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Supported by Alexion, Ernest and Evelyn Rady, the J. Willard and Alice S. Marriott Foundation, and a grant (UL1TR002550) from the National Institutes of Health.

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

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DOI: 10.1056/NEJMc2100365

Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351)

TO THE EDITOR: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 501Y.V2 lineage (also known as B.1.351), first identified in South Africa in October 2020,¹ has mutations that confer increased resistance to plasma from convalescent patients and vaccine recipients, as well as to some monoclonal antibodies.²⁻⁴ However, the immune response to 501Y.V2 is unknown. Similarly, the ability of antibodies elicited by 501Y.V2 infection to cross-react with other variants is unknown, but such cross-reactivity would have implications for the ability of second-generation vaccines based on the 501Y.V2 spike protein to protect against infection with the original and emerging SARS-CoV-2 lineages.⁵

We characterized the SARS-CoV-2 infections in a cohort of patients with coronavirus disease 2019 (Covid-19) who were hospitalized in the Groote Schuur Hospital, Cape Town (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), after the emergence and dominance of 501Y.V2 in South Africa. Blood samples were obtained from 89 patients between December 31, 2020, and January 15, 2021; of these patients, 28 (31%) were randomly selected for SARS-CoV-2 sequencing, all of whom were shown by phylogenetic analysis to be infected with 501Y.V2 (Fig. S1A). Furthermore, at this time, the epidemic in Cape Town (Fig. S1B) and in South Africa as a whole was dominated by 501Y.V2, which accounted for more than 90% of infections. No patient in our study reported previous SARS-CoV-2 infection.

We first assessed the binding and neutraliz-

ing antibody responses of these patients to the 501Y.V2 spike protein. As with the original variant (D614G), 501Y.V2 elicited high-titer binding and neutralizing antibody responses (Fig. S2). Furthermore, titers of binding antibodies to the receptor-binding domain (including all of sub-domain 1) and the full spike protein of the original variant were highly correlated with titers of binding antibodies to the corresponding proteins of the 501Y.V2 variant. Titration of a subset of 46 samples revealed that plasma samples had higher titers to the spike protein of 501Y.V2 than to the spike protein of the original variant (mean of 1.7 times as high), but high-level binding to the original variant remained (Fig. S3).

We previously reported that plasma from persons infected with the original variant showed substantially lower neutralization of the 501Y.V2 variant than of the original variant (Figs. 1A and S4A).² In the current study, we performed the reverse experiment by assessing the cross-reactivity of the plasma neutralizing responses in the Groote Schuur Hospital cohort of patients with 501Y.V2 infection against the original variant and against 501Y.V3 (P.1), the variant first described in Brazil. We first tested 57 plasma samples from patients at Groote Schuur Hospital against both 501Y.V2 and the original variant and found that 53 of 57 samples maintained neutralization activity against the original variant, with a geometric mean titer of 203 (95% confidence interval, 141 to 292), approximately one third of the titer against the 501Y.V2 variant (Figs. 1B and S5A). When we limited the analysis

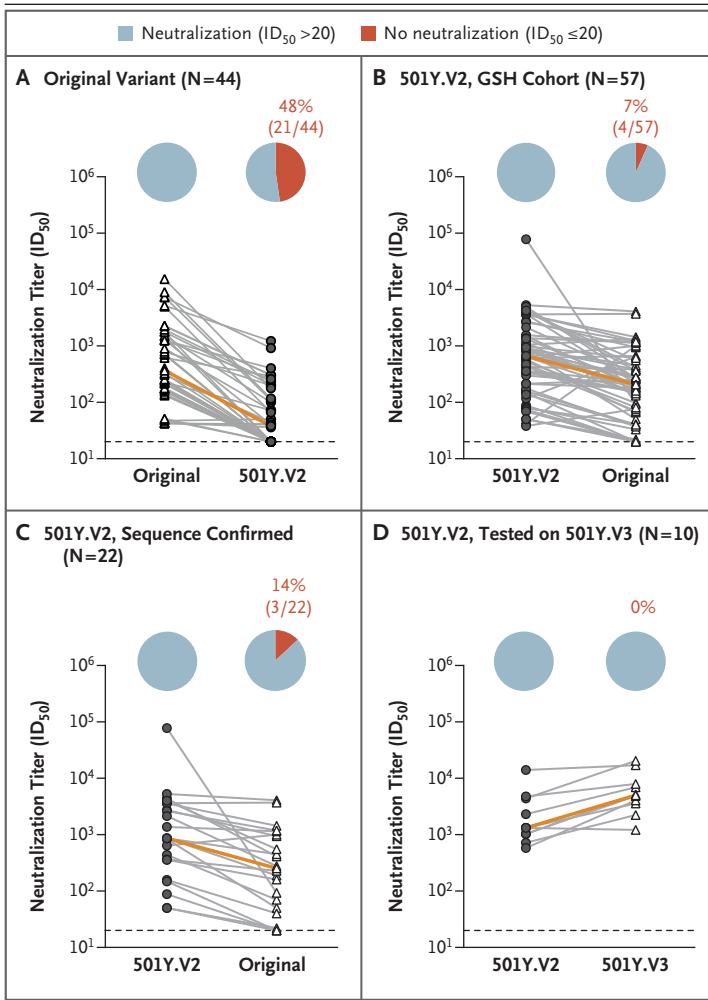


Figure 1. Cross-Reactivity of Neutralizing Antibody Responses.

Plasma samples from patients infected with the original variant (D614G) (Panel A) and from patients in the Groote Schuur Hospital (GSH) cohort who were infected with the 501Y.V2 variant (Panels B, C, and D) were compared for their neutralization cross-reactivity against other variants. One analysis (Panel C) was limited to samples from the 22 patients who had positive titers of binding antibodies and in whom sequencing had confirmed infection with 501Y.V2. A subset of 10 samples (Panel D) was assayed against 501Y.V3 pseudoviruses. Neutralizing antibody responses elicited by 501Y.V2 infection were more cross-reactive than those elicited by infection with the original variant. Plasma from patients infected with the original variant elicited titers against 501Y.V2 that were, on average, approximately one ninth of the titer elicited against the original variant (Panel A). In contrast, plasma from patients who had been infected with 501Y.V2 elicited responses against the original variant that were one third (Panel B) and one fourth (Panel C) of those elicited against the 501Y.V2 variant. Plasma from some of the patients infected with 501Y.V2 elicited even greater responses against 501Y.V3 than against 501Y.V2 (approximately three times as high) (Panel D). In each graph, the orange line indicates the slope between the median neutralization potencies of the samples tested. In the pie charts, blue indicates the percentage of samples with neutralization activity and red the percentage of samples with no detectable neutralization activity. The threshold of detection for the neutralization assay is a 50% inhibitory dilution (ID_{50}) of 20. All experiments were performed in duplicate, and the mean values are shown. Data for the original variant plasma are from Wibmer et al.²

to the 22 donors who had sequencing-confirmed infection with 501Y.V2 and had positive titers of binding antibodies, we observed the same pattern (Fig. 1C). Finally, we tested a subset of 10 plasma samples against the 501Y.V3 (P.1) variant and found high levels of neutralization of this variant, with some samples showing higher potency against 501Y.V3 (P.1) than against 501Y.V2, a finding that may be due to the very different N-terminal domains of these variants (Fig. 1D).

Overall, we found that 501Y.V2 elicits robust neutralizing antibody responses against both the original variant and 501Y.V3 (P.1), which indicates high levels of cross-reactivity. Our data indicate that vaccines built on the spike protein of 501Y.V2 may be promising candidates for the elicitation of cross-reactive neutralizing antibody responses to SARS-CoV-2.

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Supported by the South African Medical Research Council (grants 96825, SHIPNCD 76756, and DST/CON 0250/2012), the Centers for Disease Control and Prevention (grant 5 U01IP001048-05-00), the ELMA South Africa Foundation (grant 20-ESA011) and the Wellcome Centre for Infectious Diseases Research in Africa, which is supported by core funding from the Wellcome Trust (grant 203135/Z/16/Z). Dr. Wibmer is supported by the Fogarty International Center of the National Institutes of Health (award number R21TW011454) and the FLAIR Fellowship program (award number FLR\|R1\|201782). Dr. Burgers is supported by the European and Developing Countries Clinical Trials Partnership 2 of the European Union Horizon 2020 program (grant TMA2016SF-1535-CaTCH-22). Dr. Moore is supported by the South African Research Chairs Initiative of the Department of Science and Innovation and the National Research Foundation (grant 98341).

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This letter was published on April 7, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2104192

Mutant *UBA1* and Severe Adult-Onset Autoinflammatory Disease

TO THE EDITOR: Beck and colleagues (Dec. 31 issue)¹ describe a new autoinflammatory disorder named the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome exclusively in male patients showing somatic mutations in *UBA1*. We report here the occurrence of the VEXAS syndrome in two female patients.

An 87-year-old woman was referred for relapsing chondritis, prolonged fever, and an inflammatory syndrome lasting for 2 months. Unclassified myelodysplastic syndrome was diagnosed: she presented with macrocytic anemia, thrombocytopenia, and myeloid dyspoiesis with vacuoles in myeloid precursors (Fig. S1A in the Supplementary Appendix, available with the full

text of this letter at NEJM.org) and acquired X monosomy in the bone marrow karyotype. Her disease was refractory to glucocorticoids and methotrexate. She died 1 year after diagnosis from severe infection. DNA that was obtained from a cytogenetic pellet was used to perform Sanger sequencing and allowed us to identify a heterozygous p.Met41Val mutation. We also identified a p.Met41Leu *UBA1* mutation in a 78-year-old woman referred for an inflammatory syndrome and chondritis. She harbored vacuoles in myeloid precursors with dysmyelopoiesis (Fig. S1B) and also acquired X monosomy in the bone marrow karyotype. These data support the occurrence of the VEXAS syndrome in female patients,