CORRESPONDENCE

Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report

TO THE EDITOR: BNT162b2 is a nucleoside-modified RNA vaccine expressing the full-length prefusion spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a randomized, placebo-controlled clinical trial involving approximately 44,000 participants, immunization conferred 95% efficacy against coronavirus disease 2019 (Covid-19).[1]

New, highly transmissible SARS-CoV-2 variants that were first detected in the United Kingdom (B.1.1.7 lineage), South Africa (B.1.351 lineage), and Brazil (P.1 lineage) with mutations in the S gene are spreading globally. To analyze effects on neutralization elicited by BNT162b2, we engineered S mutations from the B.1.351 lineage into USA-WA1/2020, a relatively early isolate of the virus (in January 2020) (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We subsequently produced three recombinant viruses. The first had an N-terminal domain deletion and the globally dominant D614G substitution (Δ242-244+D614G),[2,3] the second had mutations affecting three amino acids at the receptor-binding site (K417N, E484K, and N501Y) and a D614G substitution (B.1.351-RBD+D614G), and the third had all the mutations found in the S gene in the B.1.351 lineage (B.1.351-spike). All the mutant viruses yielded infectious titers exceeding 10^7 plaque-forming units per milliliter. The B.1.351-spike virus formed plaques that were smaller than those of the other viruses (Fig. S2).

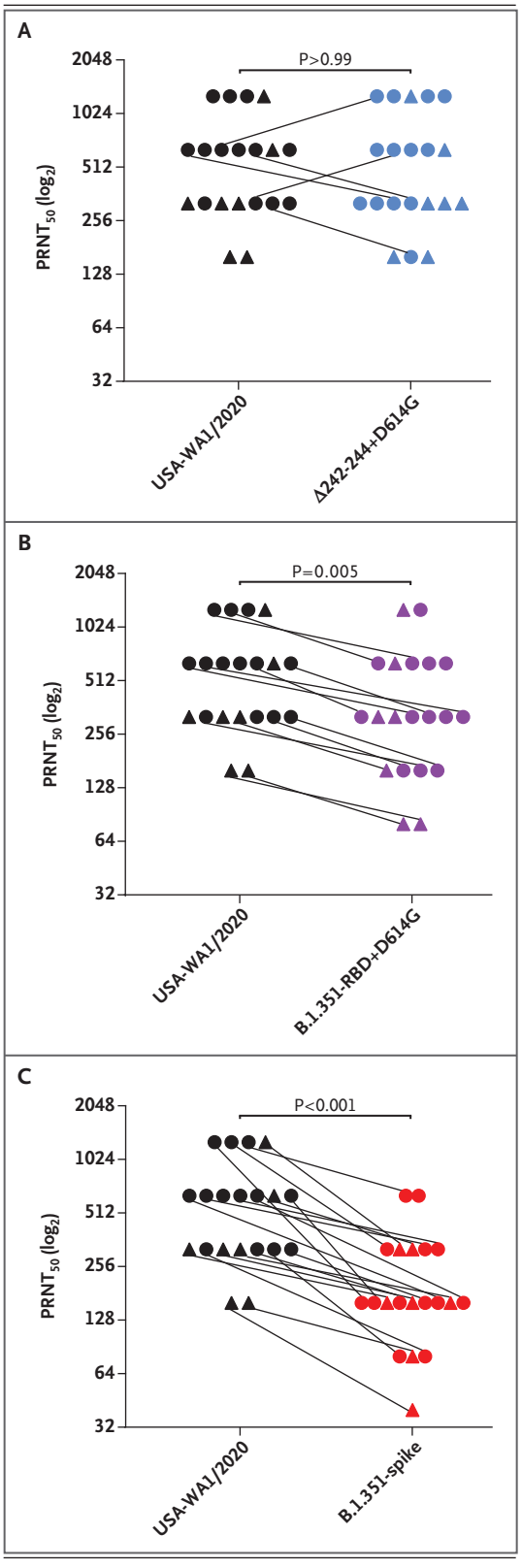
We performed 50% plaque reduction neutralization testing ($PRNT_{50}$) using 20 serum samples that had been obtained from 15 participants in the pivotal trial[1,4] 2 or 4 weeks after the administration of boost immunization with 30 μg of BNT162b2 (which occurred 3 weeks after the first immunization) (Fig. S3). All the serum samples neutralized USA-WA1/2020 and all mutant viruses at titers of 1:40 or greater. Geometric mean neutralizing titers against USA-WA1/2020, Δ242-244+D614G, B.1.351-RBD+D614G, and B.1.351-spike viruses were 501, 485, 331, and 184, respectively (Fig. 1 and Table S1). Thus, as compared with neutralization of USA-WA1/2020, neutralization of Δ242-244+D614G virus was similar and neutralization of the B.1.351-spike virus was weaker by approximately two thirds. Our data are also consistent with poorer neutralization of the virus with the full set of B.1.351-spike mutations than virus with either subset of mutations and suggested that virus with mutant residues in the receptor-binding site (K417N, E484K, and N501Y) is more poorly neutralized than virus with Δ242-244, which is located in the N-terminal domain of the spike protein.

Limitations of the study include a lack of systematic examination of individual mutations and the potential for mutations to alter neutralization by affecting spike function rather than antigenicity. The onset of protection after one dose of BNT162b2 precedes the development of high neutralizing titers, and BNT162b2 immunization also elicits CD8+ T-cell responses.[1,4,5] Thus, it is unclear what effect a reduction in neutralization by approximately two thirds would have on BNT162b2-elicited protection from Covid-19 caused by the B.1.351 lineage of SARS-CoV-2.

Yang Liu, Ph.D.
Jianying Liu, Ph.D.
Hongjie Xia, Ph.D.
Xianwen Zhang, B.S.
Camila R. Fontes-Garfias, Ph.D.
University of Texas Medical Branch
Galveston, TX

Figure 1. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

Shown are the results of 50% plaque reduction neutralization testing ($PRNT_{50}$) with the use of 20 samples obtained from 15 trial participants 2 weeks (circles) or 4 weeks (triangles) after the administration of the second dose of the BNT162b2 vaccine. The mutant viruses were obtained by engineering the full set of mutations in the B.1.351 lineage or subsets thereof into USA-WA1/2020. Results are shown for serum neutralization of USA-WA1/2020 and Δ242-244+D614G virus (Panel A), B.1.351-RBD+D614G virus (Panel B), and B.1.351-spike virus (Panel C). Samples that have measurably different $PRNT_{50}$ values against USA-WA1/2020 and mutant viruses are indicated by solid lines. Each $PRNT_{50}$ data point is the geometric mean of results obtained by duplicate assays performed on each serum sample. No differences were observed in the two results from the duplicate assays. Statistical analysis was performed with the use of the Wilcoxon signed-rank test.



Kena A. Swanson, Ph.D.
Hui Cai, Ph.D.
Ritu Sarkar, M.A.
Wei Chen, M.S.
Mark Cutler, Ph.D.
David Cooper, Ph.D.

Pfizer Vaccine Research and Development
Pearl River, NY

Scott C. Weaver, Ph.D.

University of Texas Medical Branch
Galveston, TX

Alexander Muik, Ph.D.
Ugur Sahin, M.D.

BioNTech
Mainz, Germany

Kathrin U. Jansen, Ph.D.

Pfizer Vaccine Research and Development
Pearl River, NY

Xuping Xie, Ph.D.

University of Texas Medical Branch
Galveston, TX
xuxie@utmb.edu

Philip R. Dormitzer, M.D., Ph.D.

Pfizer Vaccine Research and Development
Pearl River, NY
philip.dormitzer@pfizer.com

Pei-Yong Shi, Ph.D.

University of Texas Medical Branch
Galveston, TX
peshi@utmb.edu

Drs. Y. Liu and J. Liu contributed equally to this letter.

Supported by Pfizer and BioNTech.

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

This letter was published on February 17, 2021, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
2. Plante JA, Liu Y, Liu J, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature 2020 October 26 (Epub ahead of print).
3. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020;182(4):812-827.e19.
4. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020;383:2439-50.
5. Sahin U, Muik A, Vogler I, et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. December 11, 2020 (https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1). preprint.

DOI: 10.1056/NEJMc2102017