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Coronavirus Disease 2019 Vaccine Dosage in Children, Adolescents, and Young Adults: Is Less More?

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The lower efficacy of the COVID-19 mRNA vaccines in 5–11 year old children was unexpected. Neutralizing antibody titers elicited by the vaccines in children, adolescents, and young adults suggest that the lower efficacy is not due to the lower dosage. Confirming the efficacy of these vaccines in children, determining if mRNA vaccination strategies are less effective in younger children, as well as optimizing the dosage, dosing intervals, and number of doses needed in children, adolescents, and young adults are critical to improve vaccination strategies for these populations going forward.

Keywords. COVID-19; COVID-19 vaccination; Dosage; Dosing intervals; Boosters; Myocarditis; Covid-19 vaccination associated myocarditis; children; adolescents; young adults.

The recently reported lower efficacy of the BNT162b2 coronavirus disease 2019 (COVID-19) vaccine in children 5–11 years of age was unexpected, because the messenger RNA (mRNA) vaccines have been remarkably effective against the COVID-19 pandemic in other age groups. In addition to preventing multi-system inflammatory syndrome in children [1], severe disease, hospitalization, and death [2], these vaccines have reduced transmission perhaps to a greater degree than expected for a respiratory pathogen. Despite the reduced efficacy of the current mRNA vaccines against the Omicron variant, the vaccines still offer considerable protection with greater

preservation of protection against severe disease than infection [3]. Given that vaccine efficacy appears to be lower in children aged 5–11 years than in adolescents and adults in the most recent testing [4], understanding why is critical for developing appropriate vaccination strategies for this population going forward.

Prior to the appearance of the Omicron variant in the United States, BNT162b2 vaccine efficacy (VE) in 5- to 11-year-olds against infection was 91% during the 2-month follow-up period in a clinical trial (NCT04816643) [5]. Approval of the vaccine on 29 October 2021 led to children being fully vaccinated the week of 13 December 2021, coinciding with the arrival of the Omicron variant. However, preprint data from the New York State Department of Health show that VE in 5- to 11-year-olds for cases declined from 68% to 12% and for hospitalization from 100% to 48% [4] during the week of 13 December 2021 vs 24 January 2022. In contrast, VE in 12- to 17-year-olds decreased from 66% to 51% for cases and 85% to 73% for hospitalization. The time period studied coincides with the rise in Omicron infections in New York, from 19% the week of 13 December 2021 to >99% the week of 24 January 2022. The median

time since vaccination was 51 days in 5- to 11-year-olds vs 211 days in 12- to 17-year-olds. In an analysis of newly vaccinated children in New York, removing the confounding factor of time since vaccination, the incidence rate ratio against infection was 1.1 for 5- to 11-year-olds vs 2.3 for 12- to 17-year-olds at 28–34 days postvaccination. Data from the Centers for Disease Control and Prevention (CDC) show less of a difference by age when restricting analysis to the Omicron period, with VE of 51% in 5- to 11-year-olds (14–67 days postvaccination) vs 45% and 34% in 12- to 15-year-olds and 16- to 17-year-olds (14–149 days postvaccination), respectively [3]. However, 2-dose VE against COVID-19-associated hospitalization for ages 5–11, 12–15, and 16–17 years remained 73%–94% during the combined Omicron- and Delta-predominant periods. The data available are concerning for a decreased efficacy of BNT162b2 in younger children, but more study is needed to confirm these findings.

One hypothesis is that the lower efficacy in 5- to 11-year-olds is a result of the lower dosage, 10 µg of BNT162b2 administered 21 days apart [4], although neutralizing antibody data suggest that this is not the case. Data presented at the United States Food

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and Drug Administration (FDA) and CDC Advisory Committee Meetings, the Vaccines and Related Biological Products Advisory Committee meeting on 26 October 2021 and the Advisory Committee on Immunization Practices meeting on 2 November 2021, suggest that children, adolescents, and young adults may achieve a maximum humoral response [6] with the current doses of the BNT162b2 vaccine. Two 30- μ g doses of BNT162b2 given 21 days apart elicited severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) geometric mean 50% neutralization titers of 1239.5 and 1146.5 in 12- to 15-year-olds and 16- to 25-year-olds, respectively, 1 month following the second dose (Table 1) [5, 7]. Children aged 5–11 years achieved essentially the same titers, 1197.6, 1 month following two 10- μ g doses, also given 21 days apart. When further evaluated by age subgroup, children aged 5–6, 7–8, and 9–11 years all achieved essentially the same titers of 1164.1, 1236.1, and 1191.5 [8]. These titers are >3 times greater than the peak titers achieved by adults 7 days after the second dose, demonstrating the robust humoral immune responses of children and young adults [9]. Thus, it is possible that doses lower than the 10- μ g dose tested in children aged 5–11 years may still achieve high neutralizing antibody titers. Trial arms of 10- μ g doses of BNT162b2 for ages 12 to <18 years have been added to the ongoing clinical trial (NCT04816643). Since children, adolescents, and young adults achieve significantly higher titers than adults with the current dosing, other reasons for the reduced efficacy need to be considered.

There is reduced efficacy of the COVID-19 vaccines in all populations with the Omicron variant [3], and this likely accounts for much of the reduced efficacy in children aged 5–11 years. Other potential mechanisms include the shorter interval between vaccination and infection in the younger cohort, differences in circulating variants in the age cohorts, prior exposure to SARS-CoV-2, and not yet identified reduced efficacy of mRNA vaccines in younger populations. B- and T-cell responses continue to mature for many months following vaccination as does protection from severe disease [2, 10]; therefore, the shorter duration postvaccination for the 5- to 11-year-olds of 51 days vs 211 days for 12- to 17-year-olds in New York may have contributed to the reduced efficacy against hospitalization observed in the younger cohort in New York. Additionally, as the Omicron prevalence increased dramatically during the study period, there may have been differences between the variants circulating in elementary vs middle and high schools. Moreover, seroprevalence for SARS-CoV-2 in the United States is high and in June 2021, 5- to 11-year-olds had the highest prevalence at 42% [11], prior to the Delta variant surge. Prior infection is associated with a reduced likelihood of severe outcomes [2], and how prior exposure to SARS-CoV-2 may have altered the immune responses in the population is unknown. Finally, mRNA vaccination is a new vaccination strategy, inducing both B- and T-cell responses, and appears promising for making improved

vaccines against multiple pathogens, some already in development. However, the initial trial of BNT162b2 in 2- to 5-year-olds was reportedly not effective as a 2-dose series and the trial has been modified to test a 3-dose series. It may be that factors such as prior exposure to seasonal coronaviruses play a role in a characteristically different immune response in older individuals that is not elicited in younger children without or with less seasonal coronavirus exposure. Determining the mechanism(s) of reduced efficacy of BNT162b2 in children is critical to optimizing coronavirus vaccination in children.

One step that has been taken to improve immunogenicity in people aged 12–39 years is to alter the dosing intervals. Emerging data demonstrated that increasing the interval between the first and second dose of mRNA vaccines improves immunogenicity [12, 13] while lowering adverse events [14].

The ACIP reviewed the emerging data on extended dosing intervals 4 February 2022 and issued the guidance that “an 8-week interval may be optimal for some people ages 12 years and older, especially for males ages 12–39 years” [15]. Formal testing of the lower 10- μ g dose, 2 doses 8 weeks apart for ages 12 to <18 years has been added to the ongoing clinical trial of BNT162b2. Trials evaluating longer dosing intervals in children <12 years of age are indicated to determine if this strategy may improve the immunogenicity and efficacy of mRNA vaccines in younger children.

In addition to lower efficacy, children, adolescents, and young adults experience more adverse events with the current dosing of the mRNA vaccines. While the etiology of COVID-19 vaccination-associated myocarditis is unknown [16], the frequency of this rare event is more common following vaccination with mRNA-1273 (100 μ g per dose) than BNT162b2 (30 μ g per dose) [17], supporting the possibility that the myocarditis may be related to dosage (although a contribution of differences in

Table 1. Neutralizing Antibody Titers by Age

	Age Group, Years					
	All 5–11	5–6	7–8	9–11	12–15	16–25
No.	264	59	74	131	190	253
GMT	1197.6	1164.1	1236.1	1191.5	1239.5	1146.5 ^a
BNT162b2 doses, μg	10	10	10	10	30	30

Geometric mean severe acute respiratory syndrome coronavirus 2 neutralization titers are shown for serum specimens obtained at approximately 1 month following dose 2.

Abbreviation: GMT, geometric mean 50% neutralization titer.

^aTiters for 253 participants 16–25 years of age used for the immunogenicity comparison [5]. The GMT initially reported on 170 participants 16–25 years of age was 705.1 [4].

formulations cannot be excluded). COVID-19 vaccination-associated myocarditis is also more common following the second dose, particularly with dosing intervals of ≤ 28 days [14], and extending the interval to 8 weeks between the first and second vaccine doses decreases the frequency of myocarditis. While initial data suggested that COVID-19 vaccination-associated myocarditis was likely related to dosage and dose number as noted in the FDA Brief for the 26 October 2021 meeting, the decreased incidence of myocarditis following the third or booster dose, combined with the decreased incidence with longer dosing intervals, suggests that interval spacing, rather than the number of doses, may be the key to reducing myocarditis. This is reassuring as additional doses may be required to maintain immunity or cope with emerging variants.

With the robust immune responses and less severe disease in children, adolescents, and young adults, determining if, for those previously infected, when, and how many doses of the mRNA vaccines will be indicated will require ongoing surveillance both of severe disease by age and VE against circulating variants. Furthermore, with the decreased VE in younger children with current doses and/or dosing intervals, careful study of the immune responses and effectiveness of the immune responses elicited by mRNA vaccination are needed. Finally, whether mRNA vs other vaccine strategies will offer the best protection for

children needs to be urgently studied. The time to reassess and optimize COVID-19 vaccination dosages, dosing intervals, and vaccination strategies for children, adolescents, and young adults is now.

Notes

Patient consent. This study did not include factors necessitating patient consent.

Potential conflicts of interest. Both authors: No reported conflicts of interest.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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