CORRESPONDENCE

Effectiveness of Homologous or Heterologous Covid-19 Boosters in Veterans

TO THE EDITOR: Vaccine effectiveness against coronavirus disease 2019 (Covid-19) wanes over time, and boosters are now recommended for residents of the United States starting at the age of 12 years.[1] Clinical trials have shown that receipt of a booster that does not match the primary vaccination (heterologous booster) may result in a higher neutralizing-antibody response than the receipt of a matching (homologous) booster, particularly after primary vaccination with an adenoviral-vector vaccine.[2-5] Whether the choice of booster affects real-world vaccine effectiveness is poorly understood.

We performed a study involving 4,806,026 veterans and linked their information to the Veterans Affairs Covid-19 Shared Data Resource, a database that was created in response to the Covid-19 pandemic and that contains information on all veterans with a confirmed laboratory diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We created two analysis cohorts based on the primary vaccine that each veteran received (adenoviral-vector or messenger RNA [mRNA]) to compare the effectiveness of heterologous and homologous boosters. (Details regarding the study participants are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

For each participant who had received a heterologous booster, we identified a matched control who had received a homologous booster. Matching was based on age, sex, race, Charlson Comorbidity Index, geographic location, primary vaccine type, week of booster administration, and interval between the primary vaccination and the booster. We calculated adjusted rate ratios and used robust error estimates to derive 95% confidence intervals using Poisson regression.

The primary outcome was the incidence of documented SARS-CoV-2 infection after a booster dose. Additional outcomes included the incidence of moderate disease (defined as Covid-19–related hospitalization within 14 days after documented infection) and severe or critical disease (defined as admission to an intensive care unit or death within 28 days after documented infection).

Among the veterans in the database who had at least two primary care visits before vaccine rollout, 43,394 had received a booster after vaccination with the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen). Similarly, we identified 965,063 veterans who had received a booster after primary vaccination with either the BNT162b2 vaccine (Pfizer–BioNTech) or the mRNA-1273 vaccine (Moderna). The matched analysis cohorts contained 25,972 veterans with Ad26.COV2.S primed boosters (Ad26.COV2.S vaccine cohort: 12,986 homologous and 12,986 heterologous boosters) and 35,850 veterans with mRNA-primed boosters (mRNA vaccine cohort: 17,925 homologous and 17,925 heterologous boosters) (Table S1 in the Supplementary Appendix).

In the Ad26.COV2.S-primed vaccine cohort, we observed 415 documented infections, including 34 participants with moderate disease and 12 with severe or critical disease (Table 1). Of these infections, 278 occurred in participants who had received a homologous booster and 137 in those who had received a heterologous booster. The incidence of infection after heterologous boosting was approximately 50% lower than that after homologous boosting (adjusted rate ratio, 0.49; 95 confidence interval [CI], 0.40 to 0.60). Similarly, adjusted rate ratios for moderate and severe or critical disease were lower after heterologous boosting.

In the mRNA-primed cohort (which included recipients of either the BNT162b2 or mRNA-1273 vaccine), we observed 362 documented infections, including 23 participants with moderate disease and 8 with severe or critical disease. No material difference was noted in the incidence of SARS-CoV-2 infection, including moderate and severe or critical disease, among participants who had received heterologous or homologous boosting after primary mRNA vaccination (adjusted rate

Table 1. Documented SARS-CoV-2 Infection in the Study Veterans, According to the Receipt of Homologous or Heterologous Boosters.*

Primary Vaccination Series	Homologous Booster	Heterologous Booster	Adjusted Rate Ratio (95% CI)†
Ad26.COV2.S vaccine			
No. of participants	12,986	12,986	
Total follow-up time — person-days	558,210	556,880	
Documented infection — no. of participants	278	137	0.49 (0.40–0.60)
Moderate disease	19	15	0.78 (0.40–1.53)
Severe or critical disease	9	3	0.33 (0.09–1.23)
Combined mRNA vaccines			
No. of participants	17,925	17,925	
Total follow-up time — person-days	905,896	905,127	
Documented infection — no. of participants	172	190	1.10 (0.90–1.35)
Moderate disease	8	15	1.87 (0.79–4.42)
Severe or critical disease	4	4	1.00 (0.25–3.99)
BNT162b2 mRNA vaccine			
No. of participants	7,848	7,848	
Total follow-up time — person-days	375,965	375,749	
Documented infection — no. of participants	77	82	1.07 (0.78–1.45)
Moderate disease	3	5	1.66 (0.40–6.94)
Severe or critical disease	1	3	2.96 (0.31–28.3)
mRNA-1273 vaccine			
No. of participants	10,077	10,077	
Total follow-up time — person-days	529,930	529,378	
Documented infection — no. of participants	95	108	1.12 (0.85–1.48)
Moderate disease	5	10	2.00 (0.68–5.84)
Severe or critical disease	3	1	0.50 (0.04–5.56)

* Homologous boosters were the same as the primary vaccine, and heterologous boosters were different from the primary vaccine. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.
† The adjusted rate ratio is for participants who received a heterologous booster as compared with those who received a homologous booster.

ratio, 1.10; 95% CI, 0.90 to 1.35). Outcomes for the individual mRNA vaccines were similar to those in the combined mRNA category. (Additional data regarding individual vaccines are provided in Table S2.)

Recent clinical trials examining the safety and immunogenicity of SARS-CoV-2 boosters in healthy adults have shown greater increases in antibody titers after heterologous boosting than after homologous boosting.[2,5] In particular, neutralizing immunoglobulin G antibodies were lowest after homologous Ad26.COV2.S boosting and remained below the predicted efficacy threshold for preventing symptomatic Covid-19.[2]

Our findings support the results of these clinical trials since we observed the largest number of documented breakthrough infections in participants who had received a homologous Ad26.COV2.S booster. Our analysis provides further evidence that the infection rate is lower in persons who are boosted with a heterologous mRNA vaccine.

Overall, documented infections, including moderate and severe or critical disease, were uncom-

mon among veterans who had received either homologous or heterologous boosters. Heterologous mRNA boosting may better protect against incident infection in persons who were initially vaccinated with an adenoviral-vector vaccine.

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