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REVIEW ARTICLE

SARS-CoV-2 vaccines in children and adolescents: Can immunization prevent hospitalization?

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants of concern can infect people of all ages and can cause severe diseases in children, such as encephalitis, which require intensive care. Therefore, vaccines are urgently required to prevent severe disease in all age groups. We reviewed the safety and efficacy profiles of mRNA vaccines—BNT162b2 and mRNA-1273—demonstrated by clinical trials or observed in the real world. mRNA-1273 is effective in preventing SARS-CoV-2 infection in preschool children (6 months-6 years old). Both BNT162b2 and mRNA-1273 are effective in preventing SARS-CoV-2 infection in school-aged children and adolescents, thereby preventing post-coronavirus disease (COVID) conditions. The common side effects of vaccination are pain at the injection site, fatigue, and headache. Myocarditis and pericarditis are uncommon. Monitoring post-vaccination troponin levels may help prevent severe cardiac events. The SARS-CoV-2 coronavirus mutates its genome to overcome the herd immunity provided by mass vaccinations; therefore, we may need to develop new generations of vaccines, such as those using viral nucleocapsid proteins as antigens. In conclusion, the mRNA vaccines are generally safe and effective in preventing severe diseases and hospitalization among children and adolescents.

Keywords: Adolescents; Child; COVID-19; Immunization; Pediatrics; SARS-CoV-2; Vaccines

1. INTRODUCTION

Since late 2019, a new coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept the globe in less than a year.[1] This infectious disease is coined as coronavirus disease 2019 (COVID-19) by the world health organization. Countries from various continents were indiscriminately affected by this pandemic, causing multifaceted problems such as medical system failure, disruption of the global supply chain, and global economic recession.[2,3] Many cities were repeatedly quarantined; schools were completely closed for almost a full year. Moderna (Cambridge, MA, USA; mRNA-1273) and Pfizer-BioNTech (New York, NY, USA; BNT162b2) were the first companies to successfully develop COVID-19 vaccines, followed by Oxford-AstraZeneca (Cambridge, UK; ChAdOx1), Johnson & Johnson (New Brunswick, NJ, USA; Jcovden), and others.[4-7] Once the vaccines had been demonstrated to be safe for immunization and effective in eliciting neutralizing antibodies, national authorities around the globe were justified in mass immunizing residents with these vaccines, with the goals of blocking viral transmission and protecting people from severe diseases that require hospitalization or intensive care.

To date, most COVID-19 vaccinated people are adults because the initial clinical trials demonstrating the safety and efficacy of COVID-19 vaccination were conducted on adults.[4-7] The real world data from mass vaccinations demonstrated that the vaccines can effectively protect adults against infection and severe COVID-19–related hospitalization.[7] Children's immune profiles differ from those of adults. When children are infected by SARS-CoV-2, they are less likely to develop severe diseases, and their mortality rate is lower than that of adults. Severe conditions in children include encephalitis and neurological manifestations as well as respiratory, cardiovascular, and gastrointestinal disorders (Fig. 1). The infection may occasionally trigger the lethal multisystem inflammatory syndrome in children (MIS-C), also known as pediatric

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inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[8] MIS-C/PIMS-TS often requires hospitalization or intensive care treatments. Vaccination is necessary to protect children and adolescents, so they can attend school, where interpersonal contacts are frequent and social distancing may be difficult to maintain. The viral transmission must be blocked from children to children and from children to adults. Consequently, studies have started evaluating the use of COVID-19 vaccines in adolescents and children. To date, BNT162b2 has been approved for people older than 5 years by the US Food and Drug Administration.[9] mRNA-1273 has been approved for people older than 17 years.[10] Jcovden has been approved for people older than 18 years.[11] The intended use of mRNA-1273 in children aged from 6 months to 6 years was filed on April 28, 2022, based on the positive interim findings of the KidCOVE trial.[12]

ChAdOx1 and Jcovden are both adenoviral vectors engineered for encoding the antigenic spike protein of SARS-CoV-2. These vaccines could direct the production of antigens in the human body, thereby educating the immune system to recognize these antigens. During the mass vaccination, a small percentage of ChAdOx1 and Jcovden vaccine recipients developed serious thrombosis with thrombocytopenia syndrome.[13] These adverse events slowed the progress of clinical trials in children and adolescents. The other two pioneering vaccines, BNT162b2 and mRNA-1273, are both mRNA vaccines. These vaccines are single-stranded, 5′-capped spike protein-encoding mRNAs manufactured using cell-free in vitro transcription systems. Once the mRNA enters the human body, it can direct the production of antigenic spike proteins. Clinical trials of these vaccines have begun in children and adolescents.[14]

The aforementioned vaccines were designed to produce spike proteins as if generated by the wild-type SARS-CoV-2. However, the SARS-CoV-2 is an RNA virus whose genome is prone to change. The SARS-CoV-2 virus has been mutating its genomes since 2019, resulting in many variants of concern. These mutations can cause structural changes in the spike protein. The widespread use of first-generation vaccines has offered herd immunity in people and put SARS-CoV-2 under selective pressure. Since late December 2021, Omicron strains, which include several substrains such as BA1, BA2, BA4, and BA5, have become dominant worldwide. Omicron strains contain more variants in the spike protein than previous variants of concern such as delta, beta, alpha, and the wild type.[15] The human immunological system trained to recognize wild-type spike proteins may have less sensitivity in recognizing and neutralizing Omicron strains, which poses an unprecedentedly high threat to humans regardless of vaccination.

2. EFFICACY OF mRNA VACCINATION IN CHILDREN AND ADOLESCENTS

The interim results of the BNT162b2 clinical trial for children aged 5 to 11 years old have been published.[17] The dose-escalation study in phase 1 of the trial revealed that 10 μg of BNT162b2 provides adequate immunogenicity. During phases 2 to 3, 2268 children from the United States, Spain, Finland, and Poland were recruited and randomly assigned to receive either the primary series (ie, the first two doses) of 10 μg of BNT162b2 or placebo at a ratio of 2:1.[16] The prospective observation demonstrated that BNT162b2 is effective in preventing infection after immunization, reducing the cumulative incidence of infection at 100 days from 2.5% of the placebo group to <0.2% of the vaccinated group. The estimated vaccine efficacy was 90.7%.[16] The SARS-CoV-2 neutralizing antibody titers of children aged 5 to 11 years who received two shots of 10 μg of BNT162b2 are comparable to those of young adults (16-25 years old) who received 30 μg of BNT162b2, resulting in a calculated geometric mean ratio (GMR) of 1.04 (95% confidence interval [CI] = 0.93-1.18; Fig. 2).

In the investigation of BNT162b2 vaccination in adolescents (12-15 years old), the GMR of neutralizing antibody titers after the second dose, in contrast to that of young adults (16-25 years old), was 1.76, suggesting that the vaccine can elicit comparable titers in both age groups.[17] No cases in the vaccinated group had an onset of COVID-19 during the observational period after the primary series (Fig. 2).[17]

Moderna initiated the kidCOVE trial for evaluating mRNA-1273 vaccination in children across three age groups: infants (6 months-2 years old), preschool children (2-6 years old), and school-aged children (6-11 years old), with 11,700 pediatric participants recruited from the United States and Canada.[12,18] The mRNA-1273 doses received by the three groups (infants, preschool children, and school-aged children) were 25, 25, and 50 μg, respectively. The interim analysis revealed that infants and preschool children who received the primary series of 25

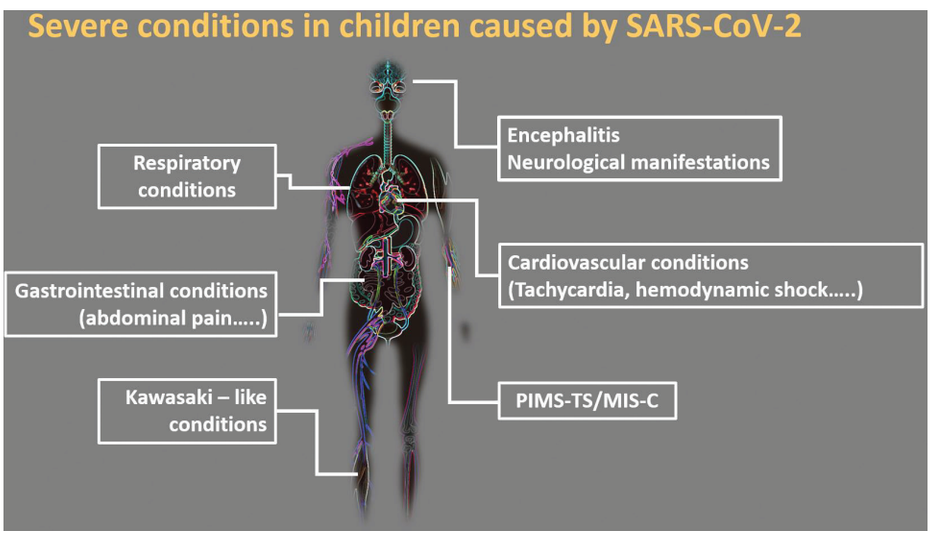

Fig. 1 Severe conditions caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children.

Pfizer-BioNTech BNT162b2		Moderna mRNA-1273	
Preschooler		**Preschooler (6 month - 6 years)**	
Primary series dose:	N/A	Primary series dose:	25 μg
Immunogenicity:	N/A	Immunogenicity:	Positive (6m-2y GMR= 1.3; 2y-6y GMR= 1.0)
Protection against infection:	N/A	Protection against infection:	Effective
Common side effects:	N/A	Common side effects:	Fever > 38°C (6m-2y 17.0%; 2y-6y 14.6%)
Information source:	N/A	Information source:	Moderna news release 3/23/2022
School-age child (5-11 years)		**School-age child (6-11 years)**	
Primary series dose:	10 μg	Primary series dose:	50 μg
Immunogenicity (vs. adults)	Positive (GMR= 1.04)	Immunogenicity (vs. adults):	Positive (GMR= 1.2)
Protection against infection:	Effective	Protection against infection:	Effective
Common side effects:	Pain at injection side, fatigue and headache	Common side effects:	Pain at injection side, fatigue, fever and headache
Information source:	N Engl J Med 2022;386:35-46.	Information source:	N Engl J Med 2022;DOI: 10.1056/NEJMoa2203315
Adolescent (12-15 years)		**Adolescent (12-17 years)**	
Primary series dose:	30 μg	Primary series dose	100 μg
Immunogenicity (vs. adults):	Positive (GMR= 1.76)	Immunogenicity (vs. adults):	Positive (GMR= 1.08)
Protection against infection:	Effective	Protection against infection	Effective
Common side effects:	Pain at injuction side, fatigue and headache	Common side effects:	Pain at injection side, fatigue and headache
Information source:	N Engl J Med 2021;385:239-50.	Information source:	N Engl J Med 2021;385:2241-51.

Fig. 2 Comparison of the efficacy and safety of mRNA vaccines—Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273—in children and adolescents.

μg of mRNA-1273 exhibited immunogenicity comparable to that of young adults (18-25 years old) who received 100 μg of mRNA-1273. The GMR of infants and preschool children to young adults was 1.0 and 1.3, respectively (95% CI = 0.9-1.2 and 1.1-1.5, respectively).[18] Effective protection against infection was demonstrated, with efficacy in infants estimated to be 43.7% and that of preschool children estimated to be 37.5%. The interim analysis of school-aged children with the primary series of 50 μg of mRNA-1273 revealed that the neutralizing antibody titer is comparable in children and young adults, with a GMR of 1.5 (95% CI = 1.3-1.8; Fig. 2).[19]

Moderna published the results of its clinical trial in adolescents (12-17 years old).[14,20] A cohort of 3732 participants were randomly assigned to receive either mRNA-1273 or placebo in a ratio of 2:1. The results demonstrated that the SARS-CoV-2 neutralizing antibody titers of mRNA-1273 in adolescents are comparable with those in young adults, with a GMR of 1.08 (95% CI = 0.94-1.24; Fig. 2).[21] Currently, European Medical Agencies recommend emergency approval of Moderna mRNA-1273 for children above 6 years old. For 6- to 11-year-old children, 50 μg mRNA-1273 has to be administered, whereas for children above 12 years old, 100 μg mRNA-1273 has to be administered. Two doses must be administered 4 months apart (Fig. 2).[20]

Data analyses conducted during the Omicron-dominating period demonstrated the efficacy of vaccines at preventing hospitalization among children.[21,22] Among 1475 school-aged children (5-11 years old), 397 were hospitalized due to COVID-19; among them, 87% had no prior vaccination. A total of 30% had no underlying medical condition, and 19% were admitted to the intensive care unit.[22] The analyses revealed that unvaccinated children are vulnerable to hospitalization and severe diseases requiring intensive care, regardless of underlying medical conditions.

3. SIDE EFFECTS OF MRNA VACCINATION IN CHILDREN AND ADOLESCENTS

Myocarditis and pericarditis were observed sporadically following the mass vaccination of BNT162b2 and mRNA-1273.[23] Consequently, these side effects must be monitored in vaccinated people, including children and adolescents. In the randomized trial of BNT162b2 in school-aged children (5-11 years old), the immunization group had slightly higher rates of side effects than the placebo group.[16,24] Pain at the injection site is the most common local reaction, whereas fatigue and headache are the most common systemic reactions. The severity of the side effects is low and often subsides within a couple of days. No cases of myocarditis, pericarditis, hypersensitivity, anaphylaxis, MIS-C, or death were observed in this clinical trial.[16,24]

The side effects of receiving the primary series of mRNA-1273 were mild to moderate, and they occurred more frequently after the second dose.[18-20] The most frequent side effects were fatigue, headache, and pain at the injection site. The rates of fever greater than 38°C of infants (6 months-2 years old), preschool children (2-6 years old), and adolescents (12-17 years old) were 17.0%, 14.6%, and 23.9%, respectively. No cases of death, myocarditis, pericarditis, or MIS-C were reported in young recipients of mRNA-1273 in this clinical trial.

Based on the real-world statistics from the Vaccine Adverse Event Reporting System (VAERS) of the United States, the most frequent serious side effects of children who received the primary series of BNT162b2 are fever, vomiting, and increased troponin. The most frequent serious side effects of adolescents are chest pain, increased troponin, and myocarditis. The most frequent serious side effects of 16- to 24-year-olds who received BNT162b2 as a booster are chest pain, myocarditis, nausea, fever, and increased troponin. Consequently, monitoring troponin levels, myocarditis, and pericarditis remain crucial in children and adolescents who received mRNA vaccines.

4. BALANCING THE BENEFITS AND RISKS OF IMMUNIZATION

Based on the aforementioned analysis, BNT162b2 and mRNA-1273 are both safe and effective mRNA vaccines that can stimulate the human immune system to prevent infections, thereby protecting children and adolescents from severe MIS-C/PIMS-TS

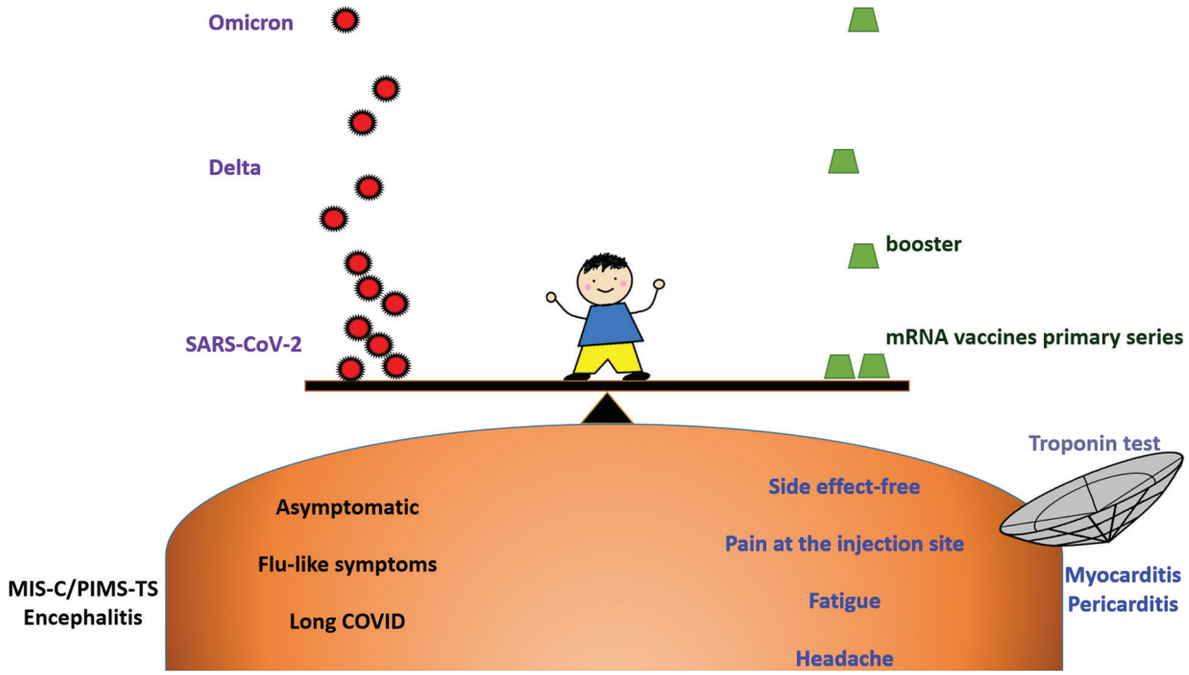

Fig. 3 Using mRNA vaccines to prevent hospitalization among children. Children may develop encephalitis or multisystem inflammatory syndrome in children (MIS-C)/pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants of concern, such as Omicron strains. The mRNA vaccines may be used to stimulate the human immune system to counteract the virus, but the rare events of myocarditis and pericarditis must be closely monitored. The troponin test may provide an early warning signal before such severe side effects.

disease (Fig. 3). Recent Omicron strains caused new waves of infection in previously exposed populations with or without mass vaccinations. These new strains are also virulent in different ways. According to recent data, the hospitalization rate of infants (0-4 years old) infected during the Omicron-predominant period is five times higher than that of the delta-predominant period.[25] Infants less than 6 months of age have the highest hospitalization rate.[25] Neurological manifestations of COVID-19 have been increasingly recognized.[27] Encephalitis also occurred in children infected during the Omicron-predominant period, which increased the mortality rate in Taiwan and Southeast Asia regions.

In contrast, the vaccination may trigger rare events of myocarditis and pericarditis that must be monitored.[23] The troponin test can provide an early warning signal for medical interventions, preventing severe side effects (Fig. 3).[27] As post-vaccination monitoring of troponin levels is not yet a standard practice, authorities must investigate the feasibility of including troponin evaluation after the immunization of mRNA vaccines.

5. FUTURE PERSPECTIVES

The symptoms of SARS-CoV-2 infection usually subside after a few days. However, some children and adults may develop post-COVID conditions, which can occur 3 months after the infection and last for months.[28] This is also known as Long COVID, which refers to the long-term sequelae of acute infections. Common long COVID conditions include systematic, reproductive/genitourinary/endocrine, cardiovascular, musculoskeletal, immunologic, pulmonary/respiratory, gastrointestinal, dermatologic, and neuropsychiatric conditions.[29] The discovery of common post COVID conditions emphasizes the importance of vaccination, which not only prevents severe conditions during the acute phase but also reduces the probability of post COVID conditions.

As the virus mutates its genome to overcome the herd immunity provided by mass vaccinations, we may require new generations of vaccines to prevent future outbreaks of the new viral strain. One approach is to develop new vaccines based on viral nucleocapsid antigens. The rationale is that if vaccination trains the immunological system to recognize both the spike and nucleocapsid antigens, then the breakthrough of immunological surveillance is less likely to occur unless a large number of mutations accumulate in the genomic regions of the spike and nucleocapsid proteins. A recent animal study demonstrated the efficacy of double vaccinations with both spike and nucleocapsid antigens.[30]

In conclusion, all age groups, including infants, children, adolescents, adults, and elders, are susceptible to SARS-CoV-2 and its variants of concern, including the most recent Omicron strains. The currently available data from clinical trials and the real world indicate that the mRNA vaccines are generally safe and effective against SARS-CoV-2. The benefits of vaccination outweigh the risks.

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