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Real Life Evidence From the Use of COVID-19 mRNA Vaccines in Pediatric Populations

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hit pediatric populations globally, accounting for approximately 13.5 million coronavirus disease 2019 (COVID-19) cases, although with lower morbidity rates compared with adults and mortality rate less than 0.02%.[1] Nevertheless, children paid their own toll to SARS-CoV-2 pandemic due to a novel clinical entity called multi-system inflammatory syndrome (MIS-C), described solely in children and adolescents.[1] Moreover, indirect effects of the pandemic attributed to interruption of education and social isolation had more profound effect on younger ages.

Several vaccines against COVID-19 have been approved for emergency use by the Food and Drug Administration (FDA) and the European Medicines Agency, aiming to protect not only high-risk individuals but also the general population from severe disease. Besides, the widespread implementation of the vaccines aimed to change the dynamics of the pandemic by decreasing transmission rates and building herd immunity.

Considering the potential benefits of universal vaccination, many countries have recommended the vaccination of all pediatric populations over the age of 5 years old, with 2 doses of mRNA vaccines; BNT162b2 (Pfizer/New York/USA-BioNTech/Mainz/Germany) and mRNA-1273 (Moderna/Massachusetts/USA). As of June 2022, the FDA revised the emergency use authorization for BNT162b2 as a 3-dose series to include children 6 months to 4 years old, with the first 2 doses administered 21 days apart and the third dose administered at least 60 days after dose 2 with a dosage of 3 μg. This vaccine was already approved for individuals 5 years of age and older (10 μg for 5–11 years old and 30 μg for ages above 12). The FDA also approved mRNA-1273 for those 6 months to 17 years old. The dose is 100 μg for ages 12 years and up, 50 μg for ages 6–11 years and 25 μg for ages 6 months to 5 years. The European Medicines Agency authorized BNT162b2 for children 5–11 years old (10 μg) and mRNA-1273 for those 6–11 years of age (50 μg). Both vaccines are also approved for children 12 years old and above (30 μg of BNT162b2 and 100 μg of mRNA-1273). All European Union countries are offering vaccination for all children 5−17 years old except Sweden where vaccination for children 5−11-year-old, is recommended only for those with risk factors. Fifteen European Union countries recommend boosters for adolescents, whereas the United States extended this recommendation to children 5 years of age. For immunocompromised adolescents, there is recommendation for 2 boosters with an interval of 4 months between the 2 doses.

Despite significant knowledge gaps on the safety against vaccine-associated rare adverse events, duration of protection offered, and most importantly, the contribution of vaccines to the control of viral transmission, approximately 20 million doses have been administered to those younger than 18 years old.[2]

Here, we review the prelicensure and real-life evidence of mRNA vaccines regarding safety and effectiveness in the prevention of infection and disease including MIS-C, and their effect on viral spread in the light of continuous emergence of novel variants of concern and discuss to what extent the implementation of mRNA vaccines has met initial expectations.

PRELISENCURE PEDIATRIC CLINICAL TRIALS

The safety and immunogenicity of the 2 mRNA vaccines, BNT162b2 and mRNA-1273, were evaluated by placebo-controlled, observer-blinded studies among adolescents who received a dual dose schedule and clinical effectiveness was assessed by bridging immunogenicity data with those obtained by adult studies.

Safety, immunogenicity and efficacy of the BNT162b2 vaccine was evaluated in 2260 adolescents 12–15 years of age who received a 2-dose schedule of 30 μg with a 21-day interval and a 2-month follow-up.[3] BNT162b2 had a favorable safety profile, with mild to moderate reactogenicity. Any adverse

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events resolved in 1–2 days; pain at the site of injection was the most frequently reported local reaction. Headache and fatigue were the main systemic reactions, mainly following the second dose. Immunogenicity of BNT162b2 among 12-to-15-year-old adolescents was noninferior to that observed in the 16-to-25-year-old population and a 100% vaccine efficacy against COVID-19 was recorded during 1-month follow-up period.

A similar study evaluated the safety, immunogenicity and efficacy of mRNA-1273 in 3732 healthy adolescents who received either a dual dose of 100 µg of the vaccine or placebo, 28 days apart.[4] The person-years of follow-up for efficacy were 513–522 in the mRNA-1273 group and 238–248 in the placebo group and 83 days for safety. The most common adverse reactions included injection-site pain, headache and fatigue. Vaccine immunogenicity met the noninferiority criterion compared with adult studies, while its efficacy against COVID-19 was >90%. Nevertheless, the study had some limitations including a lower incidence of mild COVID-19 among adolescents compared with adults that may have affected the efficacy analysis results. Besides, this study demonstrated that mRNA-1273 vaccine was approximately 40% effective in preventing asymptomatic SARS-CoV-2 infection in adolescents post second dose.

Immunogenicity of BNT162b2 was also assessed among 2268 children 5-to-11-years-old who received 2 doses of 10 µg of vaccine or placebo.[5] Immune responses were comparable to those recorded among vaccine recipients 16-to-25-year-olds who had received dual immunization with 30-µg vaccines. The median follow-up for vaccine efficacy against COVID-19 was 2.3 months. The BNT162b2 vaccine was safe, immunogenic and efficacious. This schedule showed a similar safety profile with that observed in adolescents and adults but with a higher incidence of injection-site irritation and lower incidence of systemic events, that is, fever and chills. There were no reported events of MIS-C, myocarditis or pericarditis. A robust virus-neutralizing response was observed which was comparable to that among recipients 16-to-25-years-old with a 90.7% vaccine efficacy against COVID-19. Notably, among children who developed COVID-19, symptoms were milder in vaccine recipients.

A clinical trial was also conducted to assess the efficacy of mRNA-1273 vaccine schedule (2 doses of 50 µg with a 28-day interval) in 4016 children 6–11 years of age. The study took place during the era of B1.617.2 (Delta) variant and vaccine efficacy against COVID-19, assessed 14 days or more following the second dose, was 88.0%.[6]

In conclusion, phase 3 studies despite the caveats of the small numbers of young participants and the very short follow-up period showed a favorable safety profile and met the noninferiority criterion, paving the way toward the authorization for emergency use of mRNA vaccines in pediatric populations ≥5 years old.

REAL-LIFE EVIDENCE FOR MRNA VACCINE SAFETY AND EFFECTIVENESS AGAINST SARS-COV2 INFECTION AND DISEASE

Soon after the introduction of massive vaccination campaigns in adolescents, early safety signals for vaccine-associated myocarditis were detected. The accumulation of cases among adolescents and young adults was up to 5 times higher than the prepandemic incidence of all-cause acute myocarditis in the general population.[7] Following these early findings, active surveillance programs confirmed an elevated risk for myocarditis in mRNA COVID-19 vaccine recipients, particularly among males 12–29 years of age, with an incidence range 3.9–4.7 per 100,000 second vaccine doses.[7] Fortuitously, similar safety signals have not been detected in children receiving the pediatric dose of BNT162b2.

Pediatric use of mRNA vaccines was generated shortly before the emergence of the Delta variant. Several studies conducted in the second half of 2021 showed an effectiveness above 90% 1 month post dual vaccination that decreased up to 67% 4–5 months thereafter although effectiveness against hospital admissions remained high up to 6 months.[8] Remarkably, vaccine effectiveness (VE) against ICU admission was 98% while all deaths occurred in unvaccinated adolescents.[9] Importantly, during the dominance of Delta variant, 2 doses of BNT162b2 reduced the likelihood of MIS-C by 91% in adolescents.[10]

Considering that neutralizing antibodies correlate with protection against mucosal infection, the observed waning of antibody titers soon after primary immunization could explain the progressively higher rates of breakthrough disease among fully vaccinated subjects. In contrast, protection against hospitalization and severe COVID-19 is mediated by B and T cellular immunity which has been shown to have longer duration than humoral response.[11] The important role of cellular immunity for protection against severe COVID-19 is further supported by the fact that the interval between onset of the disease and clinical deterioration is long enough to allow B and T memory cells pass from a dormant state to activation and ultimately lead to the resolution of infection.

MRNA VE AGAINST BA2.12.1 (OMICRON) VARIANT

Omicron variant displaying a highly mutated S protein spread globally in the last trimester of 2021 and its dominance was associated with increased incidence of breakthrough cases raising concerns about VE against the new variant.

Serum neutralizing activity against Omicron evaluated in children and adolescents was significantly reduced compared with the ancestral strains, implying further reduction of VE against the novel variant.[12] This hypothesis was confirmed by epidemiological studies from the United States during the Omicron wave, where VE against symptomatic infection for children 5–11 years of age was estimated at 60.1% 2–4 weeks and 28.9% 2 months after the second dose. Among adolescents 12–15 years old, the estimated VE was 59.5% and 16.6%, respectively.[13]

Based on adult studies showing that booster doses improve protection against Omicron by augmenting neutralizing antibody concentrations, Advisory Committee on Immunization Practices expanded the eligibility for a third dose to everyone over 5 years old. However, the merit of a booster in healthy children requires monitoring of the duration of antibodies stimulated by the additional dose. In contrast, enhancement of protection from severe COVID induced by a booster could be very important since Omicron is very contagious and the number of children who will become seriously ill will increase. If there is sufficient evidence that additional doses enhance protection against severe COVID through enrichment of B and T cellular memory this will be in favor for recommending boosters in children at risk. From the public health point of view, the effect of a booster could promote a barrier of immunity against viral spread since there is evidence for reduced transmission by booster-vaccinated individuals compared with dual-vaccinated individuals.[14] However, this effect could be transient if there is a rapid immunity waning following booster.

CONCLUSIONS

Real-life evidence confirmed that mRNA vaccines protect pediatric populations from severe COVID-19 and possibly MIS-C but failed to prevent infection and viral transmission due to the rapid waning of humoral immunity against continuously emerging new variants. The elucidation of the immunological characteristics of recall responses is required to access the potential benefits of boosters before universal recommendations are issued. Most importantly, if continued monitoring of disease severity is reassuring that novel variants cause mild disease, it will be essential to move towards the perception that COVID-19 vaccines should be used for protection of children at risk against an endemic virus rather than utilized to interrupt the pandemic.

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