CORRESPONDENCE

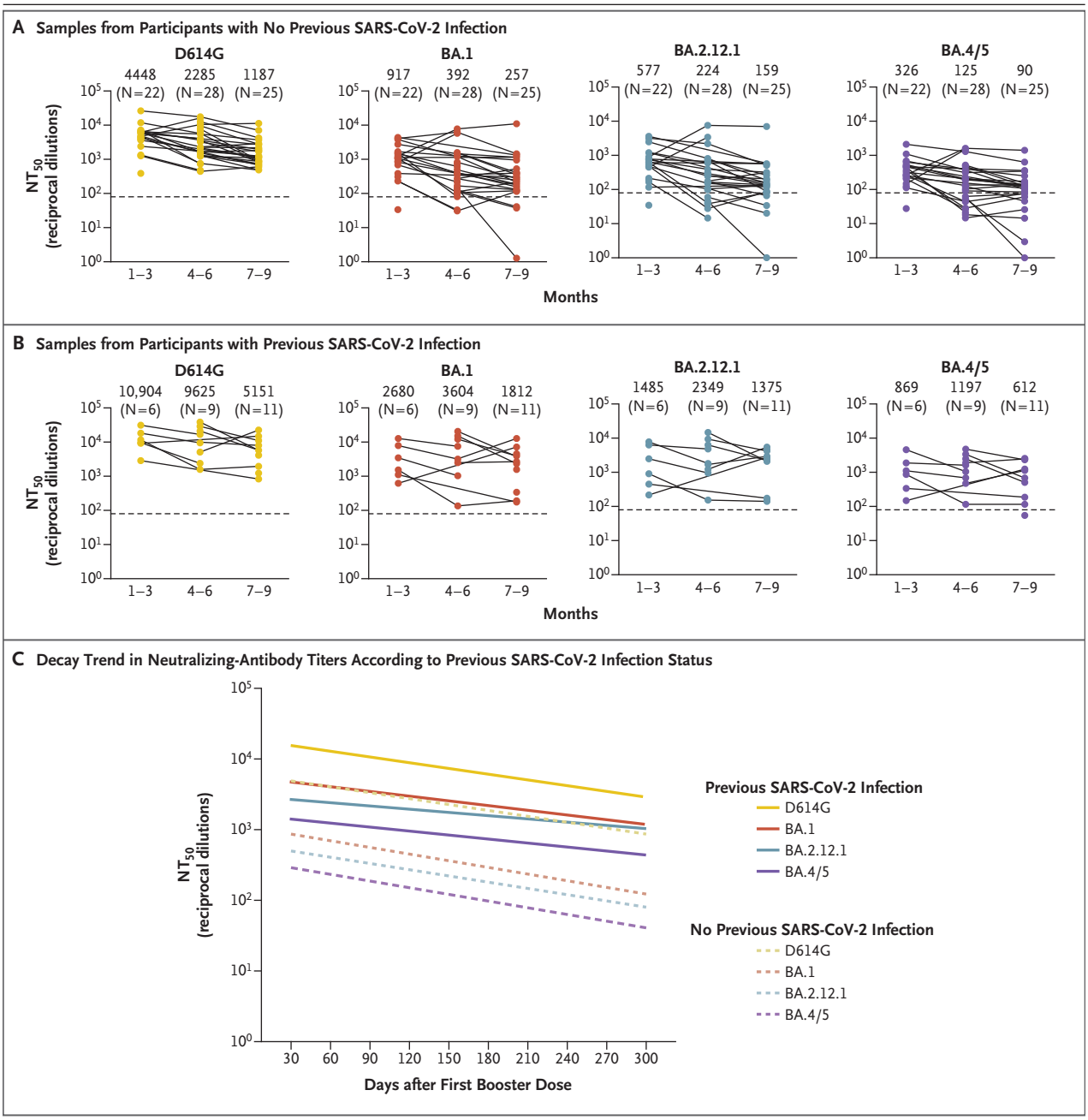
# Durability of Booster mRNA Vaccine against SARS-CoV-2 BA.2.12.1, BA.4, and BA.5 Subvariants

**TO THE EDITOR:** Mounting concern about the long-term efficacy of messenger RNA (mRNA) booster vaccines against coronavirus disease 2019 (Covid-19)[1] has been exacerbated by the recent emergence of the B.1.1.529 (omicron) subvariants BA.2.12.1 and BA.4 and BA.5 (hereafter, BA.4/5) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which have high degrees of immune escape.[2] To address this concern, we used our previously reported pseudotyped lentivirus neutralization assay (see the Supplementary Appendix, available with the full text of this letter at NEJM.org) to examine neutralizing-antibody titers against major SARS-CoV-2 variants in a longitudinal cohort of health care workers from the Ohio State University Wexner Medical Center in Columbus who had received homologous vaccine and booster doses of an mRNA vaccine. A total of 24 participants received the mRNA-1273 vaccine (Moderna), and 22 received the BNT162b2 vaccine (Pfizer–BioNTech). We classified participant samples into three groups according to the timing of booster-dose administration: 1 to 3 months, 4 to 6 months, and 7 to 9 months before the sample was obtained (Table S1 in the Supplementary Appendix). Over the course of the study, 14 participants had a breakthrough infection; 9 cases occurred during the omicron waves.

Booster durability waned more substantially in participants who did not have breakthrough infection than in those who had breakthrough infection, with neutralizing-antibody titers, presented as 50% neutralization titers ($NT_{50}$), against all variants at 1 to 3 months after the booster dose being approximately 1.7 times (95% confidence interval [CI], 1.4 to 2.2) as high as those observed at 7 to 9 months after the booster dose (Figs. 1 and S1). Linear modeling showed a mean 30-day rate of decay in neutralizing-antibody titers of 17.53% (95% CI, 11.87 to 22.79) against virus with the D614G mutation, 19.50% (95% CI, 9.82 to 28.10) against the omicron BA.1 subvariant, 18.44% (95% CI, 9.24 to 26.68) against BA.2.12.1, and 19.55% (95% CI, 10.54 to 27.66) against BA.4/5 (Fig. 1C). Participants with previous SARS-CoV-2 infection, including infection with the omicron variant, had a somewhat less steep rate of decay in neutralizing-antibody titers (Figs. 1B and 1C and S2), with 30-day rates of 17.07% (95% CI, 2.70 to 29.29) against virus with the D614G mutation, 14.22% (95% CI, −6.87 to 31.13) against the BA.1 subvariant, 9.97% (95% CI, −11.95 to 27.64) against BA.2.12.1, and 12.12% (95% CI, −7.14 to 27.94) against BA.4/5 (Fig. 1C). At all time points tested, all the omicron subvariants, especially BA.4/5, had lower neutralizing-antibody titers than virus with the D614G mutation.

Two participants received a second booster dose of mRNA vaccine (Table S2). After a substantial decrease in neutralizing-antibody titers was observed approximately 4 months after receipt of the initial booster dose in these participants, the administration of a second booster dose led to recovered neutralizing-antibody titers (Fig. S3).

The decrease in booster durability appeared to be slower than the decrease that was previously reported for two doses of mRNA vaccine alone.[3] Although the rate of booster neutralizing-antibody decay was similar among variants, the omicron subvariants, especially BA.4/5, had substantial neutralization resistance. Our observed trends are consistent with the waning of vaccine protection and natural immunity,[4,5] and our data




suggest that both SARS-CoV-2 variant evolution and waning neutralizing-antibody titers reduce booster-induced immune protection. Our anecdotal experience in two participants indicates that a fourth dose of vaccine may be effective. A variant-specific booster may become necessary as new variants evolve.

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**Figure 1 (facing page). Durability of mRNA Booster–Induced Neutralizing Antibodies According to Previous SARS-CoV-2 Infection.**

Panel A shows neutralizing-antibody titers against virus pseudotyped with spike protein from the ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the D614G mutation and the B.1.1.529 (omicron) subvariants BA.1, BA.2.12.1, and BA.4 and BA.5 (hereafter, BA.4/5) in serum samples obtained from health care workers with no previous SARS-CoV-2 infection. Samples were obtained from participants who had received a booster dose of messenger RNA (mRNA) vaccine 1 to 3 months, 4 to 6 months, or 7 to 9 months previously. Neutralizing-antibody titers against virus with the D614G mutation and the omicron subvariants BA.1, BA.2.12.1, and BA.4/5 in serum samples obtained from participants with previous SARS-CoV-2 infection are shown in Panel B; samples were obtained according to the same time categories as in Panel A. In both panels, dots represent individual samples, and the horizontal dashed lines represent the limit of detection. Solid lines connect samples that were obtained from the same participant. Geometric mean values for the 50% neutralization titers ($NT_{50}$) are shown at the top of the plots for each time point. Panel C shows the trend lines in neutralizing-antibody decay over the study period as determined by linear mixed-effects modeling with accounting for repeated measures in participants with no previous SARS-CoV-2 infection against virus with the D614G mutation (slope, −0.0028; 95% CI, −0.0037 to −0.0018) or subvariants BA.1 (slope, −0.0031; 95% CI, −0.0048 to −0.0015), BA.2.12.1 (slope, −0.0030; 95% CI, −0.0045 to −0.0014), or BA.4/5 (slope, −0.0032; 95% CI, −0.0047 to −0.0016) and in participants with previous SARS-CoV-2 infection against virus with the D614G mutation (slope, −0.0027; 95% CI, −0.0050 to −0.0004) or subvariants BA.1 (slope, −0.0022; 95% CI, −0.0054 to −0.0010), BA.2.12.1 (slope, −0.0015; 95% CI, −0.0047 to −0.0016), or BA.4/5 (slope, −0.0019; 95% CI, −0.0047 to −0.0010). The 95% confidence intervals for each trend-line slope have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

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**3.** Evans JP, Zeng C, Carlin C, et al. Neutralizing antibody responses elicited by SARS-CoV-2 mRNA vaccination wane over time and are boosted by breakthrough infection. Sci Transl Med 2022;14:eabn8057.

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