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

Theano Lagouisi, MD, PhD,**† Panagiota Tsagkli, MD,*, and Vana Spoulou, MD, MPhil, PhD**†

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
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.5 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 immunogenicity and efficacy of mRNA-1273 were comparable to those recorded among children who developed COVID-19, symptoms were milder in vaccine recipients and severe COVID-19 is mediated by B and T cellular immunity which has been shown to 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.6

Concluding 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.6

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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