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Perspective

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Bivalent Covid-19 Vaccines — A Cautionary Tale

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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.

Disclosure forms provided by the author are available at NEJM.org.

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1. Tenforde MW, Self WH, Zhu Y, et al. Protection of mRNA vaccines against hospitalized COVID-19 in adults over the first year following authorization in the United States. Clin Infect Dis 2022 May 17 (Epub ahead of print).
2. Gray G, Collie S, Goga A, et al. Effectiveness of AD26.COV2.S and BNT162b2 vaccines against omicron variant in South Africa. N Engl J Med 2022;386:2243-5.
3. Wang Q, Bowen A, Valdez R, et al. Antibody responses to omicron BA.4/BA.5 bivalent mRNA vaccine booster shot. October 24, 2022 (https://www.biorxiv.org/content/10.1101/2022.10.22.513349v1). preprint.
4. Collier AY, Miller J, Hachmann NP, et al. Immunogenicity of the BA.5 bivalent mRNA vaccine boosters. October 25, 2022 (https://www.biorxiv.org/content/10.1101/2022.10.24.513619v1). preprint.
5. Link-Gelles R, Ciesla AA, Fleming-Dutra KE, et al. Effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection — increasing community access to testing program, United States, September–November 2022. MMWR Morb Mortal Wkly Rep 2022;71:1526-30.

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A "Method of Use" to Prevent Generic and Biosimilar Market Entry

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Brand-name drug manufacturers employ several strategies for forestalling competition in the United States. One approach has been to amass multiple patents on aspects of a drug or biologic other than its active ingredient, such as its formulation, manufacturing process, and method of use (i.e., its use to prevent or treat a disease). For example, AbbVie protected its blockbuster immunosuppressant adalimumab (Humira), which generated $17.3 billion in U.S. sales in 2021, with more than 70 patents on inventions ranging from the active pharmaceutical ingredient and primary indications to the drug's purity, various formulations, and secondary indications.[1] Such a so-called patent thicket can delay or deter the entry of generic or biosimilar drugs because each patent claim must first be considered and, if necessary, addressed. In part for this reason, adalimumab biosimilars won't be available in the United States until later this year, 5 years later than in the European Union, which doesn't permit this type of patent gamesmanship.

A critical pathway that manufacturers of generics and biosimilars have been able to use to circumvent patent thickets in the United States has been "skinny labeling" — the carving out of patent-protected indications from the labels of generic and biosimilar drugs. A recent federal appellate court ruling has placed this pathway under threat, however, thereby prompting a need for action by the Supreme Court or Congress if it is to be maintained.

Patent thickets often contain multiple method-of-use patents. These patents are problematic for generics manufacturers because they can expire long after original active-ingredient patents and because a generic drug's label must generally be the same as the corresponding brand-name drug's label. Compounding this problem is the fact that various method-of-use patents often cover indications with overlapping pa-