CORRESPONDENCE

Protective Effect of Previous SARS-CoV-2 Infection against Omicron BA.4 and BA.5 Subvariants

TO THE EDITOR: The BA.4 and BA.5 subvariants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 (omicron) variant have shown the capacity of escaping from neutralizing antibodies.[1] These subvariants had an appreciable presence in Qatar by early May 2022 (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org) and had become the dominant subvariants by June 8 (Fig. S2). We estimated the effectiveness of previous SARS-CoV-2 infection in preventing reinfection with BA.4 and BA.5 subvariants using a test-negative, case–control study design (Section S1).[2]

We extracted data regarding SARS-CoV-2 laboratory testing, clinical infection, vaccination, and demographic details from the national SARS-CoV-2 databases, which include all results of polymerase-chain-reaction (PCR) and rapid antigen testing conducted at health care facilities in Qatar. Previous infection was defined as a positive test result at least 90 days before a new positive test finding; persons with negative results were used as controls.[2] To control for differences in SARS-CoV-2 infection risk in Qatar, we matched cases and controls according to sex, 10-year age group, nationality, number of coexisting medical conditions, calendar week of testing, method of testing, and reason for testing.[2] Previous infection was further categorized according to its occurrence in Qatar before the December 19, 2021, initiation of the omicron wave (pre-omicron infections) or after that date (post-omicron infections).[3]

In the main analysis, we estimated the effectiveness of previous infection against reinfection with BA.4 or BA.5 using the determination of S-gene target failure (SGTF) on PCR testing between May 7 and July 28, 2022 (Fig. S3). The SGTF designation indicates the deletion of codons 69 and 70 in the S gene, which is common to omicron subvariants BA.1, BA.4, and BA.5. Because the incidence of BA.1 was negligible during the study, as confirmed by sequencing (Section S2), SGTF was used as a proxy marker for BA.4 or BA.5 infection. The incidence of other variants that were characterized by SGTF was negligible during the study. We also estimated effectiveness on the assumption that all diagnosed SARS-CoV-2 infections between June 8 and July 28, 2022, were BA.4 or BA.5 infections, since these were the dominant subvariants during this period. Details regarding the study population are shown in Figures S3 and S4. The baseline characteristics of the study population are shown in Table S1. The study population was broadly representative of the population of Qatar (Table S2).

The effectiveness of pre-omicron infection against symptomatic BA.4 or BA.5 reinfection was 35.5% (95% confidence interval [CI], 12.1 to 52.7); the effectiveness against any BA.4 or BA.5 reinfection regardless of the presence of symptoms was 27.7% (95% CI, 19.3 to 35.2) (Table 1). The effectiveness of post-omicron infection against symptomatic BA.4 or BA.5 reinfection was 76.2% (95% CI, 66.4 to 83.1); the effectiveness against any BA.4 or BA.5 reinfection was 78.0% (95% CI, 75.0 to 80.7).

In the analysis of the effectiveness of previous infection in which we assumed that all diagnosed infections were BA.4 or BA.5, we found results that were similar to those of the main analysis. An analysis of effectiveness that was stratified according to the interval since previous infection showed waning protection over time (Section S3 and Table S3). Sensitivity analyses that were performed after adjustment for vaccination status and after matching according to the number of vaccine doses confirmed the results of the main analysis (Tables S3 and S4). Analyses that were categorized according to vaccination status also confirmed the study results but suggested that effectiveness could be slightly higher among vaccinated persons. Limitations of the study design are discussed in Section S1.

Protection from a previous SARS-CoV-2 infec-

Table 1. Effectiveness of Previous SARS-CoV-2 Infection in Preventing Reinfection with Omicron BA.4 and BA.5 Subvariants.*

Type of Analysis	Cases			Controls			Effectiveness of Previous Infection (95% CI)†
	Days after Previous Infection	Previous Infection	No Previous Infection	Days after Previous Infection	Previous Infection	No Previous Infection	
	median no.	*no. of patients*		*median no.*	*no. of patients*		%
SGTF status as proxy for BA.4 or BA.5 infection‡							
Effectiveness against symptomatic BA.4 or BA.5 infection							
Pre-omicron previous infection	518	63	549	489	265	1,763	35.5 (12.1–52.7)
Post-omicron previous infection	189	49	549	181	477	1,763	76.2 (66.4–83.1)
Effectiveness against any BA.4 or BA.5 infection							
Pre-omicron previous infection	490	484	4,234	482	2,139	14,466	27.7 (19.3–35.2)
Post-omicron previous infection	181	294	4,234	179	4,131	14,466	78.0 (75.0–80.7)
Any infection during BA.4 and BA.5 dominance§							
Effectiveness against symptomatic BA.4 or BA.5 infection							
Pre-omicron previous infection	496	244	2,509	490	1,089	7,634	38.1 (27.7–46.9)
Post-omicron previous infection	184	134	2,509	175	2,086	7,634	84.5 (81.1–87.2)
Effectiveness against any BA.4 or BA.5 infection							
Pre-omicron previous infection	493	1417	14,060	490	7,139	49,063	33.5 (29.3–37.5)
Post-omicron previous infection	182	855	14,060	177	13,421	49,063	80.2 (78.7–81.7)

* Cases and controls were matched one-to-five according to sex, 10-year age group, nationality, number of coexisting medical conditions, calendar week of testing, method of testing (polymerase chain reaction or rapid antigen), and reason for testing. Results of sensitivity analyses are provided in Tables S3 and S4 in the Supplementary Appendix. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.

† The effectiveness of previous infection in preventing reinfection was estimated with the use of a test-negative, case–control study design. Confidence intervals (CI) were not adjusted for multiplicity and thus should not be used to infer definitive differences between groups.

‡ Infections that indicated S-gene target failure (SGTF) were diagnosed between May 7 and July 28, 2022.

§ This category included all SARS-CoV-2 infections that were diagnosed between June 8 and July 28, 2022, when BA.4 and BA.5 subvariants were dominant. Larger case numbers mean that the statistical precision of this estimate is improved; however, the estimate provides only an upper boundary for effectiveness, since some of the infections that occurred during this period were caused by the BA.2 subvariant, which has been associated with less immune-system evasion than BA.4 or BA.5. (The BA.1 subvariant was no longer circulating in the population during the study period.)

tion against BA.4 or BA.5 reinfection was modest when the previous infection had been caused by a pre-omicron variant but strong when it had been caused by a post-omicron subvariant (including BA.1 or BA.2). Protection of a previous infection against reinfection with a BA.4 or BA.5 subvariant was lower than that against reinfection with a BA.1 or BA.2 subvariant[3-5] because of more waning of immune protection over time and a greater capacity for immune-system evasion with the BA.4 and BA.5 subvariants.

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Supported by the Biomedical Research Program and the Biostatistics, Epidemiology, and Biomathematics Research Core at Weill Cornell Medicine–Qatar; the Qatar Ministry of Public Health; Hamad Medical Corporation; and Sidra Medicine. The Qatar Genome Program and Qatar University Biomedical Research Center supported viral genome sequencing.

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

This letter was published on October 5, 2022, at NEJM.org.

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DOI: 10.1056/NEJMc2209306