had completed the primary series.^{81,82} In Thailand, 51% of the 5–11 years population and 1% of the less than 5 years population completed the primary series.⁸³ Although the COVID-19 vaccines are efficacious and safe, vaccine hesitancy still results in poor primary and booster uptake. Reasons for vaccine hesitancy differ by country; however, acceptance is usually affected by vaccine literacy, fear of side effects, and political circumstances.^{84,85} Moreover, Hammershaimb et al. reported that vaccine acceptance amongst parents is associated with accepting routine childhood immunizations and prior receipt of a seasonal influenza vaccine.⁸⁶ Parents must balance the perceived risks of COVID-19 disease against the perceived risks and benefits of COVID-19 vaccination. The media often report that pediatric COVID-19 disease is mild, and therefore parental beliefs regarding COVID-19 risk and severity tend to be more focused on adults when compared to children. However, the parental perception that pediatric COVID-19 disease is severe predicts positive vaccination intentions for children up to 11 years old. However, Marks KJ et al. reported 3 million COVID-19 cases and more than 500 associated deaths among children aged < 5 years in the US.⁸⁷

Moreover, some parents are concerned that the novel vaccines, particularly mRNA vaccines, have not been used previously and may harbor safety concerns about mRNA vaccines - particularly concerning myopericarditis and long-term side effects. Despite estimated incidence of myocarditis is about 1 in 50,000 across all age groups.⁸⁸ The meta-analysis study reported that the incidence of myocarditis in children aged 5 to 11 years was 1 in 500,000 and is usually self-limiting, and not severe.⁸⁹ In addition, confidence in vaccine safety varies by race or ethnicity and household income. For example, in the US, Hispanic or Black children or children in lower-income households have lower vaccine coverage and acceptance.⁹⁰

To improve COVID-19 immunization coverage amongst young children and decrease related morbidity and mortality, enhanced evidence-based practices are required to lower vaccination barriers and boost parental confidence in the COVID-19 vaccine. Moreover, healthcare providers could increase vaccination coverage by providing information and reassurance of COVID-19 vaccine safety.

III. Knowledge gap and future directions

Several considerations about the next generation of COVID-19 vaccines are in progress as follows.

Seasonal COVID-19 vaccine

The increasing pattern of seasonal COVID-19 cases is similar to influenza infection, i.e., during winter in the United States and rainy season in Thailand, and correlates with when new variants develop, which can achieve immune escape. Therefore, the US FDA proposed an annual COVID-19 vaccination plan or updated COVID vaccine, aiming to simplify vaccination scheduling and reduce vaccine fatigue. It is important to not calling booster dose vaccine, due to it is not just boosting existing immunity from previous vaccination; rather, the vaccine builds a new immune response to variants that are currently circulating.

COVID-19 Vaccine for children born post-pandemic

Due to high infection rates and increased vaccine coverage during the pandemic, the next generation of vaccines will primarily be used in the context of pre-existing immunity from vaccination, prior infection, or both - except in children. The necessity and recommendations for the COVID-19 vaccine for infants born after the pandemic or unvaccinated young children are still debatable. Infants and young children remain at risk of hospitalization and severe disease. In the US, the hospitalization rates are higher among children 6 months to < 2 years of age compared to children 2–4 years of age. More research is needed to determine the efficacy and safety between the primary series of monovalent ancestral strains and bivalent ones, as well as the cost-effectiveness in this group.

COVID-19 vaccine in combination with other respiratory virus vaccines: ongoing clinical trials

A “triple epidemic” or triple epidemic of respiratory viruses influenza, RSV, and SARS-CoV-2, which can occur as seasonal epidemics, remains a concern. Seasonal influenza continues, and the recommendation of annual influenza vaccination among individuals over six months aims to decrease illness, hospital admission, and deaths. RSV can cause severe disease in premature infants, infants under six months, children under two years with chronic lung disease or congenital heart disease, immunocompromised children, and children with neuromuscular disorders, as well as in older adults and individuals with chronic heart and lung disease. In February 2023, US-FDA approved two RSV vaccines for older adults aged over 60 years; a single dose AS01E-adjuvanted RSV prefusion F (RSVpreF) protein-based

vaccine from GlaxoSmithKline Biological and a bivalent RSVpreF protein-based vaccine from Pfizer.^{91,92} Developers are currently exploring the use of mRNA technology to create a single injection that combines vaccines for COVID-19 and other respiratory viruses like influenza and RSV. The goal is to reduce the need for multiple injections and enhance overall immunity. However, there are some concerns, including side effects, vaccination timing, and disease prevalence variability. Phase I clinical trials have been conducted on combination mRNA vaccines. These trials include the mRNA-1230 (influenza, RSV, and SARS-CoV-2) in healthy older adults from Moderna (NCT05585632) and the combination of modRNA quadrivalent influenza vaccine (qIRV 22/23) and bivalent BNT162b2 (original/Omicron BA.4/BA.5) vaccine in healthy adults from Pfizer-BioNtech (NCT05596734).

Other routes of COVID-19 vaccines administration

The intramuscular route remains the main route of administration for most vaccines due to a strong and effective immune response, better absorption into the bloodstream, and convenience. However, mucosal vaccines are under development, including those delivered via a dropper, nebulizer, sprayer, inhaler, and tablet. The mucosal vaccines aim to reduce infection and transmission of SARS-CoV-2 by stimulating local immune responses (mucosal IgA) at the infection site and enhancing systemic immune responses, including neutralizing IgG and T-cell response, in order to protect against symptomatic and severe disease.⁹³ Several intranasal SARS-CoV-2 vaccines are developing based on live-attenuated respiratory viruses or replication-incompetent viral vectors with mucosal tropism. They can achieve protection against SARS-CoV-2 infection in animal models, including mice, hamsters, and macaques. However, there are currently limited studies in human clinical trials.⁹⁴

As of December 2022, five mucosal vaccines for SARS-CoV-2 including iNCOVACC® from Bharat Biotech, India, Convidecia from CanSinoBIO, China, Gam-COVID-Vac from Gamaleya, Russia, Razi Cov Pars from Razi Institute Iran and Pneumoclin from Beijing Wantai, China have been authorized for use or registered to be reviewed by a regulatory agency; although none have been approved in the United States or Europe or achieved emergency use listing by the WHO.⁹³ The study of ChAd36-SARS-CoV-2-S (Recombinant) (iNCOVACC®), a replication-defective chimpanzee adenovirus (ChAd)-vectored intranasal (IN) COVID-19 vaccine by Bharat Biotech International Limited, reported good toleration and good immune response following 2 doses by dropper 4 weeks apart among nearly 3000 adults in Phase III clinical trial (not yet published). It has received restricted emergency use approval in adults from the Drugs Controller General of India (DCGI).⁹⁵⁻⁹⁸ The study of an orally administered aerosolized Ad5-nCoV (Convidecia) as a booster after two-dose priming with an inactivated SARS-CoV-2 vaccine (CoronaVac) in 420 Chinese adults reported safe and higher neutralizing antibodies against SARS-CoV-2 than those induced by a third intramuscular

dose of CoronaVac.⁹⁹ The important issue to investigate is the correlation between protection in mucosal immunity and the effect of preventing infection and transmission, as previous data is based on the induction of antibody responses to spike protein.

Conclusion

Pediatric COVID-19 vaccines were successfully developed and widely used during the pandemic period. They were proven to reduce hospitalization, MIS-C, and severity, especially in immunocompromised children. However, the real-world effectiveness in preventing infection is generally lower than during clinical trials due to changes in variants of concern, especially Omicron strains. This leads to the challenge of developing bivalent strains for seasonal vaccination and for new babies born. The vaccine implementation challenge was based upon perceived low severity of disease compared with elderly population, concern of longterm safety of mRNA vaccines, and lack of access of pediatric vaccine in timely manner. COVID-19 vaccine has a direct benefit especially among children with underlying diseases and clinical risk, therefore immunization should be promoted as COVID19 becomes endemic disease.

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