

CORRESPONDENCE



Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants

TO THE EDITOR: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 (omicron) variant has three major sublineages: BA.1, BA.2, and BA.3.¹ BA.1 rapidly became dominant and has shown substantial escape from neutralizing antibodies induced by vaccination.²⁻⁴ The number of cases of BA.2 has recently increased in many regions of the world, suggesting that BA.2 has a selective advantage over BA.1. BA.1 and BA.2 share multiple common mutations, but each also has unique mutations¹ (Fig. 1A). The ability of BA.2 to evade neutralizing antibodies induced by vaccination or infection is unclear.

We evaluated neutralizing antibody responses against the parental WA1/2020 strain of the virus, as well as against the omicron BA.1 and BA.2 variants, in 24 persons who had been vaccinated and boosted with the BNT162b2 mRNA vaccine (Pfizer–BioNTech)⁵ and had not had infection with SARS-CoV-2 and in 8 persons with a history of SARS-CoV-2 infection, irrespective of vaccination status. Demographic and clinical characteristics of the study population are provided in Tables S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

After the initial two doses of the BNT162b2 vaccine, the median pseudovirus neutralizing antibody titers against WA1/2020, BA.1, and BA.2 were 658, 29, and 24, respectively (Fig. 1B), indicating that the median neutralizing antibody titer against WA1/2020 was 23 and 27 times those for BA.1 and BA.2, respectively. Six months after the initial vaccination, the median neutralizing antibody titers declined to 129 for WA1/2020 and to less than 20 for both BA.1 and BA.2. Two weeks after the third dose (booster) of the BNT162b2 vaccine, the median neutralizing antibody titers increased substantially to 6539 for WA1/2020, 1066 for BA.1, and 776 for BA.2, indicating that the median neutralizing antibody titer against WA1/2020 was 6.1 and 8.4 times those for BA.1 and BA.2,

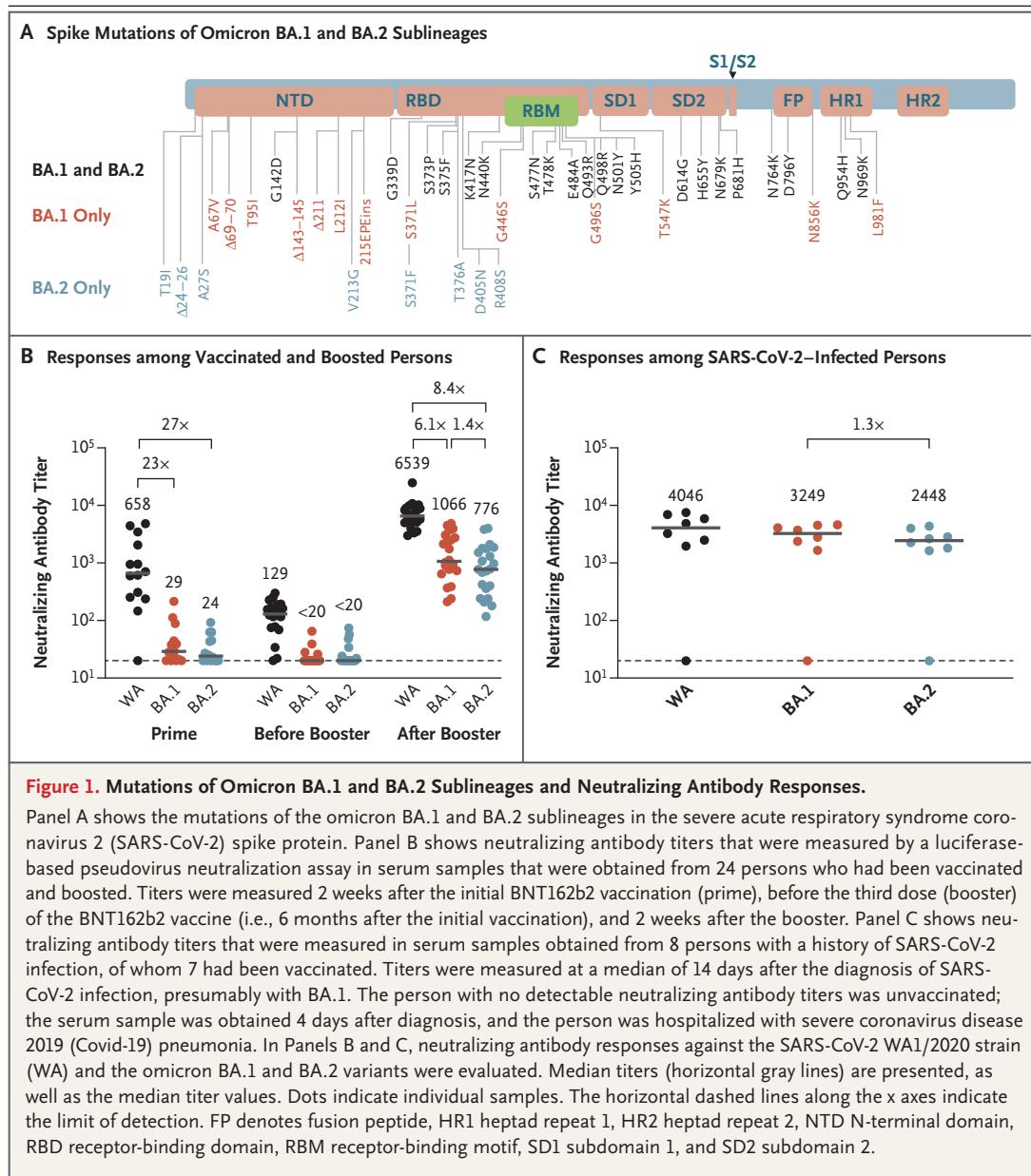
respectively (Fig. 1B). The median BA.2 neutralizing antibody titer was lower than the median BA.1 neutralizing antibody titer by a factor of 1.4.

We next evaluated neutralizing antibody titers in the 8 persons with a history of SARS-CoV-2 infection (see Tables S1 and S2) at a median of 14 days after SARS-CoV-2 infection, which was diagnosed during a time when the omicron BA.1 sublineage was responsible for more than 99% of new infections. The median neutralizing antibody titers were 4046 for WA1/2020, 3249 for BA.1, and 2448 for BA.2 (Fig. 1C). The median BA.1 neutralizing antibody titer was 1.3 times the median BA.2 neutralizing antibody titer. The one person who did not have detectable neutralizing antibody titers was unvaccinated, and the serum sample was obtained 4 days after diagnosis of SARS-CoV-2 infection.

Overall, these data show that neutralizing antibody titers against BA.2 were similar to those against BA.1, with median titers against BA.2 that were lower than those against BA.1 by a factor of 1.3 to 1.4. A third dose of the BNT162b2 vaccine was needed for induction of consistent neutralizing antibody titers against either BA.1 or BA.2.^{3,4} Moreover, in vaccinated persons who had presumably been infected with BA.1, robust neutralizing antibody titers against BA.2 developed, which suggests a substantial degree of cross-reactive natural immunity. These findings have important public health implications and suggest that the increasing frequency of BA.2 in

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the context of the BA.1 surge is probably related to increased transmissibility rather than to enhanced immunologic escape.

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This work was supported by the National Institutes of Health (grant CA260476), the Massachusetts Consortium on Pathogen Readiness, the Ragon Institute, and the Musk Foundation (Dr. Barouch). Dr. Collier is supported by the Reproductive Scientist Development Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Burroughs Wellcome Fund (grant HD000849).

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

This letter was published on March 16, 2022, at NEJM.org.

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DOI: 10.1056/NEJMc2201849

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