

## CORRESPONDENCE

## Substantial Neutralization Escape by SARS-CoV-2 Omicron Variants BQ.1.1 and XBB.1

**TO THE EDITOR:** The omicron BA.5 subvariant was the dominant variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>1</sup> from July to November 2022 and showed substantial neutralization escape as compared with previous variants.<sup>2,3</sup> Additional omicron variants have recently emerged, including the BA.4 sublineage BA.4.6, the BA.5 sublineages BF.7 and BQ.1.1, the BA.2 sublineage BA.2.75.2, and the BA.2 lineage recombinant XBB.1 (Fig. 1A, and Figs. S1 through S5 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). All these variants have the R346T mutation in the spike protein. BQ.1.1 and XBB.1 have rapidly increased in frequency and have replaced BA.5 as dominant variants worldwide. However, the ability of these variants to evade neutralizing antibodies induced by vaccination and infection is unclear.

We first assessed neutralizing antibody titers in 16 participants who had been vaccinated and boosted with the monovalent mRNA vaccine BNT162b2 (Pfizer–BioNTech) in 2021 (Table S1). After the booster, the median neutralizing antibody titer to the WA1/2020 strain was 45,695 and the titers to the BA.5, BF.7, BA.2.75.2, BQ.1.1, and XBB.1 variants were 887, 595, 387, 261, and 105, respectively (Fig. 1B). The median neutralizing antibody titers to the BQ.1.1 and XBB.1 variants were lower than the median titer to BA.5 by factors of 3 and 8, respectively.

We next evaluated neutralizing antibody titers in 15 participants who had received a monovalent mRNA booster in 2022 and in 18 participants who had received a bivalent mRNA booster in 2022, most of whom had received three previous doses of vaccine. In these two cohorts, 33% of the participants had had a documented SARS-CoV-2 omicron infection, but we suspect that the majority of participants had probably

been infected owing to the high prevalence of omicron infection in 2022.

Before the booster, neutralizing antibody titers to the WA1/2020 strain and omicron variants were higher in the two 2022 cohorts than in the 2021 cohort. After the monovalent booster in 2022, the median neutralizing antibody titer to the WA1/2020 strain was 21,507 and the titers to the BA.5, BF.7, BA.2.75.2, BQ.1.1, and XBB.1 variants were 2829, 2276, 745, 406, and 170, respectively (Fig. 1C). After the bivalent booster in 2022, the median neutralizing antibody titer to the WA1/2020 strain was 40,515, and the titers to the BA.5, BF.7, BA.2.75.2, BQ.1.1, and XBB.1 variants were 3693, 2399, 883, 508, and 175, respectively (Fig. 1D). The median neutralizing antibody titers to the BQ.1.1 and XBB.1 variants were lower than the median titers to BA.5 by factors of 7 and 17, respectively, in the monovalent booster cohort and by factors of 7 and 21, respectively, in the bivalent booster cohort.

Our data show that the BQ.1.1 and XBB.1 variants escaped neutralizing antibodies substantially more effectively than the BA.5 variant by factors of 7 and 17, respectively, after monovalent mRNA boosting and by factors of 7 and 21, respectively, after bivalent mRNA boosting. The neutralizing antibody titers to BQ.1.1 and XBB.1 were dramatically lower than titers to the WA1/2020 strain by factors of 53 and 127, respectively, in the monovalent booster cohort and by factors of 80 and 232, respectively, in the bivalent booster cohort. These findings suggest that the BQ.1.1 and XBB.1 variants may reduce the efficacy of current mRNA vaccines and that vaccine protection against severe disease with these variants may depend on CD8 T-cell responses.<sup>5</sup> The higher neutralizing antibody titers against omicron variants after monovalent mRNA boost-

**A Spike Protein Sequence Mutations for Subvariants**

	N-Terminal Domain		Receptor-Binding Domain	
<b>BA.2</b>	T191	L245	L245	T191
	P25-	P25-	P25-	P26-
	P26-	P26-	P26-	P26-
	A27-	A27-	A27-	A27-
	G142D	K147E	W152R	F157L
		V157L		
		G1210V		
		V213G		
		G257S		
		G339H		
		R346T		
		S371F		
		S373P		
		S373P		
		S375F		
		T376A		
		D405N		
		R408S		
		K417N		
		N440K		
		N440K		
		V445P		
		G446S		
		N460K		
		S477N		
		T478K		
		E484A		
		F486S		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
		P681H		
		N764K		
		D796Y		
		Q954H		
		N969K		
		D191N		
		H655Y		
		N679K		
	</			

**Figure 1 (facing page). Neutralizing Antibody Responses to Omicron Subvariants.**

Panel A shows spike protein sequences for the omicron BA.2, BA.2.75.2, XBB.1, BA.5, BF.7, and BQ.1.1 subvariants; mutations as compared with the WA1/2020 spike protein are shown. Mutations as compared with the BA.2 variant are indicated by gray boxes, and individual subvariant mutations are shown in colored font. The blank cells under Q493R represent reversions to the ancestral amino acid at this position. Panel B shows neutralizing antibody titers by luciferase-based pseudovirus neutralization assays in participants in 2021 at 6 months after the initial BNT162b2 vaccination (before booster) and after receipt of the BNT162b2 booster. In Panels B through D, dots indicate results in individual participants, red bars indicate medians, and factor differences are shown. The dashed line in each graph indicates the limit of detection. Panel C shows neutralizing antibody titers in participants before and after receipt of a monovalent mRNA booster in 2022, and Panel D shows neutralizing antibody titers in participants before and after receipt of a bivalent mRNA booster in 2022. Neutralizing antibody responses were measured against the WA1/2020 strain and the BA.5, BF.7, BA.2.75.2, BQ.1.1, and XBB.1 variants. The data regarding neutralizing antibodies against the WA1/2020 strain and the BA.5 variant in Panels C and D are from a separate study<sup>4</sup> and are included here for comparison.

ing in the 2022 cohort than in the 2021 cohort probably reflect the greater numbers of vaccine doses and infections in the 2022 cohort. The incorporation of the R346T mutation into multiple new SARS-CoV-2 variants suggests convergent evolution.

Jessica Miller, B.S.  
Nicole P. Hachmann, B.S.  
Ai-ris Y. Collier, M.D.  
Ninaad Lasrado, Ph.D.  
Camille R. Mazurek, M.S.  
Robert C. Patio, M.S.  
Olivia Powers, B.S.  
Nehalee Surve, M.S.

Beth Israel Deaconess Medical Center  
Boston, MA

James Theiler, Ph.D.

Bette Korber, Ph.D.

Los Alamos National Laboratory  
Los Alamos, NM

Dan H. Barouch, M.D., Ph.D.

Beth Israel Deaconess Medical Center  
Boston, MA  
dbarouch@bidmc.harvard.edu

Supported by grants (CA260476 to Dr. Barouch; AI69309 to Dr. Collier) from the National Institutes of Health, the Massachusetts Consortium for Pathogen Readiness, and the Ragon Institute (to Dr. Barouch).

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

This letter was published on January 18, 2023, at NEJM.org.

1. Barouch DH. Covid-19 vaccines — immunity, variants, boosters. *N Engl J Med* 2022;387:1011-20.
2. Hachmann NP, Miller J, Collier AY, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022;387:86-8.
3. Wang Q, Guo Y, Iketani S, et al. Antibody evasion by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4 and BA.5. *Nature* 2022; 608:603-8.
4. Collier AY, Miller J, Hachmann NP, et al. Immunogenicity of BA.5 bivalent mRNA vaccine boosters. *N Engl J Med*. DOI: 10.1056/NEJMc2213948.
5. Wherry EJ, Barouch DH. T cell immunity to COVID-19 vaccines. *Science* 2022;377:821-2.

DOI: 10.1056/NEJMc2214314

Correspondence Copyright © 2023 Massachusetts Medical Society.