EDITORIAL

Covid-19 Boosters — Where from Here?

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On December 10, 2020, Pfizer presented results from a 36,000-person, two-dose, prospective, placebo-controlled trial of its Covid-19 messenger RNA (mRNA) vaccine, BNT162b2, to the Food and Drug Administration (FDA).[1] The vaccine was 95% effective at preventing severe illness in all age groups, independent of coexisting conditions or racial or ethnic background. A remarkable result. Six months later, studies showed that protection against severe disease was holding up.[2] The results of these epidemiologic studies were consistent with those of immunologic studies showing long-lived, high frequencies of Covid-19–specific memory B and T cells, which mediate protection against severe disease.[3]

In September 2021, 10 months after the BNT162b2 vaccine had become available, Israeli researchers found that protection against severe illness in people 60 years of age or older was enhanced by a third dose.[4] In response, the Centers for Disease Control and Prevention (CDC) recommended that people 65 years of age or older should receive three doses of an mRNA vaccine.

In a study now reported in the *Journal*,[5] Israeli researchers found that in a study population with a median age of 72 years, protection against severe disease was further enhanced by a fourth dose of mRNA vaccine during the wave of infections caused by the B.1.1.529 (omicron) variant of SARS-CoV-2. These findings were considered by the FDA and CDC in their decision-making process regarding the use of an additional booster dose of mRNA vaccine for people 50 years of age or older.

What about booster dosing for persons who are younger? One year after the BNT162b2 vaccine became available, studies in the United States showed that a third dose of vaccine also enhanced protection against severe disease for people as young as 18 years of age.[6,7] Unfortunately, these studies did not stratify patients according to whether they had coexisting conditions. Therefore, it was unclear who among these younger age groups most benefited from an additional dose. Nonetheless, the CDC later recommended that everyone 12 years of age or older should receive three doses of BNT162b2, regardless of whether risk factors were present. This universal booster recommendation led some summer camps, high schools, universities, hospitals, and businesses to require three doses of mRNA vaccine. In February 2022, in a study that did not support the booster recommendation for children, CDC researchers found that two doses of BNT162b2 induced long-lived protection against serious illness in children 12 to 18 years of age.[8]

In addition to protection against severe disease, the initial phase 3 trial of BNT162b2 — which was performed over a period of several months — also showed 95% protection against mild illness.[1] Unlike protection against severe illness, however, protection against mild illness, which is mediated by high titers of virus-specific neutralizing antibodies at the time of exposure, declined after 6 months, as would have been expected.[2] In response, studies by Pfizer were published in which a booster dose was shown to restore protection against mild illness[9]; unfortunately, this protection did not persist for more than a few months.[6] Short-lived protection against mild illness will limit the ability of booster dosing to lessen transmission.

People are now confused about what it means to be fully vaccinated. It is easy to understand

how this could happen. Arguably, the most disappointing error surrounding the use of Covid-19 vaccines was the labeling of mild illnesses or asymptomatic infections after vaccination as "breakthroughs." As is true for all mucosal vaccines, the goal is to protect against serious illness — to keep people out of the hospital, intensive care unit, and morgue. The term "breakthrough," which implies failure, created unrealistic expectations and led to the adoption of a zero-tolerance strategy for this virus. If we are to move from pandemic to endemic, at some point we are going to have to accept that vaccination or natural infection or a combination of the two will not offer long-term protection against mild illness.

In addition, because boosters are not risk-free, we need to clarify which groups most benefit. For example, boys and men between 16 and 29 years of age are at increased risk for myocarditis caused by mRNA vaccines.[10] And all age groups are at risk for the theoretical problem of an "original antigenic sin" — a decreased ability to respond to a new immunogen because the immune system has locked onto the original immunogen. An example of this phenomenon can be found in a study of nonhuman primates showing that boosting with an omicron-specific variant did not result in higher titers of omicron-specific neutralizing antibodies than did boosting with the ancestral strain.[11] This potential problem could limit our ability to respond to a new variant.

It is now incumbent on the CDC to determine who most benefits from booster dosing and to educate the public about the limits of mucosal vaccines. Otherwise, a zero-tolerance strategy for mild or asymptomatic infection, which can be implemented only with frequent booster doses, will continue to mislead the public about what Covid-19 vaccines can and cannot do.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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