THE BEST OF THE WEEK (30 gen – 05 feb 2023)

Covid Vaccines — Playing the Long Game
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Bivalent Covid-19 Vaccines — A Cautionary Tale
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Abstract
In November 2019, a bat coronavirus made its debut in humans in Wuhan, China. Two months later, the original strain of SARS-CoV-2, called the Wuhan-1 or ancestral strain, was isolated and sequenced. It was now possible to make a vaccine. All the vaccines, including the mRNA vaccines made by Pfizer–BioNTech and Moderna, the viral vector vaccines made by Johnson & Johnson–Janssen and AstraZeneca, and the purified protein vaccine made by Novavax, were designed to prevent disease caused by the ancestral strain.
As the virus evolved, the ancestral strain was soon replaced by a series of variants. In the United States in 2020 and 2021, such variants included D614G, alpha, and delta, each of which was more contagious than the previous variant. In a U.S. study involving 8100 immunocompetent adults conducted between March and December 2021, two doses of mRNA vaccines — which were authorized by the Food and Drug Administration (FDA) and recommended by the Centers for Disease Control and Prevention (CDC) in December 2020 — continued to protect against hospitalization caused by these three virus variants.1 For vaccines against SARS-CoV-2, a mucosal infection with a short incubation period, protection from severe disease is the only reasonable and attainable goal.
In November 2021, a new variant, called omicron (subvariant BA.1), was detected in southern Africa. The omicron variant contained an alarming number of mutations (more than 30) in the spike protein, including at least 15 mutations in the receptor-binding domain, the primary target of neutralizing antibodies. Researchers found that serum samples obtained from people who were vaccinated against or previously infected with SARS-CoV-2 exhibited substantially lower neutralizing activity against BA.1 than against the ancestral strain and other strains. Furthermore, many commercially available monoclonal-antibody preparations were ineffective against this variant. Although it was reassuring that early data from southern Africa showed that previous infection or vaccination protected against severe disease caused by omicron,2 public health officials worried that the BA.1 strain posed a serious threat to the effectiveness of existing Covid-19 vaccines and therapies.
Given the ability to use mRNA technology to respond quickly to variant strains, bivalent vaccines were created to counter this new threat. In January and February 2022, Pfizer–BioNTech produced a bivalent vaccine containing 15 µg of mRNA directed against the ancestral strain of SARS-CoV-2 and 15 µg directed against BA.1. Moderna used 25 µg of mRNA directed against each of the same two strains. The combined quantities mirrored the amount of mRNA in each company's monovalent booster dose for adults (30 µg for Pfizer–BioNTech and 50 µg for Moderna).

On June 28, 2022, researchers from Pfizer–BioNTech and Moderna presented data on their bivalent vaccines to the FDA's Vaccines and Related Biological Products Advisory Committee (of which I am a member). The results were underwhelming. Bivalent boosters resulted in levels of neutralizing antibodies against BA.1 that were only 1.5 to 1.75 times as high as those achieved with monovalent boosters. Previous experience with the companies' vaccines suggested that this difference was unlikely to be clinically significant. Safety data were reassuring. At the time of the FDA presentation, BA.1 was no longer circulating in the United States, having been replaced by more immune-evasive and contagious omicron subvariants. But winter was around the corner. The FDA advisory committee, sensing the urgency of responding to these immune-evasive strains, voted to authorize bivalent vaccines with an understanding that they would target omicron subvariants BA.4 and BA.5, which at the time had accounted for more than 95% of circulating strains.

A series of rapid-fire policy decisions followed. On June 29, 2022, the day after the advisory committee meeting, the Biden administration agreed to purchase 105 million doses of Pfizer–BioNTech's bivalent vaccine containing BA.4 and BA.5 mRNA. One month later, on July 29, 2022, the administration agreed to purchase 66 million doses of Moderna's bivalent vaccine, intending to offer both vaccines in the fall and winter. On September 1, 2022, the FDA withdrew its emergency use authorization for monovalent vaccine boosters and the CDC recommended bivalent vaccine boosters for everyone 12 years of age or older. On October 12, 2022, the CDC extended this recommendation to include everyone 5 years of age or older. At that point, no data from humans, including immunogenicity data, were available for comparing the relative capacities of the monovalent and bivalent vaccines to protect against BA.4 and BA.5.

On October 24, 2022, David Ho and colleagues released the results of a study examining levels of neutralizing antibodies against BA.4 and BA.5 after receipt of a monovalent or bivalent booster dose. They found "no significant difference in neutralization of any SARS-CoV-2 variant," including BA.4 and BA.5, between the two groups.3 One day later, Dan Barouch and colleagues released the results of a similar study, finding that "BA.5 [neutralizing-antibody] titers were comparable following monovalent and bivalent mRNA boosters." Barouch and colleagues also noted no appreciable differences in CD4+ or CD8+ T-cell responses between participants in the monovalent-booster group and those in the bivalent-booster group.4 Neither research group found the bivalent boosters to elicit superior immune responses. The results are now published in the Journal.

Why did the strategy for significantly increasing BA.4 and BA.5 neutralizing antibodies using a bivalent vaccine fail? The most likely explanation is imprinting. The immune systems of people immunized with the bivalent vaccine, all of whom had previously been vaccinated, were primed to respond to the ancestral strain of SARS-CoV-2. They therefore probably responded to epitopes shared by BA.4 and BA.5 and the ancestral strain, rather than to new epitopes on BA.4 and BA.5. This effect could possibly be moderated by immunizing people either with BA.4 and BA.5 mRNA alone or with a greater quantity of BA.4 and BA.5 mRNA. Evidence in support of these strategies can be found in Pfizer–BioNTech's data regarding its BA.1-containing bivalent vaccine, which showed that BA.1-specific neutralizing-antibody responses were greater in persons who were injected with a monovalent vaccine containing 30 μg or 60 μg of BA.1 mRNA or a bivalent vaccine containing 30 μg of BA.1 mRNA and 30 μg of ancestral-strain mRNA than in those who received a bivalent vaccine containing 15 μg of each type of mRNA.

On November 22, 2022, the CDC published data on the effectiveness of the BA.4 and BA.5 mRNA vaccines for preventing symptomatic infection within 2 months after receipt of the booster dose. For people who had received a monovalent vaccine 2 to 3 months earlier, the extra protection associated with the bivalent booster dose ranged from 28 to 31%. For those who had received a monovalent vaccine more than 8 months earlier,

the extra protection ranged from 43 to 56%.5 Given the results of previous studies, it's likely that this moderate increase in protection against probably generally mild disease will be short lived. As of November 15, 2022, only about 10% of the population for whom the bivalent vaccine had been recommended had received it.5 By December 2022, the BA.4 strain was no longer circulating, and BA.5 accounted for less than 25% of circulating SARS-CoV-2 strains, having been partially replaced by more immune-evasive strains, such as BQ.1, BQ.1.1, BF.7, XBB, and XBB.1.

What lessons can be learned from our experience with bivalent vaccines?

Fortunately, SARS-CoV-2 variants haven't evolved to resist the protection against severe disease offered by vaccination or previous infection. If that happens, we will need to create a variant-specific vaccine. Although boosting with a bivalent vaccine is likely to have a similar effect as boosting with a monovalent vaccine, booster dosing is probably best reserved for the people most likely to need protection against severe disease — specifically, older adults, people with multiple coexisting conditions that put them at high risk for serious illness, and those who are immunocompromised. In the meantime, I believe we should stop trying to prevent all symptomatic infections in healthy, young people by boosting them with vaccines containing mRNA from strains that might disappear a few months later.

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A Covid-19 Milestone Attained — A Correlate of Protection for Vaccines

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Abstract

The rapid identification of a correlate of protection (CoP) for Covid-19 vaccines — on the basis of several harmonized randomized phase 3 trials using common validated assays — constitutes an important success in vaccinology. A CoP is an immune marker that can be used to reliably predict a vaccine's level of efficacy in preventing a clinically relevant outcome. The level of this marker is measured shortly (2 to 4 weeks) after completion of the vaccination regimen and provides an actionable basis for decisions such as regulatory approval of an efficacious vaccine for a new population that was not included in the pivotal randomized phase 3 trials, or approval of a refined version of a vaccine that was previously shown to be efficacious.

Once established, a CoP can be used as the primary end point for provisional or full approval of a vaccine for a specific use, if a clinical immunobridging study confirms that high enough levels of the CoP are achieved. For example, the Food and Drug Administration (FDA) extended approval of the mRNA-1273 (Moderna) and BNT162b2 (Pfizer–BioNTech) Covid vaccines from older to younger age groups on the basis of a comparison of neutralizing antibody titers. Moreover, FDA guidance and a European Medicines Agency declaration from the International Coalition of Medicines Regulatory Authorities recommended that approval of new vaccine strains and booster doses be based on clinical immunobridging studies showing noninferiority or superiority with respect to a CoP end point. Other applications of a CoP include ensuring vaccine consistency from lot to lot, supporting recommendations for coadministration with other vaccines, and determination of appropriate expiration dates.

Confusion about CoPs is understandable, given the myriad complicated issues involved in identifying them and the fact that different uses for CoPs require different validation measures. Evidence that a marker is a CoP is generally derived from five main sources: natural history studies

that correlate infection-induced immune responses with outcomes; vaccine-challenge studies in animals or humans; studies that experimentally manipulate the immune marker to directly assess mechanistic causation (e.g., by administering various vaccine doses or using passive antibody transfer); efficacy trials that quantify the relationship between vaccine efficacy and the level of the immune marker in individual vaccine recipients; and meta-analyses of series of efficacy trials that correlate vaccine efficacy with the mean immune-marker level.

Correlation between Covid-19 Vaccine Efficacy and Neutralizing Antibody Titers.

Strong evidence has been generated from all five of these sources for both serum anti-spike IgG concentration and anti–SARS-CoV-2 neutralizing antibody titer as CoPs for vaccines against symptomatic Covid-19; for brevity, we focus here on the neutralizing antibody titer. Meta-analyses have established high correlations between the standardized mean titer and vaccine efficacy, and the neutralizing antibody titer has consistently been shown to be a mechanistic CoP in challenge studies in nonhuman primates. The U.S. government's COVID-19 Vaccine Correlates of Protection Program assessed CoPs in phase 3 trials of four vaccines: COVE for mRNA-1273,1 ENSEMBLE for Ad26.COV2.S,2 PREVENT-19 for NVX-CoV2373,3 AZD1222 (United States/Chile/Peru) for ChAdOx1 nCoV-19, and COV002 (United Kingdom) also for ChAdOx1 nCoV-19.4 Vaccine efficacy always markedly increased with the titer (see graphs).

Both binding and neutralizing antibodies have been accepted as CoPs by regulators and have provided very high value for vaccine research, development, and use for more than a dozen vaccines against diverse viral or bacterial diseases. Large studies have generated robust evidence that these antibody markers are CoPs for Covid-19 vaccines — indeed, more evidence than is available for many CoPs for other types of vaccines. The FDA has accepted the titer of neutralizing antibodies against likely circulating strains as a CoP for multiple Covid-19 vaccines. Many open questions remain, given that this CoP was identified in trials involving people who had not previously been infected with SARS-CoV-2 and who received intramuscular, spike-only vaccines and were then exposed to pre-delta viruses. Nevertheless, while pursuing the next milestones — identifying CoPs for new viral variants, for new populations including previously infected people, for new vaccine classes, and for various aspects of Covid-19 disease (e.g., symptom types, durations, and severities) — we should acknowledge that neutralizing antibodies are the current CoP for vaccine efficacy, which merits use for near-term decisions about vaccines.