IMPORTANCE The effect of prior SARS-CoV-2 infection on vaccine protection remains poorly understood.

OBJECTIVE To assess protection from SARS-CoV-2 breakthrough infection after mRNA vaccination among persons with vs without prior SARS-CoV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS Matched-cohort studies in Qatar for the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines. A total of 1,531,736 individuals vaccinated with either vaccine between December 21, 2020, and September 19, 2021, were followed up beginning 14 days after receiving the second dose until September 19, 2021.

EXPOSURES Prior SARS-CoV-2 infection and COVID-19 vaccination.

MAIN OUTCOMES AND MEASURES Incident SARS-CoV-2 infection, defined as a polymerase chain reaction (PCR)-positive nasopharyngeal swab regardless of reason for PCR testing or presence of symptoms. Cumulative incidence was calculated using the Kaplan-Meier estimator method.

RESULTS The BNT162b2-vaccinated cohort comprised 99,226 individuals with and 290,432 matched individuals without prior PCR-confirmed infection (median age, 37 years; 68% male). The mRNA-1273–vaccinated cohort comprised 58,096 individuals with and 169,514 matched individuals without prior PCR-confirmed infection (median age, 36 years; 73% male). Among BNT162b2-vaccinated persons, 159 reinfections occurred in those with and 2,509 in those without prior infection 14 days or more after dose 2. Among mRNA-1273–vaccinated persons, 43 reinfections occurred in those with and 368 infections in those without prior infection. Cumulative infection incidence among BNT162b2-vaccinated individuals was an estimated 0.15% (95% CI, 0.12%-0.18%) in those with and 0.83% (95% CI, 0.79%-0.87%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio for breakthrough infection with prior infection, 0.18 [95% CI, 0.15-0.21]; P < .001). Cumulative infection incidence among mRNA-1273–vaccinated individuals was an estimated 0.11% (95% CI, 0.08%-0.15%) in those with and 0.35% (95% CI, 0.32%-0.40%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio, 0.35 [95% CI, 0.25-0.48]; P < .001). Vaccinated individuals with prior infection 6 months or more before dose 1 had statistically significantly lower risk for breakthrough infection than those vaccinated less than 6 months before dose 1 (adjusted hazard ratio, 0.62 [95% CI, 0.42-0.92]; P = .02 for BNT162b2 and 0.40 [95% CI, 0.18-0.91]; P = .03 for mRNA-1273 vaccination).

CONCLUSIONS AND RELEVANCE Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021. The observational study design precludes direct comparisons of infection risk between the 2 vaccines.

Published online November 1, 2021.

© 2021 American Medical Association. All rights reserved.
The effect of prior SARS-CoV-2 infection on vaccine protection against future infection remains poorly understood.\textsuperscript{1,3} Qatar launched COVID-19 immunization on December 21, 2020, first using the BNT162b2 (Pfizer-BioNTech) vaccine\textsuperscript{4} and, 3 months later, adding the mRNA-1273 (Moderna) vaccine,\textsuperscript{5} both following the US Food and Drug Administration–approved protocols.\textsuperscript{6-8} As vaccination was scaled up, the country experienced 2 back-to-back SARS-CoV-2 waves from January through June 2021, which were dominated by the Alpha\textsuperscript{9} (B.1.1.7) and Beta\textsuperscript{9} (B.1.351) variants\textsuperscript{6,7,10-12} (eFigure 1 and eMethods in the Supplement). Appreciable community transmission of the Delta\textsuperscript{9} (B.1.617.2) variant was first detected toward the end of March 2021, and by summer 2021, Delta had become the dominant variant.\textsuperscript{10-12} This provided an opportunity to assess whether persons vaccinated after a prior SARS-CoV-2 infection had a lower incidence of breakthrough infection than those vaccinated without prior infection.

Methods

This retrospective study was approved by the Hamad Medical Corporation and Weill Cornell Medicine–Qatar Institutional Review Boards with waiver of informed consent because only routinely collected data were used.

Participants

This study was conducted in the resident population of Qatar and leveraged the national, federated databases at Hamad Medical Corporation, the main public health care provider and the nationally designated provider for all COVID-19 health care needs. These databases were constructed to capture all SARS-CoV-2–related data along with related demographic details since the start of the epidemic, including all records of polymerase chain reaction (PCR) testing, COVID-19 hospitalizations, COVID-19 vaccinations, SARS-CoV-2 infection severity classification per World Health Organization (WHO) guidelines,\textsuperscript{13} and COVID-19 deaths, also assessed per WHO guidelines.\textsuperscript{14} Every PCR test conducted in Qatar, regardless of location (eg, outpatient clinic, drive-through testing site, or hospital), is classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, random testing campaigns [surveys], individual requests, routine health care testing, pretravel, and at port of entry).

Association between prior infection and acquisition of infection after vaccination was investigated using 2 retrospective, matched-cohort studies. The eligible study population included all BNT162b2–vaccinated and mRNA-1273–vaccinated individuals in the Hamad Medical Corporation database between December 21, 2020, and September 19, 2021. We compared incidence of documented SARS-CoV-2 infection 14 days or more after the second vaccine dose in the cohort of individuals who had experienced PCR-confirmed infection before vaccination vs incidence among those who had no record of a prior infection for both the BNT162b2 and mRNA-1273 vaccine cohorts.

Key Points

Question Are persons vaccinated after SARS-CoV-2 infection better protected against breakthrough infection than those vaccinated without prior infection?

Findings In this cohort study of 1531736 mRNA-vaccinated individuals in Qatar, prior SARS-CoV-2 infection was associated with a statistically significant reduced hazard of breakthrough infection among recipients of both the BNT162b2 (Pfizer-BioNTech) (adjusted hazard ratio, 0.62) and the mRNA-1273 (Moderna) vaccines (adjusted hazard ratio, 0.40).

Meaning Prior SARS-CoV-2 infection was associated with a lower risk for breakthrough infection among persons receiving the SARS-CoV-2 mRNA vaccines; however, the observational study design precludes direct comparison of infection risk between the 2 vaccines.

Exposure Exposure was a documented SARS-CoV-2 infection any time prior to first dose of BNT162b2 or mRNA-1273 COVID-19 vaccine. Documented SARS-CoV-2 infection was defined as a PCR-positive nasopharyngeal swab regardless of the reason for PCR testing or presence of symptoms.

Outcomes The primary outcome was documented SARS-CoV-2 (breakthrough) infection 14 days or more after the second dose of
either the BNT162b2 or mRNA-1273 vaccine. Fourteen days was chosen because earlier evidence indicated that BNT162b2-vaccinated or mRNA-1273-vaccinated individuals reach full vaccine-induced immunity within this time.4,5,8

Severe,13 critical,13 or fatal14 COVID-19 breakthrough disease was examined as an additional exploratory outcome. Classification of COVID-19 case severity (acute-care hospitalizations),33 criticality (intensive care unit [ICU] hospitalizations),13 and fatality14 followed WHO guidelines, and assessments were made by trained medical personnel using individual medical record reviews (eMethods in the Supplement).

Statistical Analyses
Descriptive statistics (frequency distributions and measures of central tendency) were used to characterize study samples. Standardized mean differences were used to compare groups, with a standardized mean difference less than 0.1 indicating adequate matching.17 The Kaplan-Meier estimator method18 was used to estimate the cumulative incidence of infection. Cumulative incidence of infection was defined as the proportion of individuals at risk who were identified with a breakthrough infection during follow-up among all eligible individuals in each cohort. The log-rank test was applied to assess equality of failure functions. Standard errors of failure functions were used to derive the 95% CIs of the absolute difference in cumulative incidence at different follow-up times. Incidence rates of infection were calculated by dividing the number of breakthrough infection cases identified during follow-up by the number of person-weeks contributed by all eligible individuals in the cohort. Incidence rates and corresponding 95% CIs were estimated using a Poisson log-likelihood regression model with the Stata version 17.0 stptime command.19

Follow-up person-time was calculated from the day each individual completed 14 days after the second vaccine dose up to the infection swab, all-cause death, or end-of-study censoring (September 19, 2021). The hazard ratios (HR) and corresponding 95% CIs were calculated using Cox regression adjusted for the matching factors with the Stata version 17.0 stcox command.19 Schoenfeld residuals and log-log plots were used to test the proportional-hazards assumption, which was generally met at nearly all time points, and subgroup analyses were performed to estimate adjusted HRs stratified by month of follow-up.

The analyzed national databases had no missing information for PCR testing outcomes, the matching factors, and severe, critical, or fatal COVID-19 disease. In all analyses, 2-sided P < .05 indicated statistical significance. Statistical analyses were conducted in Stata/SE version 17.0.19

Results
Study Population
A total of 1 531 736 eligible BNT162b2-vaccinated and mRNA-1273-vaccinated individuals were identified. Baseline characteristics of each vaccine cohort are shown in eTable 1 in the Supplement. There were small differences in median age and sex, but large differences in age distribution, nationality, and calendar month of dose 1 reflecting introduction of the mRNA-1273 vaccine 3 months after BNT162b2 (eFigure 1 in the Supplement), and a phased vaccine rollout prioritizing frontline health care workers, persons with severe or multiple chronic conditions, select occupational groups such as teachers, and age, all in context of associations with age, nationality, and occupation.8,15,20-22 Qatar has unusually young, diverse demographics, in that only 9% of its residents are 50 years or older, and 89% are expatriates residing in Qatar on work visas from more than 150 countries, of whom most are male.15,23

A median of 21 days (IQR, 20-22) elapsed between the first and second BNT162b2 doses; 97.4% of individuals received their second dose 30 days or less after their first dose. A median of 28 days (IQR, 28-31) elapsed between the first and second mRNA-1273 doses; 74.9% of individuals received their second dose 30 days or less after their first dose.

Of 963 899 BNT162b2-vaccinated individuals, 100 486 had prior PCR-confirmed infection; 99 226 were matched to 290 432 BNT162b2-vaccinated individuals with no record of prior infection (Figure 1). Proportions who had a PCR test done during follow-up were 45.0% and 41.8% among those with and without a prior infection, respectively.

Before matching, those with and without prior infection were well balanced in median age, age distribution, and sex, but with differences by nationality and calendar month of dose 1, which balanced with matching (Table 1).

Of 564 906 mRNA-1273–vaccinated individuals, 58 987 had prior PCR-confirmed infection; 58 096 were matched to 169 514 mRNA-1273–vaccinated individuals with no record of prior infection (Figure 1). Proportions who had a PCR test done during follow-up were 32.1% and 28.5% among those with and without prior infection, respectively.

Before matching, those with and without prior infection were well balanced in median age, age distribution, and sex, but with differences by nationality and calendar month of dose 1, which balanced with matching (Table 2).

Infection Incidence Among BNT162b2-Vaccinated Individuals
Among BNT162b2-vaccinated people with prior infection (Figure I), 159 reinfections occurred 14 days or more after dose 2 at a median follow-up of 55 days (IQR, 18-108). One progressed to severe COVID-19 disease and none to critical or fatal COVID-19 disease.

Among BNT162b2-vaccinated people without prior infection, 2509 infections occurred 14 days or more after dose 2 at a median follow-up of 60 days (IQR, 25-113). Twenty-six progressed to severe COVID-19 disease, 2 to critical disease, and 0 to COVID-19 death.

Most breakthrough infections occurred during times when the Beta or Delta variants dominated (eFigure 1 and eMethods in the Supplement). There were differences in age, nationality, and particularly calendar month of dose 1 between those with or without breakthrough infection. Those with breakthrough infection tended to have received their vaccination earlier (eTable 2 in the Supplement).

Cumulative infection incidence among BNT162b2-vaccinated individuals was an estimated 0.15% (95% CI,
In a study of SAR-CoV-2 infections after vaccination with and without prior infection, the development of cohorts was as follows:

- **Vaccinated individuals between December 21, 2020, and September 19, 2021:**
  - 1,531,736
  - 2,911 excluded due to vaccination with ChAdOx1 nCoV-19 (AZD1222)

- **Vaccinated with BNT162b2:**
  - 75,929 excluded
  - 1,163 excluded
  - 989 positive result after dose 1 but before the start of follow-up among those with no PCR-confirmed prior infection before dose 1
  - 96 antibody-positive result before dose 1 in those with no PCR-confirmed prior infection before dose 1
  - 21 died before the start of follow-up
  - 8 had no ascertained death date
  - 963,899 vaccinated

- **Vaccinated with mRNA-1273:**
  - 5,649,066
  - 79,345 excluded
  - 50,660 did not have 2 vaccine doses
  - 82 had a second dose with BNT162b2
  - 5,027 died before the start of follow-up
  - 43,16 positive result after dose 1 but before the start of follow-up among those with no PCR-confirmed prior infection before dose 1
  - 62 had a second dose with mRNA-1273
  - 2,494 died before the start of follow-up
  - 198,996 antibody-positive result before dose 1 among those with no PCR-confirmed prior infection before dose 1

- **Without reinfection to end of study:**
  - 43 reinfected with SARS-CoV-2
  - 368 infected with SARS-CoV-2
  - 367 did not develop severe, critical, or fatal disease
  - 5 died
  - 25 died

- **With prior infection before dose 1:**
  - 58,987 matched
  - 58,048 without reinfection to end of study
  - 43 reinfected with SARS-CoV-2
  - 26 developed severe disease
  - 2 died
  - 6 died

- **With no prior infection before dose 1:**
  - 426,574 not matched
  - 257,060 not matched

**PCR indicates polymerase chain reaction.**

- Individuals were exact matched based on infection status with no replacement allowed on a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose. Matching did not exactly reach a 1:3 ratio because of low frequency in older age categories and for specific nationalities.

- Severe disease included hospitalization that did not require intensive care, critical disease included patients admitted to the intensive care unit.

- Deaths were not related to COVID-19.
0.12%-0.18%) in those with and 0.83% (95% CI, 0.79%-0.87%) in those without prior infection at 120 days (Figure 2A; eFigure 2A in the Supplement). Cumulative infection incidence appeared to accelerate among those without prior infection after the 110th day of follow-up.

Overall infection incidence rate among BNT162b2-vaccinated individuals was an estimated 1.00 (95% CI, 0.86-1.17) and 5.40 (95% CI, 5.19-5.26) per 10,000 person-weeks among those with and without prior infection, respectively (adjusted HR for breakthrough infection with prior infection, 0.01).
Infection Incidence Among mRNA-1273–Vaccinated Individuals

Among mRNA-1273–vaccinated people with prior infection (Figure 1), 43 reinfections occurred 14 days or more after dose 2 at a median follow-up of 46 days (IQR, 16–81). None progressed to severe, critical, or fatal COVID-19 disease.

Among mRNA-1273–vaccinated people without prior infection, 368 infections occurred 14 days or more after dose 2 at a median follow-up of 77 days (IQR, 30–104). One progressed to severe COVID-19 disease and none to critical or fatal COVID-19 disease.

Table 2. Demographic Characteristics of Cohorts That Received the mRNA-1273 Vaccine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Matched cohortsa</th>
<th>SMDb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full cohorts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>58,987</td>
<td>58,096</td>
<td></td>
</tr>
<tr>
<td>Total follow-up time, person-weeks</td>
<td>694,259</td>
<td>685,351</td>
<td>2,008,963</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>36 (31–44)</td>
<td>36 (31–44)</td>
<td>0.01c</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>545 (0.9)</td>
<td>512 (0.9)</td>
<td>1.36</td>
</tr>
<tr>
<td>20-29</td>
<td>10,189 (17.3)</td>
<td>10,052 (17.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>30-39</td>
<td>24,973 (42.3)</td>
<td>24,771 (42.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>40-49</td>
<td>15,618 (26.5)</td>
<td>15,440 (26.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>50-59</td>
<td>6,079 (10.3)</td>
<td>5,918 (10.2)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1,328 (2.3)</td>
<td>1,206 (2.1)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>255 (0.4)</td>
<td>197 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42,653 (72.3)</td>
<td>42,180 (72.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>16,334 (27.7)</td>
<td>15,916 (27.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nationalityd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladeshi</td>
<td>6,504 (11.0)</td>
<td>6,491 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Egyptian</td>
<td>3,412 (5.8)</td>
<td>3,420 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Filipino</td>
<td>7,922 (13.4)</td>
<td>7,899 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>18,432 (31.3)</td>
<td>18,426 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Nepalese</td>
<td>5,817 (9.9)</td>
<td>5,803 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Pakistani</td>
<td>3,184 (5.4)</td>
<td>3,164 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Qatari</td>
<td>1,652 (2.8)</td>
<td>1,639 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Sri Lankan</td>
<td>2,565 (4.4)</td>
<td>2,551 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Sudanese</td>
<td>1,341 (2.3)</td>
<td>1,329 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Other nationalitiese</td>
<td>8,138 (13.8)</td>
<td>7,374 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Calendar month of dose 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>December</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>February</td>
<td>88 (0.2)</td>
<td>80 (0.1)</td>
<td></td>
</tr>
<tr>
<td>March</td>
<td>830 (14.1)</td>
<td>8218 (14.2)</td>
<td></td>
</tr>
<tr>
<td>April</td>
<td>16,359 (28.0)</td>
<td>16,379 (28.2)</td>
<td></td>
</tr>
<tr>
<td>May</td>
<td>14,833 (25.2)</td>
<td>14,613 (25.2)</td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>7,892 (13.4)</td>
<td>7,715 (13.3)</td>
<td></td>
</tr>
<tr>
<td>July</td>
<td>9,154 (15.5)</td>
<td>8,965 (15.4)</td>
<td></td>
</tr>
<tr>
<td>August</td>
<td>2,180 (3.7)</td>
<td>2,126 (3.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PCR, polymerase chain reaction; SMD, standardized mean difference.

* Cohorts were exact matched in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

b SMD is the difference in the mean of a covariate between groups divided by the pooled SD. An SMD less than 0.2 indicates adequate matching.

c SMD is for the mean difference between groups divided by the pooled SD.

d Nationalities were chosen to represent the most numerous groups in the population of Qatar.

e Individuals who received the mRNA-1273 vaccine in Qatar comprised 114 other nationalities in the full cohort of individuals with a prior PCR-confirmed infection, 163 other nationalities in the full cohort of individuals with no prior PCR-confirmed infection, 85 other nationalities in the matched cohort of individuals with a prior PCR-confirmed infection, and 85 other nationalities in the matched cohort of individuals with no prior PCR-confirmed infection.
Most breakthrough infections occurred during times when the Beta or Delta variants dominated (eFigure 1 and eMethods in the Supplement). There were differences in age, nationality, and particularly calendar month of dose 1 between those with or without breakthrough infection. Those with breakthrough infection tended to have received their vaccination earlier (eTable 2 in the Supplement).

Cumulative infection incidence among mRNA-1273–vaccinated individuals was an estimated 0.11% (95% CI, 0.08%-0.15%) in those with and 0.35% (95% CI, 0.32%-0.40%) in those without prior infection at 120 days (Figure 2B; eFigure 2B in the Supplement). Cumulative infection incidence appeared to accelerate among those without prior infection after the 80th day of follow-up.

Overall infection incidence rate among mRNA-1273–vaccinated individuals was an estimated 0.63 (95% CI, 0.47-0.85) and 1.83 (95% CI, 1.65-2.03) per 10 000 person-weeks in those with and without prior infection, respectively (adjusted HR for breakthrough infection with prior infection, 0.35 (95% CI, 0.25-0.48); P < .001). The adjusted HR by month of follow-up appeared to decline over time after dose 2 (Table 3).

**Infection Incidence by Time Interval Between Prior Infection and Vaccination**

Of 100 486 BNT162b2-vaccinated individuals with prior infection, 50 285 had the prior infection 6 months or more and 50 201 had the prior infection less than 6 months before their first vaccine dose (eFigure 3 in the Supplement). Of the 50 285 individuals whose prior infection was 6 months or more before their first dose, 29 582 were matched to 29 582 individuals whose prior infection occurred less than 6 months before their first dose.

Cumulative infection incidence among BNT162b2-vaccinated individuals with prior infection was an estimated 0.13% (95% CI, 0.09%-0.19%) when infection was 6 months or more and 0.20% (95% CI, 0.15%-0.26%) when less than 6 months before dose 1, at 120 days of follow-up (eFigure 4 in the Supplement).
Overall infection incidence rate among BNT162b2-vaccinated individuals with prior infection was an estimated 0.85 (95% CI, 0.62-1.16) and 1.41 (95% CI, 1.10-1.80) per 10,000 person-weeks in those whose infection was 6 months or more vs less than 6 months before their first vaccine dose, respectively (adjusted HR for breakthrough infection with prior infection 6 months or more before first vaccine dose, 0.62 [95% CI, 0.42-0.92]; P = .02).

Of 58,987 mRNA-1273-vaccinated individuals with prior infection, 27,388 had the prior infection 6 months or more and 31,599 individuals had the prior infection less than 6 months before their first vaccine dose (Supplement). Of the 27,388 individuals whose prior infection was 6 months or more before their first dose, 16,873 were matched to 16,873 individuals who had the prior infection less than 6 months before their first dose.

Cumulative infection incidence among mRNA-1273-vaccinated individuals with prior infection was an estimated 0.05% (95% CI, 0.02%-0.11%) when infection was 6 months or more before dose 1 and 0.20% (95% CI, 0.12%-0.31%) when it was less than 6 months before dose 1, at 120 days of follow-up (figure 3 in the Supplement).

Overall infection incidence rate among mRNA-1273-vaccinated individuals with prior infection was an estimated 0.40 (95% CI, 0.20-0.80) and 1.00 (95% CI, 0.65-1.55) per 10,000 person-weeks among those whose infection was 6 months or more vs less than 6 months before their first vaccine dose, respectively (adjusted HR for breakthrough infection with prior infection 6 months or more before first vaccine dose, 0.40 [95% CI, 0.18-0.91]; P = .03).

Discussion

In this cohort study, prior SARS-CoV-2 infection was associated with a lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines. Although the 2 vaccines were found earlier in Qatar to be highly effective against the Alpha, Beta, and Delta variants,\(^6\) prior infection among those vaccinated—a hybrid of natural and vaccine immunity—appeared to be associated with additional reduction in breakthrough infection.

Incidence of breakthrough infection also appeared to accelerate with time after the second dose among those with no prior infection, perhaps reflecting waning of vaccine-induced immunity over time, as indicated recently in Qatar.\(^8\) Incidence of breakthrough infection was statistically significantly lower among those vaccinated more than 6 months compared with less than 6 months after prior infection. Evidence suggests that mRNA-1273 induces higher neutralizing antibody titers than BNT162b2.\(^7\) The interval between doses is 1 week longer for mRNA-1273, and evidence suggests that a longer dose interval is associated with improved protection after receiving the second dose.\(^9\) The mRNA-1273 vaccine dose is also larger than BNT162b2.\(^4\) These factors could explain some of the observed differences in incidence of breakthrough infection for those vaccinated by these 2 vaccines.

The strengths of this study include the use of very large cohorts of BNT162b2-vaccinated and mRNA-1273-vaccinated persons that were followed up for several months in a setting where all PCR-confirmed infections are centrally tracked and recorded at the national level.

Limitations

This study has several limitations. First, prior infection was identified based on a record of a PCR-positive result, thereby missing those who may have been infected but were unaware of their infection or who did not seek testing to document the infection. Misclassification of prior infection status may have underestimated the association of prior infection with observed outcomes.
Second, depletion of the cohorts with prior infection by COVID-19 mortality at time of prior infection may have biased these cohorts toward healthier individuals with stronger immune responses. However, COVID-19 mortality has been low in Qatar’s predominantly young and working-age population.15,29

Third, the BNT162b2-vaccinated cohort was larger than that of the mRNA-1273-vaccinated cohort and was followed up for a longer time. However, both cohorts were very large, leading to results with statistical precision. The results were also presented at different times of follow-up to allow comparisons. Both vaccines were mass distributed across the country’s neighborhoods/areas and population social substrata. People were generally vaccinated using the vaccine that was available at the time of the vaccination. Infection incidence was also broadly distributed across the country’s neighborhoods/areas and population social substrata. Matching was implemented to control for differences in exposure risk1,15,16 and variant exposure.6,7,10-12 Therefore, it is not likely that observed differences between the 2 vaccines could be explained by clustering of vaccination or infection in specific geographies or social strata.

Fourth, vaccinated cohorts predominantly included working-age adults; therefore, results may not necessarily be generalizable to other population groups, such as children or elderly individuals.

Fifth, matching was done for age, sex, nationality, and calendar week of the first vaccine dose, and could not be done for other factors, such as comorbidities, because these were not available to study investigators. However, matching by age and sex may have served as a proxy given that comorbidities are associated with older age and may differ between women and men. Matching by nationality may have captured some of the occupational risk, given the distribution of the labor force in Qatar.20-22 The number of persons with severe or multiple chronic conditions is small in Qatar. The national list of vaccine prioritization included only 19,800 individuals of all age groups with serious comorbid conditions to be prioritized in the first phase of vaccine roll-out.

Sixth, as an observational study, there remains potential for unmeasured residual confounding that could not be controlled for.

Conclusions
Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021. The observational study design precludes direct comparisons of infection risk between the 2 vaccines.

REFERENCES
Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar


