Protecting Children Against Omicron
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Prior to emergence of the Omicron SARS-CoV-2 variant, and at the time of the issuance of the Emergency Use Authorization (EUA) for the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, the efficacy of 2 doses of the 30-μg vaccine in adolescents 12 to 15 years of age and of the 10-μg dose in children 5 to 11 years of age were 100% (95% CI, 75.3%-100%) and 90.7% (95% CI, 67.7%-98.3%), respectively.1,2 However, 2 studies published in this issue of JAMA demonstrate that the estimated vaccine effectiveness among children and adolescents with Omicron is considerably lower than in the initial studies, and protection wanes rapidly, especially with the novel SARS-CoV-2 variants.3,4

The study by Fleming-Dutra et al3 is a test-negative case-control analysis conducted from December 2021 to February 2022 using data from a large chain of pharmacy-based, drive-through SARS-CoV-2 testing sites across the US called the Increasing Community Access to Testing platform.5 A total of 30,999 test-positive cases and 43,209 test-negative controls among children 5 to 11 years of age and 22,273 cases and 25,471 controls among adolescents 12 to 15 years of age were included in the study. At 2 to 4 weeks after vaccine dose 2, estimated vaccine effectiveness was identical for the 2 age groups: 60.1% (95% CI, 54.7%-64.8%) for children and 59.5% (95% CI, 44.3%-70.6%) for adolescents. However, by 2 months after dose 2, the estimated vaccine effectiveness had declined in both groups to 28.9% (95% CI, 24.5%-33.1%) in children and 16.6% (95% CI, 8.1%-24.3%) in adolescents. Reassuringly, for adolescents, a booster dose, measured 2 to 6.5 weeks after receipt, was associated with increased estimated vaccine effectiveness of 71.1% (95% CI, 65.5%-75.7%). Due to the short duration of follow-up among booster dose recipients, the authors were unable to assess waning of the booster dose.

Similarly, the study by Dorabawila et al4 assessed the risk of SARS-CoV-2 infection and hospitalization in vaccinated and unvaccinated children and adolescents using 4 New York statewide databases from November 29, 2021, to January 30, 2022. The study compared 365,502 fully vaccinated children aged 5 through 11 years and 852,384 fully vaccinated adolescents aged 12 through 17 years with 997,554 unvaccinated children and 2,081,455 unvaccinated adolescents. They evaluated rates of COVID-19, defined as positive nucleic acid amplification test or antigen results, and hospitalizations. Incidence rate ratios (IRRs) were calculated comparing unvaccinated vs vaccinated rates (therefore, higher IRR indicates greater risk for disease in unvaccinated persons). In children 5 to 11 years, the IRR for unvaccinated vs fully vaccinated individuals was 3.1 (95% CI, 2.7-3.6) early in the Omicron surge (week of December 13) and declined to 1.1 (95% CI, 1.1-1.2) by January 24, presumably due to waning of immunity after vaccination. A similar pattern was seen among adolescents, with an IRR of 6.7 (95% CI, 6.2-7.2) the week of November 29 and 2.0 (95% CI, 1.9-2.2) the week of January 24. This study did not consider whether adolescents had received a booster dose of vaccine.

In the New York study, hospitalizations were higher among unvaccinated than fully vaccinated individuals by the week of January 24, with IRRs of 1.9 (95% CI, 0.9-4.8) for 5- to 11-year-olds and 3.7 (95% CI, 2.1-6.5) for 12- to 17-year-olds. These data are encouraging and comparable to data from adults that demonstrated estimated VE against hospital admissions in the Omicron era of 65% (95% CI, 51%-75%) after 2 doses of vaccine and 86% (95% CI, 77%-91%) after 3 doses.6 It is critical to consider severe outcomes such as hospitalizations or deaths. A recent study noted that rates of hospitalization among children aged 5 to 11 years were 50% lower for vaccinated children compared with unvaccinated children during the Omicron wave.7

Have the proper doses of vaccine been selected in children, and might those doses have an effect on these results? During the pivotal clinical trials submitted to the US Food and Drug Administration (FDA) for the EUA, the immune responses observed in adolescents at the 30-μg dose were nearly 2-fold higher than the immune responses observed in adults 16 to 32 years of age. Receipt of the 10-μg dose in children 5 to 11 years old was comparable to the immune responses in adults, but less than the immune responses to the 30-μg dose for adolescents.8 Effectiveness studies during the Delta wave demonstrated high vaccine effectiveness for adolescents.9 After the emergence of the Omicron variant, vaccine effectiveness in adolescents declined substantially and waned rapidly, but receipt of booster doses was associated with improved effectiveness. Timing of vaccine rollout for children ages 5 to 11 years was complicated by the emergence of the Omicron variant, but effectiveness appears to be comparable to that of adolescents and also wanes.

Comparing data from both pediatric age groups, similar results were found in adults using the same Increasing Community Access to Testing platform, with estimated vaccine effectiveness at 2 to 4 weeks after receipt of a second dose of vaccine of approximately 35% for adults and 60% in children and adolescents, and estimated effectiveness at 2 months of 15% for adults, 16% for adolescents, and 29% for children.10 A study published in March 2022 measured estimated vaccine effectiveness at 14 to 82 days after vaccination in children and adolescents and demonstrated similar effectiveness for children (31%; 95% CI, 9%-48%), but...
higher vaccine effectiveness for adolescents (59%; 95% CI, 22%-79%).

The study by Dorabawila et al4 also suggests that waning may be worse for children than for adolescents and postulated that the dose of 10 μg for children aged 5 to 11 years might be too small. However, this was not observed in the study by Fleming-Dutra et al.3 Further studies of the mRNA-1273 vaccine (Moderna) should provide additional details in this regard. Since all mRNA vaccines are associated with increased local and systemic adverse events, including fever, safety is an important concern because tolerance for fever and other systemic adverse events after vaccination in children will likely be less than in adults. There is a delicate balance between the vaccine dose needed to generate adequate immunity with a minimum of adverse effects. Some studies have shown higher rates of myocarditis in young men with mRNA-1273 vaccine, but whether this is due to larger doses of mRNA in this vaccine has not been determined.12,13

Also, while disease from SARS-CoV-2 occurs in children, with seroprevalence studies estimating that 75% of US children have had SARS-CoV-2 infection, the severity of illness tends to be less than in adults.14 An acceptable balance between safety and effectiveness of pediatric vaccines is paramount, particularly because many children will likely have pre-existing natural immunity.

Both studies have limitations. The study by Fleming-Dutra et al13 relied on a single pharmacy chain using a testing platform that depended on self-reported questionnaires for both vaccine status and clinical symptoms, and neither of these were verified through medical record review. Similarly, the study by Dorabawila et al4 linked multiple New York state databases that inherently may contain missing or incorrect data. Auditing of these databases was not performed. Given the timeline of issuance of the vaccine EUA for children 5 to 11 years and the booster for adolescents, and the emergence of the Omicron variant wave in the US shortly thereafter, both studies only included short follow-up periods after the vaccine recommendation for children 5 to 11 years and after the booster recommendation for adolescents.

Although these 2 studies found relatively short time periods to waning of vaccine effectiveness, hope is on the horizon. As SARS-CoV-2 infections increase in children, hybrid immunity, a combination of immunity induced by vaccine and natural infection, will likely provide additional protection against future infections.15,16 Moderna recently announced preliminary results from a trial of its bivalent booster vaccine (mRNA-1273.211), with higher neutralizing antibody responses against the ancestral SARS-CoV-2, Beta, and Omicron variants 180 days after the booster dose.17 Also promising is that the study by Fleming-Dutra and colleagues3 demonstrated an increase in vaccine effectiveness after a booster dose for adolescents. Pfizer and BioNTech recently submitted an application to the FDA for EUA of a booster dose of COVID-19 vaccine for children aged 5 to 11 years,18 although the ideal timing of booster doses for children and adolescents remains unknown. In addition, Moderna reportedly will be submitting its entire pediatric database on children to as young as 6 months of age to the FDA.19 These data will help address questions of both immunogenicity and safety.

The encouraging message should be that although vaccine protection for children and adolescents was lower in the Omicron era than with previous variants and that such protection wanes rapidly, vaccine effectiveness against hospitalization remains high and booster doses confer additional protection.

REFERENCES


