CORRESPONDENCE

Neutralization Escape by SARS-CoV-2 Omicron Subvariant BA.4.6

TO THE EDITOR: The B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has splintered into multiple subvariants with increased transmissibility and immune escape.[1] At the time of this report, omicron subvariant BA.5 is the dominant global virus and has shown substantial immune escape as compared with previous omicron subvariants.[2-5] BA.4.6 is a sublineage of BA.4 with two additional mutations in the spike protein (R346T and N658S) (Fig. 1A) and has recently increased in prevalence in certain regions currently dominated by BA.5, including in the United States. The ability of BA.4.6 to evade neutralizing antibodies that were induced by infection or vaccination remains to be determined.

We evaluated neutralizing antibody titers against five SARS-CoV-2 strains — WA1/2020 and omicron subvariants BA.1, BA.2, BA.4–BA.5, and BA.4.6 — in 19 participants who had been recently infected with the omicron BA.1 or BA.2 subvariant and in 16 participants who had been vaccinated and boosted with the original mRNA-1273 vaccine (Moderna) (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In the cohort with previous omicron infection, all the participants except for one had been vaccinated; samples were obtained a median of 21 days after diagnosis of omicron infection. In this cohort, the median pseudovirus neutralizing antibody titer was 42,067 against WA1/2020, 6352 against BA.1, 3854 against BA.2, 1673 against BA.4–BA.5, and 630 against BA.4.6 (Fig. 1B). The median neutralizing antibody titers against BA.4.6 were lower than the median titers against WA1/2020 by a factor of 67, against BA.1 by a factor of 10, against BA.2 by a factor of 6, and against BA.4–BA.5 by a factor of 2.7.

In the mRNA-1273 vaccine cohort, participants were excluded if they had a known history of SARS-CoV-2 infection or positive results on nucleocapsid serologic analysis or if they had received immunosuppressive medications or other vaccines against SARS-CoV-2. Six months after the initial two mRNA-1273 immunizations, the median neutralizing antibody titer was 951 against WA1/2020, 28 against BA.2, 30 against BA.4–BA.5, and 23 against BA.4.6 (Fig. 1C). At a median of 17 days after the first booster dose, the median neutralizing antibody titer was 16,011 against WA1/2020, 802 against BA.2, 449 against BA.4–BA.5, and 225 against BA.4.6. The median neutralizing antibody titer against BA.4.6 was lower than that against WA1/2020 by a factor of 71, against BA.2 by a factor of 4, and against BA.4–BA.5 by a factor of 2.

Our data show that the BA.4.6 omicron subvariant markedly escaped neutralizing antibodies induced by infection or vaccination, with values that were lower than BA.5 titers by a factor of 2 to 2.7, which suggests continued evolution of SARS-CoV-2. These findings provide immunologic context for the increasing prevalence of BA.4.6 in populations in which BA.5 is currently dominant. Moreover, the R346T mutation had also recently been observed in other omicron subvariants, including BA.2.75 and BA.5, which suggests the biologic relevance of this mutation. The potential effect of the emergence of the BA.4.6 subvariant on vaccine boosters containing BA.5 immunogens or on infection with BA.5 remains to be determined.

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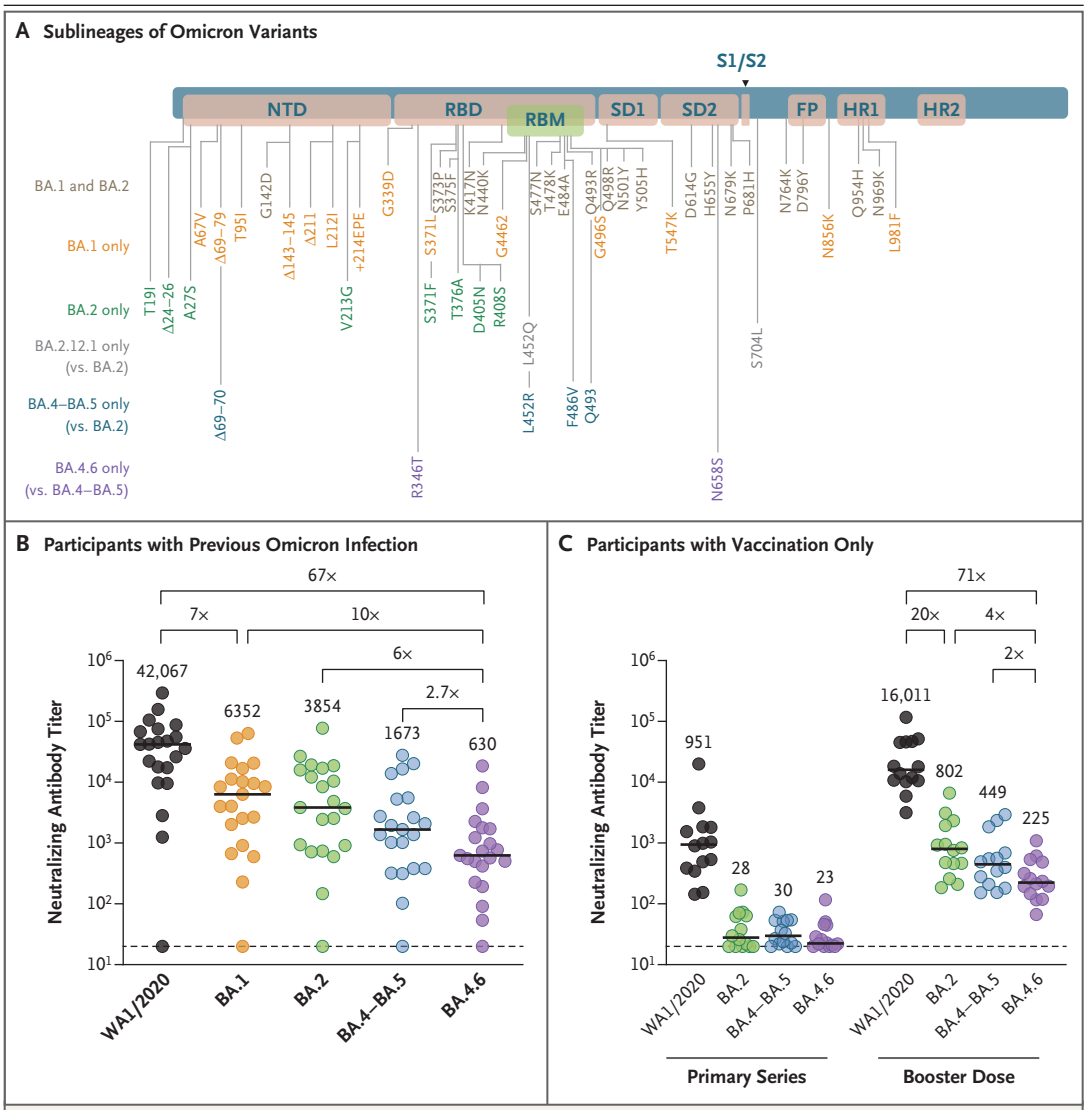

Figure 1. Neutralizing Antibody Responses to Omicron Subvariants.

Panel A shows mutations in the SARS-CoV-2 spike protein in omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4–BA.5, and BA.4.6. BA.4 and BA.5 are grouped together because they have identical spike sequences. NTD denotes N-terminal domain, RBD receptor-binding domain, RBM receptor-binding motif, SD1 subdomain 1, SD2 subdomain 2, FP fusion peptide, HR1 heptad repeat 1, and HR2 heptad repeat 2; S1 and S2 indicate spike protein domains. Panel B shows neutralizing antibody titers by a luciferase-based pseudovirus neutralization assay in 19 participants who were recently infected with the BA.1 or BA.2 subvariant. All the participants had been vaccinated except for the one participant with a negative neutralizing antibody titer. Neutralizing antibody titers were measured against the SARS-CoV-2 WA1/2020 strain and against omicron subvariants BA.1, BA.2, BA.4–BA.5, and BA.4.6. Panel C shows neutralizing antibody titers in 16 participants 6 months after the primary series of mRNA-1273 vaccination and after the mRNA-1273 booster dose. Neutralizing antibodies were measured against the SARS-CoV-2 WA1/2020 strain and against omicron subvariants BA.2, BA.4–BA.5, and BA.4.6. In Panels B and C, median neutralizing antibody titers are indicated by black horizontal bars, and factor differences between strains are indicated at the top of the graph. The horizontal dashed lines indicate the lower limit of quantification.

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

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