

actions were reported in patients who were Asian (27 [5%]); of mixed race, which included American Indian–Alaska Native and Native Hawaiian–Pacific Islander (22 [4%]); and Black (6 [1%]). Six of these patients (11%) were Hispanic. A majority of these delayed large local reactions occurred after the receipt of the first vaccine dose (in 53 patients [96%]) and after the receipt of the mRNA-1273 vaccine (in 47 [85%]). The mean time from vaccination until the onset of the reaction was 8 ± 2 days (range, 4 to 14). Eleven patients (20%) had cutaneous reactions other than at the injection site, such as diffuse itching, hives or other rash, or angioedema.

Delayed large local reactions may be less commonly recognized or reported in BIPOC vaccine recipients than in White recipients. Such reactions may result in vaccine hesitancy or incomplete vaccination; as such, proactive outreach is needed to increase education regarding these reactions across diverse communities. We hope that this letter encourages additional research and communication regarding cutaneous vaccine reactions, including delayed large local reactions, in BIPOC recipients.

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Infection and Vaccine-Induced Neutralizing-Antibody Responses to the SARS-CoV-2 B.1.617 Variants

TO THE EDITOR: A second wave of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in India is leading to the emergence of SARS-CoV-2 variants. The B.1.617.1 (or kappa) and B.1.617.2 (or delta) variants were first identified in India and have rapidly spread to several countries throughout the world. These variants contain mutations within the spike protein located in antigenic sites recognized by antibodies with potent neutralizing activity.¹⁻³ We used serum samples obtained from infected and vaccinated persons to assess neutralizing activity against the SARS-CoV-2 variants in a live-virus assay.

For the analyses, we used B.1.617.1 virus that had been isolated from a mid-turbinate swab obtained from a patient in Stanford, California, in March 2021 (hCoV-19/USA/CA-Stanford-15_S02/2021) and B.1.617.2 virus from a nasal swab

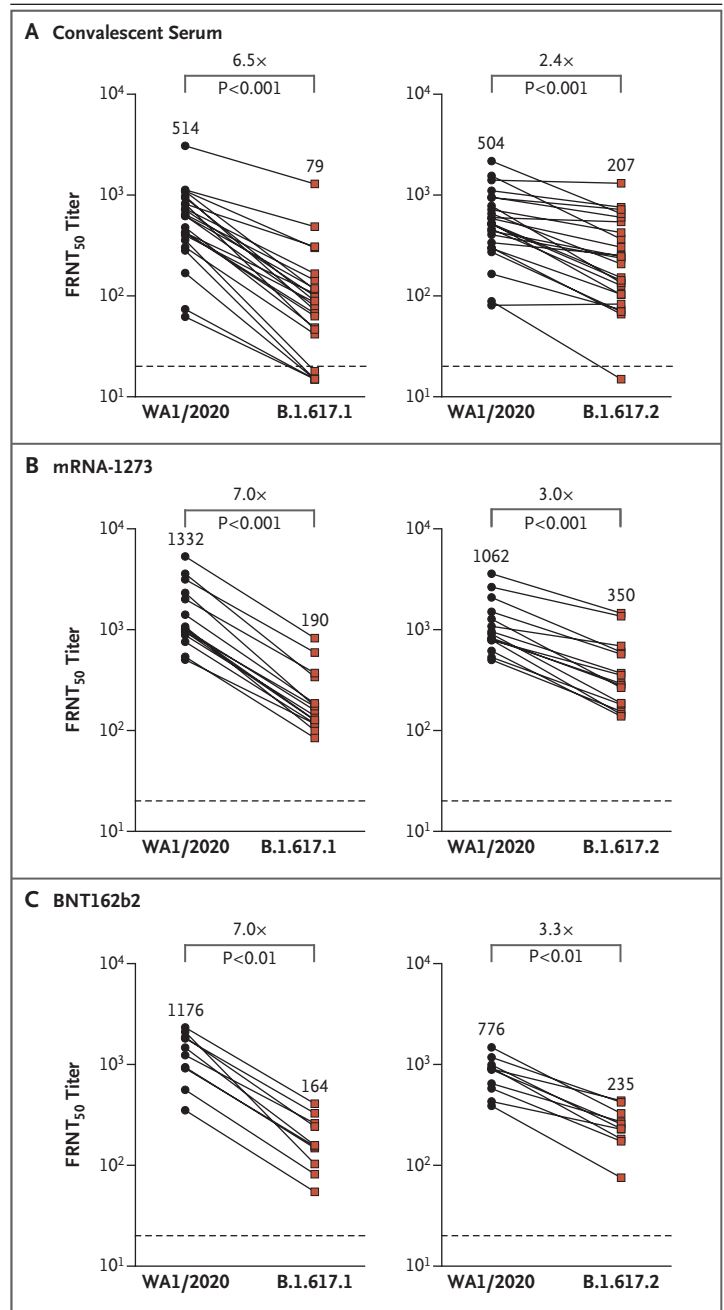
that had been obtained from a patient in May 2021 (hCoV-19/USA/PHC658/2021). As compared with the WA1/2020 variant (nCoV/USA_WA1/2020; spike 614D), the B.1.617.1 and B.1.617.2 variants contain mutations in key regions within the spike, including the N-terminal antigenic super-site,⁴ the receptor-binding domain, and the polybasic furin cleavage site (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We used an *in vitro*, live-virus focus reduction neutralization test (FRNT₅₀ [the reciprocal dilution of serum that neutralizes 50% of the input virus])⁵ on a Vero E6 cell line (engineered to express TMPRSS2) to compare the neutralizing-antibody responses against WA1/2020 in serum samples from 24 persons who had recovered from coronavirus disease 2019 (Covid-19) (obtained 31 to 91 days after

Figure 1. Neutralizing-Antibody Responses against the WA1/2020, B.1.617.1, and B.1.617.2 Variants.

Shown is the neutralizing activity against natural infection with severe acute respiratory syndrome coronavirus 2 among 24 samples from persons who had recovered from coronavirus disease 2019 (obtained 31 to 91 days after symptom onset) (Panel A), 15 samples from persons who had received the mRNA-1273 (Moderna) vaccine (obtained 35 to 51 days after the second dose) (Panel B), and 10 samples from persons who had received the BNT162b2 (Pfizer–BioNTech) vaccine (obtained 7 to 27 days after the second dose) (Panel C). Two independent neutralization assays were performed: activity against B.1.617.1 was compared with that against WA1/2020, and activity against B.1.617.2 was compared with that against WA1/2020. The focus reduction neutralization test (FRNT₅₀ [the reciprocal dilution of serum that neutralizes 50% of the input virus]) geometric mean titers for WA1/2020, B.1.617.1, and B.1.617.2 are shown in each panel. The connecting lines between WA1/2020 and B.1.617.1 or WA1/2020 and B.1.617.2 represent matched serum samples. The horizontal dashed lines along the x axes indicate the limit of detection (FRNT₅₀ geometric mean titer, 20). Normality of the data was determined with the use of the Shapiro–Wilk normality test. Nonparametric pairwise analyses for neutralization titers were performed with the use of the Wilcoxon matched-pairs signed-rank test.

symptom onset),¹ from 15 persons who had received the mRNA-1273 (Moderna) vaccine (obtained 35 to 51 days after the second dose), and from 10 persons who had received the BNT162b2 (Pfizer–BioNTech) vaccine (obtained 7 to 27 days after the second dose).

All samples from infected and vaccinated persons showed less neutralizing activity against both the B.1.617.1 and B.1.617.2 variants than against WA1/2020 (Fig. 1). Among convalescent serum samples, the FRNT₅₀ geometric mean titer (GMT) against B.1.617.1 was 79 (95% confidence interval [CI], 49 to 128), as compared with 514 (95% CI, 358 to 740) against WA1/2020 (five samples had undetectable activity against the B.1.617.1 variant); the GMT against B.1.617.2 was 207 (95% CI, 135 to 319), as compared with 504 (95% CI, 358 to 709) against WA1/2020 (one sample had undetectable activity against the B.1.617.2 variant). Among the mRNA-1273 samples, the GMT against B.1.617.1 was 190 (95% CI, 131 to 274), as compared with 1332 (95% CI, 905 to 1958) against WA1/2020; the GMT against B.1.617.2 was 350 (95% CI, 229 to 535), as compared with 1062 (95% CI, 773 to 1460) against WA1/2020. Among the BNT162b2 vaccine serum samples, the GMT against B.1.617.1 was 164



(95% CI, 104 to 258), as compared with 1176 (95% CI, 759 to 1824) against WA1/2020; the GMT against B.1.617.2 was 235 (95% CI, 164 to 338), as compared with 776 (95% CI, 571 to 1056) against WA1/2020. Among the three sample groups, the GMTs against the B.1.617.1 and B.1.617.2 variants were significantly lower than those against the WA1/2020 strain.

Our results show that the B.1.617.1 variant was 6.8 times less susceptible, and the B.1.617.2

variant was 2.9 times less susceptible, to neutralization by serum from persons who had recovered from Covid-19 and from vaccinated persons than was the WA1/2020 variant. Despite this finding, a majority of the convalescent serum samples (79% [19 of 24 samples] against B.1.617.1 and 96% [23 of 24 samples] against B.1.617.2) and all serum samples from vaccinated persons still had detectable neutralizing activity above the threshold of detection against both variants through 3 months after infection or after the second dose of vaccine. Thus, protective immunity conferred by the mRNA vaccines is most likely retained against the B.1.617.1 and B.1.617.2 variants.

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Donanemab in Early Alzheimer's Disease

TO THE EDITOR: The results of the placebo-controlled trial of donanemab conducted by Mintun et al. (May 6 issue)¹ may be misleading on three points. First, although donanemab therapy in-

duced a marked reduction in the amyloid plaque level as measured by positron-emission tomography with ¹⁸F-florbetapir tracing, the primary outcome — the change in the composite score on