CORRESPONDENCE

Protection against the Omicron Variant from Previous SARS-CoV-2 Infection

TO THE EDITOR: Natural infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits strong protection against reinfection with the B.1.1.7 (alpha),[1,2] B.1.351 (beta),[1] and B.1.617.2 (delta)[3] variants. However, the B.1.1.529 (omicron) variant harbors multiple mutations that can mediate immune evasion. We estimated the effectiveness of previous infection in preventing symptomatic new cases caused by omicron and other SARS-CoV-2 variants in Qatar. In this study, we extracted data regarding coronavirus disease 2019 (Covid-19) laboratory testing, vaccination, clinical infection data, and related demographic details from the national SARS-CoV-2 databases, which include all results of polymerase-chain-reaction (PCR) testing, vaccinations, and hospitalizations and deaths for Covid-19 in Qatar since the start of the pandemic.

The effectiveness of previous SARS-CoV-2 infection in preventing reinfection was defined as the proportional reduction in susceptibility to infection among persons who had recovered from infection as compared with those who had not been infected.[4] Previous SARS-CoV-2 infection was defined as a positive result on PCR assay at least 90 days before a new positive PCR finding.[4] We used a test-negative, case–control study design to assess the effectiveness of previous infection in preventing reinfection on the basis of a method that had recently been investigated and validated for derivation of robust estimates for such comparisons[4] (Section S1 of the Supplementary Appendix, available with the full text of this letter at NEJM.org). In addition, we performed sensitivity analyses that included adjustment for vaccination status and that excluded vaccinated persons from the analysis. Case patients (defined as persons with positive PCR results) and controls (defined as persons with negative PCR results) were matched according to sex, 10-year age group, nationality, and calendar time of PCR testing to control for known differences in the risk of exposure to SARS-CoV-2 infection in Qatar.[4]

To ensure that epidemiologically relevant reinfections were considered in the analysis, only documented infections with a PCR cycle threshold (Ct) value of 30 or less were included as cases in our study. (Reinfection often occurs with negligible symptoms and high Ct values, indicating reduced epidemiologic significance.)[5] We also estimated the effectiveness of previous infection in preventing hospitalization or death caused by reinfection.

The selection of the study population for various analyses is shown in Figures S1 through S4 and the population characteristics in Tables S1 and S2. The overall study population was broadly representative of the total population of Qatar (Table S3), with a median age of 31 to 35 years across the study samples. The median interval between previous infection and PCR testing among cases and controls was 279 days (interquartile range [IQR], 194 to 313) for analysis of the alpha variant, 285 days (IQR, 213 to 314) for analysis of the beta variant, 254 days (IQR, 159 to 376) for analysis of the delta variant, and 314 days (IQR, 268 to 487) for analysis of the omicron variant.

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Table 1. Effectiveness of Previous Infection with SARS-CoV-2 against Symptomatic Reinfection, According to Variant.*

Type of Analysis and Variant	Cases (PCR-Positive)		Controls (PCR-Negative)		Effectiveness (95% CI)†
	Previous Infection	No Previous Infection	Previous Infection	No Previous Infection	
	number of patients				*percent*
Effectiveness against symptomatic infection					
Primary analysis‡					
Alpha	2	334	94	1548	90.2 (60.2 to 97.6)
Beta	14	1322	450	6084	85.7 (75.8 to 91.7)
Delta	23	2153	1154	8782	92.0 (87.9 to 94.7)
Omicron	412	5284	1620	9053	56.0 (50.6 to 60.9)
Primary analysis after adjustment for vaccination status‡					
Alpha	2	334	94	1548	90.3 (60.4 to 97.6)
Beta	14	1322	450	6084	85.1 (74.5 to 91.3)
Delta	23	2153	1154	8782	91.9 (87.8 to 94.7)
Omicron	412	5284	1620	9053	55.9 (50.5 to 60.8)
Primary analysis after exclusion of vaccinated patients‡§					
Alpha	1	285	94	1294	95.3 (66.0 to 99.3)
Beta	10	1084	312	4976	85.4 (72.4 to 92.2)
Delta	11	1026	400	3966	90.2 (81.9 to 94.6)
Omicron	60	1031	258	1738	61.9 (48.2 to 72.0)
Effectiveness against severe, critical, or fatal Covid-19¶					
Alpha	1	44	15	199	69.4 (–143.6 to 96.2)
Beta	2	186	76	824	88.0 (50.7 to 97.1)
Delta	0	135	56	528	100 (43.3 to 100)‖
Omicron	2	70	39	167	87.8 (47.5 to 97.1)

* Covid-19 denotes coronavirus disease 2019, and PCR polymerase chain reaction.

† The effectiveness of previous infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in preventing reinfection was estimated with the use of a test-negative, case–control study design.[4]

‡ In these analyses, case patients and controls were matched in a 1:5 ratio according to sex, 10-year age group, nationality, and calendar week of PCR testing in patients with the alpha, beta, and delta variants from March 23 to November 18, 2021; or in a 1:3 ratio according to sex, 10-year age group, nationality, and calendar date of PCR testing in patients with the omicron variant from December 23, 2021, to January 2, 2022. (The populations in the various groups are shown in Figs. S1 and S2 in the Supplementary Appendix.)

§ Additional data about these groups are provided in Figures S3 and S4.

¶ Severe, critical, and fatal cases of Covid-19 caused by the alpha, beta, and delta variants were defined according to the World Health Organization guidelines (Sections S1 and S3). Because the outbreak of the omicron variant began recently in Qatar, the assessment of severe, critical, and fatal cases of omicron infections was completed for only a small number of cases. Therefore, for patients with omicron infection, any acute-bed hospital admission was used as a proxy for severe Covid-19 and any admission to an intensive care unit was used as a proxy for critical Covid-19.

‖ The confidence interval for this calculation could not be estimated by means of conditional logistic regression because no events occurred in the patients with previous infection. Thus, the confidence interval was estimated by means of the standard error of the crude odds ratio that was used to calculate effectiveness.

The effectiveness of previous infection in preventing reinfection was estimated to be 90.2% (95% confidence interval [CI], 60.2 to 97.6) against the alpha variant, 85.7% (95% CI, 75.8 to 91.7) against the beta variant, 92.0% (95% CI, 87.9 to 94.7) against the delta variant, and 56.0% (95% CI, 50.6 to 60.9) against the omicron variant (Table 1). Sensitivity analyses confirmed the study results, as expected for this study design, which is robust regardless of the approach that is used to control for vaccine-induced immunity.[4] An additional analysis that was adjusted for the

interval since previous infection also confirmed the study results (Table S4).

Among the patients with reinfection, progression to severe Covid-19 occurred in one patient with the alpha variant, in two patients with the beta variant, in no patients with the delta variant, and in two patients with the omicron variant. None of the reinfections progressed to critical or fatal Covid-19. The effectiveness with respect to severe, critical, or fatal Covid-19 was estimated to be 69.4% (95% CI, –143.6 to 96.2) against the alpha variant, 88.0% (95% CI, 50.7 to 97.1) against the beta variant, 100% (95% CI, 43.3 to 100) against the delta variant, and 87.8% (95% CI, 47.5 to 97.1) against the omicron variant. (For the delta variant, the calculation of the 95% confidence interval is clarified in a footnote in Table 1.) Limitations of the estimations (e.g., the relatively young population of Qatar) are discussed in Section S1.

Overall, in a national database study in Qatar, we found that the effectiveness of previous infection in preventing reinfection with the alpha, beta, and delta variants of SARS-CoV-2 was robust (at approximately 90%), findings that confirmed earlier estimates.[1-3] Such protection against reinfection with the omicron variant was lower (approximately 60%) but still considerable. In addition, the protection of previous infection against hospitalization or death caused by reinfection appeared to be robust, regardless of variant.

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