EDITORIAL

Booster Vaccination to Reduce SARS-CoV-2 Transmission and Infection

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The vaccines to prevent COVID-19 are remarkable for their safety, efficacy, and pace of development. Initial enthusiasm that followed the release of the preliminary results that formed the basis for distribution of the vaccines under Emergency Use Authorization (EUA) has been dampened by the inequity in access to the vaccines across the globe, vaccine hesitancy, and emergence of variants that partly evade vaccine-induced antibodies. These factors are related, and all 3 contribute to ongoing morbidity, mortality, and societal disruption related to SARS-CoV-2 in much of the world. Incomplete coverage with the vaccine leads to infection of immunocompromised persons who are likely to harbor the virus for prolonged periods (or chronically), allowing for mutations that are then selected for immune evasion and better fitness to the human host.[1] The new variants are sufficiently altered structurally such that neither prior SARS-CoV-2 infection or even much higher levels of vaccine-induced antibodies are protective.

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In this issue of *JAMA*, Spitzer and colleagues assess the effect of a booster dose of the mRNA vaccine BNT162b2 (Pfizer-BioNTech) on acquisition of SARS-CoV-2 infection among health care workers in a tertiary medical center in Tel Aviv, Israel.[2] Israel achieved high vaccination coverage of most health care workers, who were prioritized for immunization receiving both doses of the BNT162b2 vaccine by the end of January 2021. As such, when the Delta variant arose in June 2021, most health care workers had received their second dose of vaccine about 6 months earlier, and emerging data showed that the antibody titers in response to vaccination had waned.

Although Spitzer et al initially aimed to provide a booster vaccine dose only for persons with antibody titers less than the median, universal boosting was recommended by health authorities. The investigators enrolled a cohort of health care workers who had completed a 2-dose vaccination series of BNT162b2 and subsequently received a booster dose of the vaccine. Infections in the cohort were monitored by SARS-CoV-2 polymerase chain reaction (PCR) tests every 2 weeks regardless of symptoms. Anti–SARS-CoV-2 spike protein receptor-binding domain (anti-S1-RBD) was measured at baseline and 1 month after the booster.

The study cohort included 1928 health workers, and 1650 (85.6%) received a booster dose during the study. The median overall follow-up was 39 days, and the median follow-up of boosted persons, beginning 7 or more days after the receipt of the booster vaccination, was 26 days. Overall, 3552 PCR tests were obtained with 51% before and 49% after boosting. A total of 44 persons tested positive for SARS-CoV-2 during follow-up, including 31 who had symptoms of COVID-19. The incidence of SARS-CoV-2 was 116 per 100 000 person-days prior to booster vaccination and 12.8 per 100 000 after booster vaccination, for an estimated relative reduction of 93% (hazard ratio, 0.07 [95% CI, 0.02-0.2]).

The booster vaccine doses reduced equally the risk of symptomatic and asymptomatic infection. In a post hoc analysis, the authors noted an association between lower result on commercial anti–S1-RBD IgG titer at baseline and higher risk of infection. In a multivariable Cox regression, low baseline anti–S1-RBD IgG, earlier receipt of the initial vaccine, higher number of PCR tests, and having more children also were significantly associated with SARS-CoV-2 infection.

These findings clearly indicate that providing another vaccine dose following a 2-dose initial series is associated with both improvement in the immunological response to the vaccine antigen and reduction in the risk of symptomatic and asymptomatic infection. The short follow-up and the relatively young and healthy population in the study limit the generalizability of the results. However, these observations have been replicated in other studies,[3] and together, resulted in a strong recommendation from the US Centers for Disease Control and Prevention for universal third vaccine dose 6 months after the initial 2 vaccine doses, preferably with an mRNA vaccine as a safer and more effective product compared with the adenovirus-vectored vaccine.[4]

The Food and Drug Administration has recently taken the step to recommend a third dose of mRNA BNT162b2 for adolescents aged 12 to 15 years and for children aged 5 to 11 years who are immunocompromised. The third dose is recommended to be given at least 5 months after the second dose.

An important consideration is whether this vaccination is a booster dose or a third dose. The interval between vaccine doses is important in terms of resulting in durable immunity, with a longer interval more likely to establish a durable response. Both mRNA vaccines have been administered as 2-dose regimens 3 to 4 weeks apart. This may be too short to induce long-term immune memory. However, considering the rapid pace and persistence of the pandemic, it was the right thing to do to get an answer as soon as possible and roll out the vaccines. It may be that a 0, 6 months schedule would be just as good as 0, 1, and 6 months, although the pressing nature of the pandemic did not allow the luxury of comparing vaccine dose schedules, as has occurred with some other vaccines, such as human papillomavirus.[5] Thus, this is a theoretical issue regarding vaccine-induced immunity.

While careful immunological studies have established that the 2-dose vaccine regimens (for SARS-CoV-2 and previously for Middle East respiratory syndrome) result in long-lasting

memory B cells as well as bone marrow plasma cells,[6,7] indicating that the protection should be long-lasting, vaccinology remains predominantly an empirical science, with clinical trials and community surveillance supplanting laboratory observations. Immune correlates of protections have not been established for SARS-CoV-2 vaccines, although initial observations based on the mRNA-1273 (Moderna) vaccine suggest that neutralizing antibodies can serve as a measure of protection and that approximately 68% of protection can be attributed to the antibody level.[8] However, this science is still in its infancy, and individual antibody levels, as measured by myriad commercial assays, do not offer a useful indicator as to whether a booster dose is needed; their use outside of clinical research should be discouraged.

Vaccinated persons who develop breakthrough infection are much less likely to be hospitalized or to die from COVID-19,[9] reflecting multiple aspects of adaptive immunity induced by immunization. As risk of severe COVID-19 is largely confined to older and immunocompromised persons, these outcomes are rare in younger, healthy populations. However, when booster vaccine doses reduce the risk of infection (as shown in the study by Spitzer et al[2]), then these boosters will also prevent transmission. As with all infectious diseases, the pathogen is required to cause the disease, and SARS-CoV-2 infection is the sine qua non for COVID-19. Prevention of infection results in prevention of potential onward transmission from all individuals who are spared the infection. Furthermore, the viral load in individuals who are vaccinated and have a breakthrough SARS-CoV-2 infection is substantially lower than the viral load in unvaccinated people who develop infection. This was definitely true for the original SARS-CoV-2 strain[10]; for the Delta variant, it is less clear that on the first few days the viral load is lower, but certainly the viral load declines more rapidly in vaccinated individuals than in unvaccinated persons.[11,12] Viral load can be a proxy for infectiousness, as established for some infections (such as HIV), and less so for others. Thus, with SARS-CoV-2 variants of concern, booster vaccine doses could help reduce the risk of disease transmission. This is especially critical during the current Omicron surge, as this variant appears to cause infection even in persons with vaccine-induced immunity. However, higher levels of neutralizing antibody following booster vaccination provide additional protection against the Omicron variant.

Will booster vaccine doses continue to be needed at regular intervals? The additional dose of mRNA vaccines that is currently being distributed may result in more robust and long-lasting immune responses, obviating the need for further boosters. In addition, development of novel vaccines that provide protection against coronavirus proteins that are less mutable could result in broader immunity.[13] The evolution and epidemiology of SARS-CoV-2 have not been predictable, and being prepared to respond, such as with effective vaccines and booster doses of vaccine as needed as well as with nonvaccine mitigation strategies, remains critically important to help reduce SARS-CoV-2 transmission, and the morbidity and mortality from COVID-19.

ARTICLE INFORMATION

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Published Online: January 10, 2022. doi:10.1001/jama.2021.23726

Conflict of Interest Disclosures: Dr Wald reports receiving funding from the National Institutes of Health (NIH), including as a coinvestigator in the Novavax and Gritstone COVID vaccine trials. She also reports receiving financial support through her institution from Sanofi and GSK for research unrelated to COVID-19.

Funding/Support: Supported by the National Institute for Allergy and Infectious Diseases of the NIH, under award UM1AI148573.

Role of the Funder/Sponsor: The NIH had no role in the preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

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