EDITORIAL

Covid-19 mRNA Vaccines — Six of One, Half a Dozen of the Other

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In many countries, the availability of vaccines has marked a turning point in the Covid-19 pandemic. Although the vaccines are imperfect, breakthrough infections in fully vaccinated people remain quite rare, even with recently emerging variants. Countries with high vaccination rates have largely been able to reopen, and rates of severe illness and death have dropped dramatically. But this has not been a smooth process. Different vaccines have become available at different times, and access to them has varied markedly from country to country. Thus, the choice of which vaccine to use has been driven in great part by availability rather than by science. In fact, it has not been entirely clear how the vaccines we have compare with one another. Comparing the safety and effectiveness of vaccines is not simple in the absence of head-to-head trials. Data on real-world effectiveness can be subject to many limitations because the treated populations may vary in unanticipated ways. In addition, real-world data often provide relatively imprecise estimates of effectiveness that can be of limited value when highly effective agents are being compared.

Comparing the two available messenger RNA (mRNA) vaccines is particularly problematic. Both BNT162b2, produced by Pfizer–BioNTech, and mRNA-1273, from Moderna, were remarkably efficacious in phase 3 trials. Finding subtle differences in a head-to-head comparison between two agents with greater than 90% efficacy in preventing symptomatic disease would require an enormous sample size, far larger than would ever be practical in a randomized, controlled trial. But hundreds of millions of doses of the mRNA vaccines have now been administered, and an analysis of real-world data can provide an estimate of effectiveness. Dickerman and colleagues now report the results of such an analysis in the *Journal*.[1] They used a large database from Department of Veterans Affairs (VA) hospitals in the United States, which have an integrated medical record system and excellent capture of patient events, to compare how well the two mRNA vaccines work. The study included persons who received two doses of vaccine and follow-up data during two different periods — one marked by predominance of the SARS-CoV-2 B.1.1.7 (alpha) variant and a second during which the B.1.617.2 (delta) variant had largely replaced all other circulating viruses. Vaccines are thought to be less effective against the delta variant. Since the authors considered large numbers of people, they had considerable power to detect subtle differences in vaccine effectiveness.

In their analysis involving the 24-week period during which the B.1.1.7 (alpha) variant was predominant, the researchers considered two groups (219,842 persons each) of mRNA vaccine recipients who were matched 1:1 for several factors, including date of vaccination, age, sex, race, and geographic location. They measured the risk of documented infection, symptomatic infection, hospitalization on a ward or in the intensive care unit (ICU), and death in each group. In their analysis of documented SARS-CoV-2 infection over this 24-week period, they found that BNT162b2 was associated with 5.75 events per 1000 persons (95% confidence interval [CI], 5.39 to 6.23), whereas mRNA-1273 was associated with 4.52 events per 1000 persons (95% CI, 4.17 to 4.84)

— a between-group difference of 1.23 events. Differences between the groups persisted for symptomatic infection (difference, 0.44 events per 1000), hospitalization (0.55 per 1000), ICU admission (0.10 per 1000), and death (0.02 per 1000). The between-group difference with respect to documented infection persisted and in fact grew during the 12-week period dominated by the delta variant (to 6.54 events per 1000 persons).

How valid are these findings? The VA cares for a group of patients who are demographically diverse apart from one factor — they are overwhelmingly male. In addition, VA patients can obtain care outside the VA system, which results in some data loss. As in all real-world studies, we do not know why patients sought testing. Nevertheless, it seems unlikely that the type of vaccine given would result in different care-seeking behavior. Thus, at least for this demographic group, the findings are strong.

Why would vaccines that use two similar RNA sequences to specify encoded antigens vary in their effectiveness? Each of these vaccines uses a somewhat different system for the intracellular delivery of the mRNA. The total dose of mRNA differs between the vaccines, as does the dosing schedule. For both vaccines, all of this was determined empirically from a small number of variations tested in relatively limited phase 2 trials. Thus, we do not know whether either regimen would be more effective with a different mRNA dose or dosing schedule, and it seems likely that each could be improved. However, improving them would be difficult. It would require more large trials, preferably with a reliable biomarker of protection. Unfortunately, no such biomarker currently exists. And at this point, these vaccines have been so effective that it is not clear that such an effort would be worthwhile.

This brings us to the most important point. Both vaccines are highly effective. Although when we look at hundreds of thousands of recipients, mRNA-1273 is marginally more effective than BNT162b2, the death rate among vaccinated persons remains tiny, and the difference in the risk of death between the two vaccines was only approximately 0.2 per 10,000 vaccinees during the period marked by alpha-variant predominance. How the two vaccines compare with regard to side effects is difficult to assess without a head-to-head trial.

So let's review what this study means and consider what it does not mean. We have two vaccines that vary slightly in effectiveness, although they are both highly effective. For any given person, the difference in vaccine efficacy between BNT162b2 and mRNA-1273 is unmeasurable. In the United States, the availability of two mRNA vaccines has allowed us to ramp up vaccination efforts far more quickly than if we had had only one. The need in much of the rest of the world is enormous, and meeting it will require both mRNA vaccines, along with others that are currently being developed and deployed. Even if they are less able to protect against infection, many of the other available vaccines do a very good job of protecting against severe disease. Moreover, the study by Dickerman et al. gives us no idea how the vaccines will compare after an additional booster dose. So the lesson we take away is not about differences — it's about similarities. We are lucky to have such good options. Vaccination with any vaccine is far better than remaining unprotected. The message is that the best vaccine is the one that's available.

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

This editorial was published on December 1, 2021, at NEJM.org.

1. Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S. veterans. N Engl J Med. DOI: 10.1056/NEJMoa2115463.

DOI: 10.1056/NEJMe2117446