CORRESPONDENCE

Neutralization of the SARS-CoV-2 Mu Variant by Convalescent and Vaccine Serum

TO THE EDITOR: During the current pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (Covid-19), has diversified considerably. As of September 2021, the World Health Organization had defined four variants of concern (alpha [B.1.1.7], beta [B.1.351], gamma [P.1], and delta [B.1.617.2 and AY]), as well as five variants of interest (eta [B.1.525], iota [B.1.526], kappa [B.1.617.1], lambda [C.37], and mu [B.1.621]).[1]

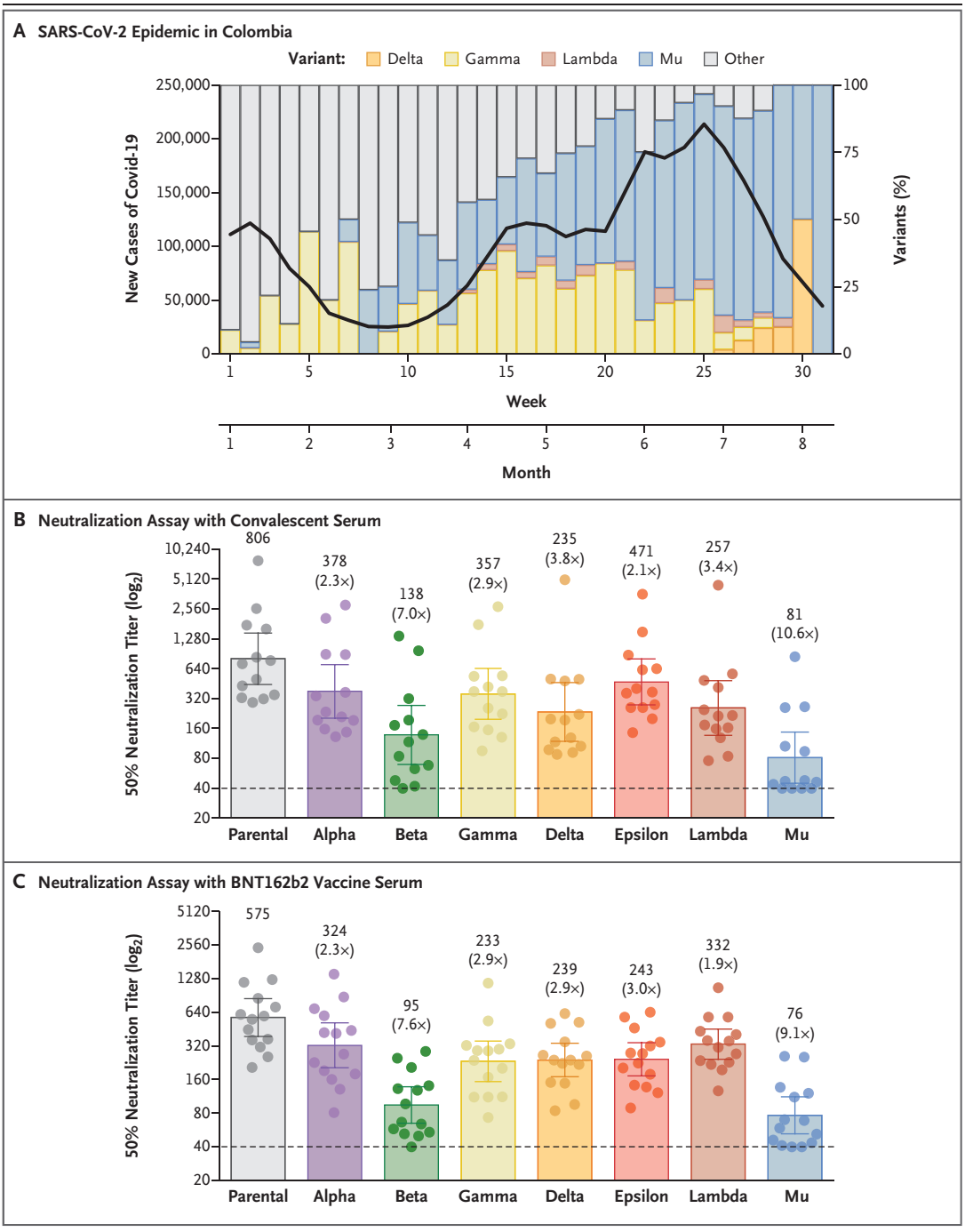
Mu represents the most recently recognized variant of interest.[1] As of August 30, 2021, the mu variant had been detected in 39 countries (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The epicenter of mu transmission is Colombia, where the variant was first isolated on January 11, 2021 (Fig. 1A and Table S2). There was a huge surge in Covid-19 cases in Colombia from March through July 2021. Although the gamma variant was dominant during the initial phase of the surge, the mu variant outnumbered all other variants in May, and it has driven the epidemic in Colombia since that time (Fig. 1A).

Newly emerging SARS-CoV-2 variants need to be carefully monitored for potentially increased transmission rate, pathogenicity, and resistance to immune responses. The resistance of variants of concern and variants of interest to serum obtained from persons who have recovered from Covid-19 and persons who have been vaccinated can be attributed to a variety of mutations in the viral spike protein.[2] The majority of mu variants harbor the T95I and YY144-145TSN mutations in the N-terminal domain; the R346K, E484K, and N501Y mutations in the receptor-binding domain; and the D614G, P681H, and D950N mutations in other regions of the spike protein (Tables S3 and S4). Some of these mutations are commonly identified in variants of concern (Table S5). Of these mutations, E484K (shared by the beta and gamma variants) has shown the greatest reduction in sensitivity to antibodies induced by natural SARS-CoV-2 infection and vaccination.[3,4]

To assess the sensitivity of the mu variant to antibodies induced by SARS-CoV-2 infection and by vaccination, we generated pseudoviruses harboring the spike protein of the mu variant or the spike protein of other variants of concern or

Figure 1 (next page). SARS-CoV-2 in Colombia and Characterization of the Mu Variant.

Panel A shows new cases of coronavirus disease 2019 (Covid-19) from January through August 2021 in Colombia. The mu variant was first isolated on January 11, 2021, in Colombia (Global Influenza Surveillance and Response System accession number, EPI_ISL_1220045). The black line reflects the number of new weekly cases, and the colored bars indicate the percentage of each variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among the cases. The raw data are summarized in Table S2 in the Supplementary Appendix. Panels B and C show the results of virus neutralization assays. Neutralization assays were performed with the use of pseudoviruses harboring the SARS-CoV-2 spike proteins of the alpha, beta, gamma, delta, epsilon, lambda, or mu variants or the B.1 lineage virus, which harbors the D614G mutation (parental virus). Serum samples were obtained from 13 persons who had recovered from Covid-19 (Panel B) and from 14 persons who had received the BNT162b2 vaccine (Panel C). The assay of each serum sample was performed in triplicate to determine the 50% neutralization titer. Each data point represents an individual sample (circles) and indicates the 50% neutralization titer obtained with each sample against the indicated pseudovirus. The heights of the bars and the numbers over the bars indicate the geometric mean titers, and the I bars indicate 95% confidence intervals. The numbers in parentheses indicate the average difference in neutralization resistance of the indicated variants as compared with that of the parental virus. The horizontal dashed lines indicate the limit of detection. The raw data and information regarding the convalescent donors (sex, age, severity of disease, and dates of testing and sampling) and vaccinated donors (sex, age, and dates of second vaccination and sampling) of serum samples are summarized in Tables S6 and S7 in the Supplementary Appendix.



variants of interest. Virus neutralization assays, performed with the use of serum samples obtained from 13 persons who had recovered from Covid-19 who were infected early in the pandemic (April through September 2020), showed that the mu variant was 10.6 times as resistant to neutralization as the B.1 lineage virus (parental virus), which bears the D614G mutation (Fig. 1B). Assays performed with serum samples obtained from 14 persons who had received the BNT162b2 vaccine showed that the mu variant was 9.1 as resistant as the parental virus (Fig. 1C). Although the beta variant (a variant of concern) was thought to be the most resistant variant to date,[3,4] the mu variant was 2.0 as resistant to neutralization by convalescent serum

(Fig. 1B) and 1.5 times as resistant to neutralization by vaccine serum as the beta variant (Fig. 1C). Thus, the mu variant shows a pronounced resistance to antibodies elicited by natural SARS-CoV-2 infection and by the BNT162b2 mRNA vaccine. Because breakthrough infections are a major threat of newly emerging SARS-CoV-2 variants,[5] we suggest that further characterization and monitoring of this variant of interest is warranted.

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Supported in part by grants from the Japan Agency for Medical Research and Development (AMED) Research Program on Emerging and Re-emerging Infectious Diseases (20fk0108146 [to Dr. Sato], 20fk0108413 [to Drs. Kaneda, Nakagawa, and Sato], and 20fk0108451 [to the Genotype to Phenotype Japan Consortium and Drs. Takaori-Kondo, Kaneda, Nakagawa, and Sato]); the AMED Research Program on HIV/AIDS (21fk0410039 [to Drs. Shirakawa and Sato]); Japan Science and Technology (JST) Strategic International Collaborative Research Program (SICORP) e-ASIA (JPMJSC20U1 [to Dr. Sato]); JST SICORP (JPMJSC21U5 [to Dr. Sato]); JST CREST (JPMJCR20H6 [to Dr. Nakagawa] and JPMJCR20H4 [to Drs. Kaneda and Sato]); Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research B (18H02662 and 21H02737 [to Dr. Sato]); JSPS Fund for the Promotion of Joint International Research (Fostering Joint International Research) (18KK0447 [to Dr. Sato]); JSPS Core-to-Core Program, Advanced Research Networks (JPJSCCA20190008 [to Dr. Sato]); JSPS Research Fellow (DC1 19J20488 [to Mr. Kimura]); and the Tokyo Biochemical Research Foundation (to Dr. Sato).

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

This letter was published on November 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2114706