CORRESPONDENCE

Risk of BA.5 Infection among Persons Exposed to Previous SARS-CoV-2 Variants

TO THE EDITOR: In recent months, omicron (B.1.1.529) became the dominant variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), displaying some degree of immune evasion.[1] The initial omicron subvariants, BA.1 and BA.2, are being progressively displaced by BA.5 in many countries, possibly owing to greater transmissibility and partial evasion of BA.1- and BA.2-induced immunity.[2,3] The protection afforded by BA.1 against infection by the BA.5 subvariant is critical because adapted vaccines under clinical trials are based on BA.1.

Portugal was one of the first countries affected by a BA.5 predominance. We used the national coronavirus disease 2019 (Covid-19) registry (SINAVE) to calculate the risk of BA.5 infection among persons with documented infection with past variants, including BA.1 and BA.2. The registry includes all reported cases in the country, regardless of clinical presentation.

The national SARS-CoV-2 genetic surveillance identified periods when different variants represented more than 90% of the isolates.[4] We identified all persons who had a first infection in periods of dominance of each variant, to calculate their infection risk during the period of BA.5 dominance (Fig. 1A). We pooled BA.1 and BA.2 because of the slow transition between the two

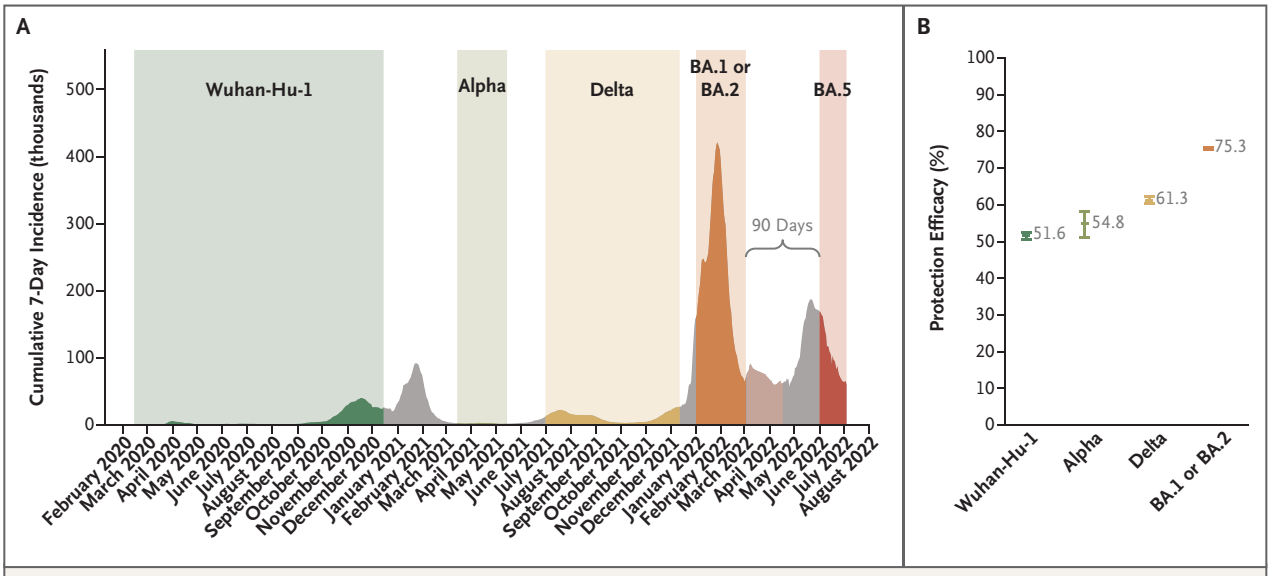

Figure 1. Protective Effect of Previous SARS-CoV-2 Infection on Infection with the Omicron BA.5 Subvariant.

As shown in Panel A, we identified the periods (in different colors) when one variant was represented in more than 90% of sample isolates (data from the national severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] genetic diversity surveillance[4]). The periods in gray represent times when more than one variant was in circulation. Given the relatively slow transition between dominance by the omicron BA.1 subvariant and dominance by the omicron BA.2 subvariant, we pooled BA.1 and BA.2 in the analysis. We did not include anyone infected in the 90 days before dominance by the omicron BA.5 subvariant. Panel B shows protection efficacy against infection during the period of BA.5 dominance (from June 1, 2022) among persons with one infection in the periods of dominance of different variants, as represented in Panel A, as compared with persons without any documented infection until June 1. Persons with two infections before June 1 were not included in the study. I bars represent 95% confidence intervals.

subvariants in the population. Finally, we calculated the risk of BA.5 infection for the population that did not have any documented infection before BA.5 dominance (June 1, 2022).

We found that previous SARS-CoV-2 infection had a protective effect against BA.5 infection (Fig. 1B and Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), and this protection was maximal for previous infection with BA.1 or BA.2. These data should be considered in the context of breakthrough infections in a highly vaccinated population, given that in Portugal more than 98% of the study population completed the primary vaccination series before 2022.

The study design cannot eliminate all confounders (see the Discussion section in the Supplementary Appendix). In addition, one limitation is the putative effect of immune waning in a population with hybrid immunity (previous infection and vaccination). We found that BA.1 or BA.2 infection in vaccinated persons provided higher protection against BA.5 than infection with pre-omicron variants, in line with a recent report with a test-negative design.[5] However, BA.1 or BA.2 infections occurred closer to the period of BA.5 dominance than infections with previous variants. There is a perception that the protection afforded by previous BA.1 or BA.2 infection is very low, given the high number of BA.5 infections among persons with previous BA.1 or BA.2 infection. Our data indicate that this perception is probably a consequence of the larger pool of persons with BA.1 or BA.2 infection than with infection by other subvariants, and it is not supported by the data.

Overall, we found that breakthrough infections with the BA.5 subvariant were less likely among persons with a previous SARS-CoV-2 infection history in a highly vaccinated population, especially for previous BA.1 or BA.2 infection, than among uninfected persons.

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

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