mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar

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Abstract

The SARS-CoV-2 pandemic continues to be a global health concern. The mRNA-1273 (Moderna) vaccine had a reported efficacy of 94.1% at preventing symptomatic COVID-19 due to infection with "wild-type" variants in a randomized clinical trial. Here, we assess the real-world effectiveness of this vaccine against SARS-CoV-2 variants of concern, specifically B.1.1.7 (Alpha) and B.1.351 (Beta), in Qatar, which is a population that comprises mainly working-age adults, using a matched test-negative, case-control study design. We show that vaccine effectiveness was negligible for two weeks after the first dose, but increased rapidly in the third and fourth weeks, immediately prior to administration of a second dose. Effectiveness against B.1.1.7 infection was 88.1% (95% CI: 83.7-91.5%) ≥14 days after the first dose but before the second dose, and was 100% (95% CI: 91.8-100.0%) ≥14 days after the second dose. Analogous effectiveness against B.1.351 infection was 61.3% after the first dose (95% CI: 56.5-65.5%) and 96.4% after the second dose (95% CI: 91.9-98.7%). Effectiveness against any severe, critical, or fatal COVID-19 disease due to any SARS-CoV-2 infection (predominantly B.1.1.7 and B.1.351) was 81.6% (95% CI: 71.0-88.8%) and 95.7% (95% CI: 73.4-99.9%), after the first and second doses, respectively. The mRNA-1273 vaccine is highly effective against B.1.1.7 and B.1.351 infections, whether symptomatic or asymptomatic, and any COVID-19 hospitalization and death, even after a single dose.

Introduction

In a randomized clinical trial, the mRNA-1273 (Moderna) vaccine had a reported efficacy of 94.1% at preventing symptomatic coronavirus disease 2019 (COVID-19) due to infection with "wild-type" variants[1]. The first immunization using this vaccine in Qatar was recorded on December 28, 2020, but mass vaccination did not start until late February, 2021 with the accelerated arrival of vaccine shipments. As the vaccination campaign was scaled up, the country experienced two, back-to-back severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) waves that were triggered by introduction and expansion of the B.1.1.7 (Alpha[2]) and B.1.351 (Beta[2]) variants[3]. This created a unique epidemiological opportunity to assess real-world effectiveness of this vaccine against infection with these variants of concern, as well as against severe forms of COVID-19 disease.

Results

Study population

Between December 28, 2020 and May 10, 2021, 256,037 individuals in Qatar had received at least one dose of the mRNA-1273 vaccine, and 181,304 completed the two-dose regimen. Among those with a vaccination record, the median date at first dose was April 5, 2021 and median date at second dose was April 29, 2021. Median time elapsed between the first dose and second dose was 28 days (interquartile range (IQR): 28-29 days) and 94.6% of individuals received their second dose ≤30 days after the first dose.

Flowcharts describing the population selection process for investigating and estimating vaccine effectiveness are presented in Extended Data 1-3. Demographic characteristics of the sample for each outcome of vaccine effectiveness are presented in Table 1. Median age in the study sample

for estimating vaccine effectiveness against infection with B.1.1.7 was 31 years (IQR: 19-38), against infection with B.1.351 was 32 years (IQR: 25-39), and against severe, critical, or fatal disease was 43 years (IQR: 37-51). Of note that Qatar has a young and diverse demographics where only 9% of its resident population are >50 years of age and 89% are expatriates from over 150 countries[4,5].

Weekly rounds of viral genome sequencing from March 8 to May 10, 2021, identified B.1.351 (n=369; 64.4%), B.1.1.7 (n=58; 10.1%), B.1.617 (n=18; 3.1%), and "wild-type"/undetermined variants (n=128; 22.3%) in 573 randomly collected polymerase chain reaction (PCR)-positive specimens. Weekly rounds of multiplex quantitative reverse-transcription PCR (RT-qPCR) based variant screening[6] from March 23 to May 10, 2021, identified B.1.351-like (n=2,605; 66.4%), B.1.1.7-like (n=970; 24.7%), and "other" variants (n=349; 8.9%) in 3,924 randomly collected PCR-positive specimens. Sanger sequencing of the receptor binding domain of SARS-CoV-2 spike protein on 109 "other" specimens confirmed that 103 were B.1.617-like, 3 were B.1-like, and three were undetermined.

As of May 10, 2021, 1,558 and 243 breakthrough infections were recorded among those who received either one or two doses of the mRNA-1273 vaccine, respectively. Seven COVID-19 deaths were also recorded among mRNA-1273 vaccine recipients, all after the first dose and none after the second dose.

Vaccine effectiveness against infection with B.1.1.7

Estimated effectiveness against infection with B.1.1.7, defined as a PCR-positive swab with B.1.1.7 variant, regardless of the reason for PCR testing or presence of symptoms (Methods), was negligible for two weeks after the first dose (Table 2 and Fig. 1), but increased rapidly in the third week, reaching 81.6% (95% confidence interval (CI): 73.1-87.8%). Effectiveness was

94.4% (95% CI: 89.1-97.5%) in the fourth week, immediately before the second dose, and reached 99.2% (95% CI: 95.3-100.0%) in the second week after the second dose. Effectiveness was 88.1% (95% CI: 83.7-91.5%) 14 or more days after the first dose, but before receiving the second dose, and was 100% (95% CI: 91.8-100.0%) 14 or more days after the second dose (Table 3).

Vaccine effectiveness against infection with B.1.351

Effectiveness against infection with B.1.351, defined as a PCR-positive swab with B.1.351 variant, regardless of the reason for PCR testing or presence of symptoms (Methods), was negligible for two weeks after the first dose (Table 2 and Fig. 1), but increased rapidly in the third week to reach 47.9% (39.5-55.2%). Effectiveness was 73.7% (95% CI: 67.6-78.8%) in the fourth week, immediately before the second dose, and reached 96.4% (95% CI: 94.3-97.9%) in the second week after the second dose. Effectiveness was 61.3% (95% CI: 56.5-65.5%) 14 or more days after the first dose, but before receiving the second dose, and was 96.4% (95% CI: 91.9-98.7%) 14 or more days after the second dose (Table 3).

Vaccine effectiveness against COVID-19 severity or fatality

Effectiveness against any severe, critical, or fatal disease due to any SARS-CoV-2 infection (predominantly B.1.1.7 and B.1.351[7]; Methods) was negligible for two weeks after the first dose (Table 2 and Fig. 1), but increased rapidly in the third week to reach 70.3% (95% CI: 48.9-83.5%). Effectiveness was 92.1% (95% CI: 78.4-97.9%) in the fourth week, immediately before the second dose, and reached 100% (95% CI: 86.9-100.0%) in the second week after the second dose. Effectiveness was 81.6% (95% CI: 71.0-88.8%) 14 or more days after the first dose, but before receiving the second dose, and was 95.7% (95% CI: 73.4-99.9%) 14 or more days after the second dose (Table 3).

Additional analyses

Sensitivity analyses matching by PCR testing date in addition to age, sex, nationality, and reason for PCR testing; adjusting for calendar week in logistic regression; or additionally adjusting for matching factors, that is sex, age, nationality, and reason for PCR testing, all confirmed main analysis results (Table 4).

An additional analysis estimated vaccine effectiveness against symptomatic infection (predominantly B.1.1.7 and B.1.351[7]) at 98.6% (95% CI: 92.0-100.0%) 14 or more days after the second dose (Supplementary Table 1). Symptomatic infection was defined as a PCR-positive test conducted because of clinical suspicion due to presence of symptoms compatible with a respiratory tract infection.

An additional analysis estimated vaccine effectiveness against asymptomatic infection (predominantly B.1.1.7 and B.1.351[7]) at 92.5% (95% CI: 84.8-96.9%) 14 or more days after the second dose (Supplementary Table 1). Asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection, that is the PCR testing was done as part of a survey, for pre-travel requirement, or at port of entry upon arrival into the country[4,8].

An additional analysis estimated vaccine effectiveness 14 or more days after the second dose using a cohort study design that compares infection incidence in those vaccinated with incidence in the national cohort of persons who were antibody-negative (Methods, Supplementary Table 2, and Extended Data 4). Incidence rate among those vaccinated was estimated at 0.0 (95% CI: 0.0-3.60) for B.1.1.7, 5.83 (95% CI: 2.62-12.99) for B.1.351, and 1.94 (95% CI: 0.49-7.78) for variants of unknown status per 10,000 persons-weeks in a total follow-up time of 10,282.86 person-weeks. Incidence rate among those antibody-negative was estimated at 20.49 (95% CI:

19.40-21.63) for B.1.1.7, 47.78 (95% CI: 46.11-49.52) for B.1.351, and 30.12 (95% CI: 28.79-31.50) for variants of unknown status per 10,000 persons-weeks in a total follow-up time of 631,171.10 person-weeks. Vaccine effectiveness was thus estimated at 100.0% (95% CI: 82.5-100.0%) against B.1.1.7, 87.8% (95% CI: 73.4-95.5%) against B.1.351, and 93.5% (95% CI: 76.6-99.2%) against variants of unknown status, supporting main analysis results.

Discussion

Our analysis demonstrates that vaccine effectiveness of mRNA-1273 was high regardless of variant, against both symptomatic infection and asymptomatic infection, and against COVID-19 hospitalization and death. Development of vaccine protection against B.1.1.7 infection and COVID-19 hospitalization and death rapidly accelerated in the third and fourth weeks after the first dose, immediately before the second dose, nearly reaching the values attained after the second dose. Protection against B.1.351 infection exhibited a similar pattern, but mounted at a slower rate and did not achieve its highest value of ~95% until after the second dose. While long-term protection of only one dose could not be assessed beyond four weeks after the first dose, these findings might suggest that most of the protection of this vaccine is attained using only one dose, apart possibly from its protection against B.1.351. Although for optimal protection the protocol for this vaccine requires a second dose 28 days after the first, given the sizable protection achieved after only one dose, in situations involving limited vaccine supplies, these findings may support a strategy of delaying the second dose in order to vaccinate the largest number of people in the shortest time, as supported also by evidence for the BNT162b2 (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (AZD1222; Oxford–AstraZeneca) vaccines[9-11]. Having said so, the optimal timing of the second dose is best determined formally through randomized

clinical trials and could also depend on both the incidence level and circulating variants, which are factors that can vary from one setting to another.

The mRNA-1273 vaccine demonstrated similar levels and patterns of protection after the first and second doses to the BNT162b2 vaccine, as estimated recently in Qatar[3,11]. However, in our study, the mRNA-1273 vaccine appears to offer greater protection against both B.1.351 and B.1.1.7. It is premature to conclude that this outcome is due to a superior vaccine-induced immune response, as other confounding variables may also have contributed to observed differences. The second dose of mRNA-1273 is administered 28 days after the first dose, one week later than for BNT162b2, which might have affected the build-up of immunity and estimated effectiveness. We also note that since the mass immunization campaigns in Qatar started with BNT162b2 in December of 2020, most older persons and those with comorbid conditions were vaccinated with the BNT162b2 vaccine before the mRNA-1273 vaccine became widely available in March to May of 2021. Those vaccinated with the mRNA-1273 vaccine (Table 1) tended to be slightly younger than those vaccinated with the BNT162b2 vaccine[3].

Effectiveness in our study was assessed based on documented infections, but other infections might have occurred and gone undocumented, perhaps because of minimal and/or mild symptoms, or by virtue of being subclinical infections. However, with the high rate of PCR testing in Qatar, 64.2% of infections that were diagnosed during the study period were identified not because of clinical symptoms, but for other reasons, including random testing campaigns (surveys), contact tracing, individual requests, and routine healthcare and travel-related testing. This indicates that the vaccine was robustly effective not only against symptomatic clinical disease, but also against asymptomatic and subclinical infection. That said, there was evidence for a slight gradient in vaccine effectiveness by appearance of symptoms, that is greater

protection against more symptomatic or severe infections, as observed for the BNT162b2 vaccine[3,11].

This study has some limitations. Estimated effectiveness against severe, critical, or fatal COVID-19 disease had somewhat wider 95% confidence intervals, as a consequence of the relatively lower severity of COVID-19 in the young population of Qatar compared to populations where the median age is higher[4,12], the younger cohort of those vaccinated with mRNA-1273, and that the majority of vaccinated persons had their second dose after each of the B.1.1.7 and B.1.351 waves peaked in early March and early April of 2021, respectively. The median date of receiving the second dose in our study population was April 29, 2021. For the same reasons, we could not precisely estimate effectiveness against severe, critical, or fatal COVID-19 disease attributable to each of the B.1.1.7 and B.1.351 variants.

Severe, critical, or fatal COVID-19 disease was assessed up to end of study (May 10, 2021), and it is possible that cases confirmed as PCR positive right before end of the study may have progressed to a severe outcome only after end of the study, and were thus not included in our sample. This, however, should not affect our estimates, as the study, by design, contrasts confirmed COVID-19 disease cases to PCR-negative cases. For reasons that remain unclear, among persons 7-13 days after the first dose, risk of infection with B.1.351 was higher compared to those who remained unvaccinated, an outcome observed elsewhere for both COVID-19 vaccines[13-15] and other vaccines[16]. This might reflect a higher underlying risk of infection, bias due to uncontrolled confounding such as differences in social behavior at or following vaccination, an immunological effect[16], or an artifact of the estimation method, possibly because the first vaccine dose coincided often with the peak of the B.1.351 wave.

Imperfect assay sensitivity and specificity of PCR testing may also have affected infection ascertainment. However, all PCR testing was performed with extensively used, investigated, and validated commercial platforms having essentially 100% sensitivity and specificity (Methods). The baseline analysis did not factor matching or control for calendar time, but sensitivity analyses factoring calendar time confirmed the main findings. Data on co-morbid conditions were not available and hence could not be factored explicitly in our analysis. However, adjusting for age may have served as a proxy given that co-morbidities are associated with old age. Furthermore, with the young population structure in Qatar[4,5], we anticipate that only a small proportion of the study population may have had serious co-morbid conditions. However, our findings might not be entirely generalizable to other settings where the elderly population constitutes a sizable proportion of the population. Effectiveness was assessed using an observational test-negative case-control study design[17,18], rather than a randomized clinical trial, but the cohort study design also yielded similar findings, supporting the validity of this approach in assessing vaccine effectiveness. In some instances, there were zero events among cases and/or controls thus precluding estimation of effectiveness and/or associated confidence interval.

In conclusion, the mRNA-1273 vaccine is very effective against B.1.1.7 and B.1.351 infections, whether symptomatic or asymptomatic, and against COVID-19 hospitalization and death in the population of Qatar. Most of the protection of this vaccine accrued in the third and fourth weeks after the first dose, and before the second dose, although its effectiveness against B.1.351 increased significantly more after the second dose. These findings justify optimism that vaccine-induced immunity will prove robust against known variants of concern, thereby reducing the likelihood of a protracted pandemic for years to come.

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Author contributions

HC co-designed the study, performed the statistical analyses, and co-wrote the first draft of the article. LJA conceived and co-designed the study, led the statistical analyses, and co-wrote the first draft of the article. AAB and RB co-designed the study. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and to the writing of the manuscript. All authors have read and approved the final manuscript.

Competing interests

Dr. Butt has received institutional grant funding from Gilead Sciences unrelated to the work presented in this paper. Otherwise, we declare no competing interests.

References

1. Baden, L.R., *et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* **384**, 403-416 (2021).
2. World Health Organization. Tracking SARS-CoV-2 variants. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed on: June 5, 2021. (2021).
3. Abu-Raddad, L.J., Chemaitelly, H., Butt, A.A. & National Study Group for Covid-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med* (2021).
4. Abu-Raddad, L.J., *et al.* Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. *Scientific Reports* **11**, 6233 (2021).
5. Planning and Statistics Authority-State of Qatar. Qatar Monthly Statistics. Available from: https://www.psa.gov.qa/en/pages/default.aspx. Accessed on: May 26, 2020. (2020).
6. Vogels, C., Fauver, J. & Grubaugh, N. Multiplexed RT-qPCR to screen for SARS-COV-2 B.1.1.7, B.1.351, and P.1 variants of concern V.3. dx.doi.org/10.17504/protocols.io.br9vm966. (2021).
7. National Project of Surveillance for Variants of Concern and Viral Genome Sequencing. Qatar viral genome sequencing data. Data on randomly collected samples between February 1-May 10, 2021. (2021).
8. Bertollini, R., *et al.* Associations of Vaccination and of Prior Infection With Positive PCR Test Results for SARS-CoV-2 in Airline Passengers Arriving in Qatar. *JAMA* (2021).
9. Lopez Bernal, J., *et al.* Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* **373**, n1088 (2021).
10. Voysey, M., *et al.* Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* **397**, 881-891 (2021).
11. Abu-Raddad, L.J., *et al.* Pfizer-BioNTech mRNA BNT162b2 Covid-19 vaccine protection against variants of concern after one versus two doses. *J Travel Med* (2021).
12. Seedat, S., *et al.* SARS-CoV-2 infection hospitalization, severity, criticality, and fatality rates. *medRxiv 2020.11.29.20240416* (2020).
13. Hitchings, M.D.T., *et al.* Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. *medRxiv*, 2021.2004.2007.21255081 (2021).
14. Hunter, P.R. & Brainard, J. Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel. *medRxiv*, 2021.2002.2001.21250957 (2021).
15. Hall, V.J., *et al.* COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet (London, England)* **397**, 1725-1735 (2021).
16. Daum, R.S., Siber, G.R., Ballanco, G.A. & Sood, S.K. Serum anticapsular antibody response in the first week after immunization of adults and infants with the Haemophilus influenzae type b-Neisseria meningitidis outer membrane protein complex conjugate vaccine. *The Journal of infectious diseases* **164**, 1154-1159 (1991).

17. Jackson, M.L. & Nelson, J.C. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* **31**, 2165-2168 (2013).
18. Verani, J.R., *et al.* Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. *Vaccine* **35**, 3295-3302 (2017).
19. Thermo Fisher Scientific. TaqPath™ COVID-19 CE-IVD RT-PCR Kit instructions for use. Available from: https://assets.thermofisher.com/TFS-Assets/LSG/manuals/MAN0019215_TaqPathCOVID-19_CE-IVD_RT-PCR%20Kit_IFU.pdf. Accessed on December 02, 2020. (2020).
20. European Centre for Disease Prevention and Control. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf. Accessed on: February 10, 2021. (Stockholm; 2020, 2020).
21. Galloway, S.E., *et al.* Emergence of SARS-CoV-2 B.1.1.7 Lineage - United States, December 29, 2020-January 12, 2021. *MMWR Morb Mortal Wkly Rep* **70**, 95-99 (2021).
22. Challen, R., *et al.* Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. *BMJ* **372**, n579 (2021).
23. World Health Organization. COVID-19 clinical management: living guidance. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed on: May 15, 2021. (2021).
24. World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19-20200420-EN.pdf?ua=1. Document Number: WHO/HQ/DDI/DNA/CAT. Accessed on May 15, 2021. (2020).

Fig. 1. Effectiveness of the mRNA-1273 vaccine against A) B.1.1.7 infections, B) against B.1.351 infections, and C) against severe, critical, or fatal COVID-19 disease after the first dose and the second dose. Analyses were performed on independent samples of n=25,034 PCR-positive cases and n=25,034 PCR-negative controls examined between February 1 and May 10, 2021 for B.1.1.7, n=52,442 PCR-positive cases and n=52,442 PCR-negative controls examined between March 8 and May 10, 2021 for B.1.351, n=4,497 PCR-positive cases that progressed to severe, critical, or fatal disease and n=4,497 PCR-negative controls examined between February 1 and May 10, 2021. Data are presented as effectiveness point estimates with error bars indicating the corresponding 95% confidence intervals.

Table 1. Demographic characteristics of A) B.1.1.7 cases (PCR-positive) and controls (PCR-negative), B) B.1.351 cases (PCR-positive) and controls (PCR-negative), and C) severe, critical, or fatal COVID-19 disease cases (any PCR-positive case) and controls (PCR-negative).

Sample type	A) Any infection with the B.1.1.7 variant between February 1-May 10, 2021		B) Any infection with the B.1.351 variant between March 8-May 10, 2021		C) Any severe, critical, or fatal disease with any SARS-CoV-2 infection between February 1-May 10, 2021	
Characteristics*	Cases† (PCR positive)	Controls† (PCR negative)	Cases† (PCR positive)	Controls† (PCR negative)	Cases† (PCR positive)	Controls† (PCR negative)
Median age (IQR) — years	31 (19-38)	31 (19-38)	32 (25-39)	32 (25-39)	43 (37-51)	43 (37-51)
Age group — no. (%)						
<30 years	9,770 (45.9)	9,770 (45.9)	17,821 (39.8)	17,821 (39.8)	200 (5.9)	200 (5.9)
30-39 years	6,885 (32.3)	6,885 (32.3)	16,652 (37.2)	16,652 (37.2)	1,011 (29.8)	1,011 (29.8)
40-49 years	3,330 (15.6)	3,330 (15.6)	7,857 (17.6)	7,857 (17.6)	1,224 (36.1)	1,224 (36.1)
50-59 years	1,042 (4.9)	1,042 (4.9)	2,025 (4.5)	2,025 (4.5)	687 (20.2)	687 (20.2)
60-69 years	230 (1.1)	230 (1.1)	338 (0.8)	338 (0.8)	203 (6.0)	203 (6.0)
70+ years	48 (0.2)	48 (0.2)	44 (0.1)	44 (0.1)	69 (2.0)	69 (2.0)
Sex						
Male	12,483 (58.6)	12,483 (58.6)	33,410 (74.7)	33,410 (74.7)	2,765 (81.5)	2,765 (81.5)
Female	8,822 (41.4)	8,822 (41.4)	11,327 (25.3)	11,327 (25.3)	629 (18.5)	629 (18.5)
Nationality‡						
Bangladeshi	903 (4.2)	903 (4.2)	3,687 (8.2)	3,687 (8.2)	364 (10.7)	364 (10.7)
Egyptian	1,240 (5.8)	1,240 (5.8)	1,953 (4.4)	1,953 (4.4)	169 (5.0)	169 (5.0)
Filipino	2,911 (13.7)	2,911 (13.7)	4,583 (10.2)	4,583 (10.2)	507 (14.9)	507 (14.9)
Indian	4,676 (22.0)	4,676 (22.0)	15,235 (34.1)	15,235 (34.1)	827 (24.4)	827 (24.4)
Nepalese	1,159 (5.4)	1,159 (5.4)	5,251 (11.7)	5,251 (11.7)	407 (12.0)	407 (12.0)
Pakistani	1,453 (6.8)	1,453 (6.8)	1,771 (4.0)	1,771 (4.0)	188 (5.5)	188 (5.5)
Qatari	3,171 (14.9)	3,171 (14.9)	4,019 (9.0)	4,019 (9.0)	284 (8.4)	284 (8.4)
Sri Lankan	617 (2.9)	617 (2.9)	1,700 (3.8)	1,700 (3.8)	136 (4.0)	136 (4.0)
Sudanese	652 (3.1)	652 (3.1)	1,047 (2.3)	1,047 (2.3)	84 (2.5)	84 (2.5)
Other nationalities§	4,523 (21.2)	4,523 (21.2)	5,491 (12.3)	5,491 (12.3)	428 (12.6)	428 (12.6)

*These demographic characteristics are for samples used in the ≥14-days-after-second-dose analyses, but are essentially identical to those in the other analyses.
†Cases and controls were matched one-to-one by sex, age, nationality, and reason for polymerase chain reaction (PCR) testing.
‡Nationalities were chosen to represent the most populous groups in Qatar.
§These comprise 80 other nationalities in Qatar among sample A, 78 other nationalities among sample B, and 41 other nationalities among sample C.

Table 2. Effectiveness of the mRNA-1273 vaccine against B.1.1.7 and B.1.351 infections and against severe, critical, or fatal COVID-19 disease, week by week during the first six weeks after the first dose.

	0-6 days after first dose					7-13 days after first dose				
	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
Any infection with the B.1.1.7 variant†	166	23,661	170	23,657	2.4 (0.0-21.7)	202	23,681	187	23,696	0.0 (0.0-11.9)
Any infection with the B.1.351 variant‡	535	47,359	558	47,336	4.2 (0.0-15.1)	854	47,372	566	47,660	0.0 (0.0-0.0)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection**	53	4,012	65	4,000	18.7 (0.0-44.7)	85	4,016	68	4,033	0.0 (0.0-10.1)
	14-20 days after first dose					21-27 days after first dose				
Effectiveness against infection										
Any infection with the B.1.1.7 variant†	32	23,669	173	23,528	81.6 (73.1-87.8)	9	23,656	160	23,505	94.4 (89.1-97.5)
Any infection with the B.1.351 variant‡	270	47,329	516	47,083	47.9 (39.5-55.2)	114	47,249	431	46,932	73.7 (67.6-78.8)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection§	18	4,007	60	3,965	70.3 (48.9-83.5)	4	3,997	50	3,951	92.1 (78.4-97.9)
	0-6 days after second dose					7-13 days after second dose				
Effectiveness against infection										
Any infection with the B.1.1.7 variant†	4	21,454	196	21,262	98.0 (94.7-99.5)	1	21,377	119	21,259	99.2 (95.3-100.0)
Any infection with the B.1.351 variant‡	42	45,280	719	44,603	94.2 (92.1-95.9)	18	45,064	498	44,584	96.4 (94.3-97.9)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection§	0	3,432	62	3,370	100.0 (93.9-100.0)	0	3,399	29	3,370	100.0 (86.9-100.0)

*Vaccine effectiveness was estimated using the test-negative, case-control study design[17,18].

†Any B.1.1.7 PCR-confirmed infection. A B.1.1.7 infection is proxied as an S-gene "target failure" case using the TaqPath COVID-19 Combo Kit platform (Thermo Fisher Scientific, USA[19]), applying the criterion of polymerase chain reaction (PCR) cycle threshold value ≤30 for both the N and ORF1ab genes, but a negative outcome for the S-gene[20-22]. The median date of vaccination with first dose was April 8 for the cases and April 2 for their matched controls.

‡Any B.1.351 PCR-confirmed infection. With essentially only B.1.351 and B.1.1.7 cases identified in the viral genome sequencing and the multiplex real-time reverse-transcription PCR (RT-qPCR) variant screening between March 8-May 10, 2021[7], a B.1.351 infection is proxied as the complement of the B.1.1.7 criterion, that is any infection with a Ct value ≤30 for the N, ORF1ab, and S genes between March 8-May 10. The median date of vaccination with first dose was April 4 for the cases and April 3 for their matched controls.

§Any PCR-confirmed infection that led to severe, critical, or fatal COVID-19 disease. With the predominance of both B.1.1.7 and B.1.351 variants during the study period, this effectiveness is a combined measure against both of these variants. Severe disease, critical disease, and COVID-19 death were defined based on the World Health Organization criteria for classifying SARS-CoV-2 infection severity[23] and COVID-19-related death[24].

Table 3. Effectiveness of the mRNA-1273 vaccine against B.1.1.7 and B.1.351 infections and against severe, critical, or fatal COVID-19 disease ≥14 days after the first dose and ≥14 days after the second dose.

	≥14 days after first dose and no second dose					≥14 days after second dose				
	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
Any infection with the B.1.1.7 variant†	44	23,860	365	23,539	88.1 (83.7-91.5)	0	21,305	47	21,258	100.0 (91.8-100.0)
Any infection with the B.1.351 variant‡	419	47,872	1,067	47,224	61.3 (56.5-65.5)	6	44,731	165	44,572	96.4 (91.9-98.7)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection§	23	4,067	122	3,968	81.6 (71.0-88.8)	1	3,393	23	3,371	95.7 (73.4-99.9)

*Vaccine effectiveness was estimated using the test-negative, case-control study design[17,18].

†Any B.1.1.7 PCR-confirmed infection. A B.1.1.7 infection is proxied as an S-gene "target failure" case using the TaqPath COVID-19 Combo Kit platform (Thermo Fisher Scientific, USA[19]), applying the criterion of polymerase chain reaction (PCR) cycle threshold value ≤30 for both the N and ORF1ab genes, but a negative outcome for the S-gene[20-22]. The median date of vaccination with first dose was April 8 for cases and April 2 for their matched controls.

‡Any B.1.351 PCR-confirmed infection. With essentially only B.1.351 and B.1.1.7 cases identified in the viral genome sequencing and the multiplex real-time reverse-transcription PCR (RT-qPCR) variant screening between March 8-May 10, 2021[7], a B.1.351 infection is proxied as the complement of the B.1.1.7 criterion, that is any infection with a Ct value ≤30 for the N, ORF1ab, and S genes between March 8-May 10. The median date of vaccination with first dose was April 4 for cases and April 3 for their matched controls.

§Any PCR-confirmed infection that led to severe, critical, or fatal COVID-19 disease. With the predominance of both B.1.1.7 and B.1.351 variants during the study period, this effectiveness is a combined measure against both of these variants. Severe disease, critical disease, and COVID-19 death were defined based on the World Health Organization criteria for classifying SARS-CoV-2 infection severity[23] and COVID-19-related death[24].

Table 4. Sensitivity analyses for effectiveness of the mRNA-1273 vaccine against B.1.1.7 and B.1.351 infections and against severe, critical, or fatal COVID-19 disease, after A) matching by sex, age, nationality, reason for PCR testing as well as PCR test date, B) adjusting for calendar week in logistic regression analysis, and C) adjusting for sex, age, nationality, reason for PCR testing, and calendar week in logistic regression analysis.

	≥14 days after first dose and no second dose					≥14 days after second dose				
	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)[*]	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)[*]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
A) Matching by sex, age, nationality, reason for PCR testing, and PCR test date										
Effectiveness against infection										
Any infection with the B.1.1.7 variant[†]	14	12,828	97	12,745	85.7 (74.7-92.4)	0	11,689	6	11,683	100.0 (36.0-100.0)
Any infection with the B.1.351 variant[‡]	158	29,153	404	28,907	61.2 (53.2-67.9)	2	27,789	39	27,752	94.9 (80.2-99.4)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection[§]	6	1,799	30	1,775	80.3 (51.7-93.3)	0	1,580	0	1,580	Omitted[¶]
B) Adjusting for calendar week in regression analysis										
Effectiveness against infection										
Any infection with the B.1.1.7 variant[†]	44	23,860	365	23,539	88.2 (83.8-91.4)	0	21,305	47	21,258	100.0 (Omitted[**])
Any infection with the B.1.351 variant[‡]	419	47,872	1,067	47,224	67.8 (63.8-71.3)	6	44,731	165	44,572	95.8 (90.6-98.2)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection[§]	23	4,067	122	3,968	83.5 (74.0-89.6)	1	3,393	23	3,371	89.0 (15.2-98.6)
C) Adjusting for sex, age, nationality[††], reason for PCR testing, and calendar week in regression analysis										
Effectiveness against infection										
Any infection with the B.1.1.7 variant[†]	44	23,860	365	23,539	88.2 (83.8-91.4)	0	21,305	47	21,258	100.0 (Omitted[**])
Any infection with the B.1.351 variant[‡]	419	47,872	1,067	47,224	68.2 (64.3-71.7)	6	44,731	165	44,572	96.0 (90.9-98.2)
Effectiveness against disease										
Any severe, critical, or fatal disease with any SARS-CoV-2 infection[§]	23	4,067	122	3,968	83.7 (74.1-89.7)	1	3,393	23	3,371	89.5 (18.8-98.7)

[*]Vaccine effectiveness was estimated using the test-negative, case-control study design[17,18].

[†]Any B.1.1.7 PCR-confirmed infection. A B.1.1.7 infection is proxied as an S-gene "target failure" case using the TaqPath COVID-19 Combo Kit platform (Thermo Fisher Scientific, USA[19]), applying the criterion of polymerase chain reaction (PCR) cycle threshold value ≤30 for both the N and ORF1ab genes, but a negative outcome for the S-gene[20-22].

[‡]Any B.1.351 PCR-confirmed infection. With essentially only B.1.351 and B.1.1.7 cases identified in the viral genome sequencing and the multiplex real-time reverse-transcription PCR (RT-qPCR) variant screening between March 8-May 10, 2021[7], a B.1.351 infection is proxied as the complement of the B.1.1.7 criterion, that is any infection with a Ct value ≤30 for the N, ORF1ab, and S genes between March 8-May 10.

[§]Any PCR-confirmed infection that led to severe, critical, or fatal COVID-19 disease. With the predominance of both B.1.1.7 and B.1.351 variants during the study period, this effectiveness is a combined measure against both of these variants. Severe disease, critical disease, and COVID-19 death were defined based on the World Health Organization criteria for classifying SARS-CoV-2 infection severity[23] and COVID-19-related death[24].

[¶]There were no vaccinated persons among cases and controls, and thus estimate could not be attained.

[**]There were no events among vaccinated.

††Nationality was included in the regression analysis as a categorical variable comprising the most populous nationalities in Qatar as follows: Bangladeshis, Filipinos, Egyptians, Indians, Nepalese, Pakistanis, Qataris, Sudanese, Sri Lankans, and other nationalities in Qatar.

Methods

Data sources and study design

This study was conducted in the resident population of Qatar. COVID-19 laboratory testing, vaccination, clinical infection data, and related demographic details were extracted from the integrated nationwide digital-health information platform that hosts the national, federated SARS-CoV-2 databases. These databases are complete and have captured all SARS-CoV-2-related data since epidemic onset. Nearly all individuals were vaccinated (free of charge) in Qatar and not elsewhere. In rare situations where an individual received the mRNA-1273 COVID-19 vaccine outside Qatar, the individual's vaccination details were still recorded in the health system at port of entry (airport) upon return to Qatar given the national requirements and to benefit from privileges associated with vaccination such as quarantine exemption.

Vaccine effectiveness was estimated using the test-negative, case-control study design, a standard design for assessing vaccine effectiveness against influenza[17,18]. Key to this design is the control of bias arising from misclassification of infection and differences in health care-seeking behavior between vaccinated and unvaccinated individuals[17,18]. The STROBE checklist can be found in Supplementary Table 3. Cases and controls were matched one-to-one by sex, age, nationality, and reason for SARS-CoV-2 polymerase chain reaction (PCR) testing. Matching of cases and controls was performed to control for known differences in risk of exposure to the infection in Qatar[4,25-27].

Effectiveness was estimated against documented infection (defined as a PCR-positive swab regardless of the reason for PCR testing or presence of symptoms) with the B.1.1.7 or B.1.351 variants, as well as against severe, critical, or fatal disease due to any SARS-CoV-2 infection (predominantly B.1.1.7 and B.1.351[7]). Classification of COVID-19 case severity (acute-care

hospitalizations)[23], criticality (ICU hospitalizations)[23], and fatality[24] followed the World Health Organization guidelines, and assessments were made by trained medical personnel using individual chart reviews.

Classification of infections by variant type was informed by weekly rounds of viral genome sequencing and multiplex, real-time reverse-transcription PCR (RT-qPCR) variant screening[6] of randomly collected clinical samples[7], as well as by results of deep sequencing of wastewater samples[7]. Based on existing evidence[20-22], a B.1.1.7 case was defined as an S-gene "target failure" using TaqPath COVID-19 Combo Kits (Thermo Fisher Scientific, USA[19]; >85% of PCR testing in Qatar) applying the criterion of a PCR cycle threshold (Ct) value ≤30 for both the N and ORF1ab genes, and a negative outcome for the S gene[22]. Meanwhile, with essentially only B.1.351 and B.1.1.7 cases identified from March 8, 2021 until the end of study (May 10, 2021) in the viral genome sequencing and multiplex RT-qPCR variant screening[7], a B.1.351 case was proxied as the complement of B.1.1.7 criteria, that is, any infection with a Ct value ≤30 for the N, ORF1ab, and S genes[3].

With these considerations to ascertain infection by B.1.1.7 and B.1.351, the study extended from February 1-May 10, 2021 for B.1.1.7, from March 8-May 10, 2021 for B.1.351, and from February 1-May 10, 2021 for any severe, critical, or fatal COVID-19 disease. All records of PCR testing for those vaccinated and unvaccinated during the study duration were examined. All records of vaccination with one or two doses using a vaccine other than mRNA-1273 were excluded. Every case that met the inclusion criteria (a B.1.1.7 case, or a B.1.351 case, or a severe or critical or fatal COVID-19 disease case) and that could be matched to a control was included in the analysis. Both PCR-test outcomes and vaccination status were ascertained at the time of the PCR test. Each person that had a positive PCR test result and hospital admission was subject

to an infection severity assessment every three days until discharge or death. Individuals who progressed to COVID-19 disease between the time of the positive PCR test result and the end of the study were classified based on their worst outcome, starting with death[24], followed by critical disease[23], and then severe disease[23].

The study was approved by the Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards with waiver of informed consent.

Laboratory methods

Nasopharyngeal and/or oropharyngeal swabs (Huachenyang Technology, China) were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: extracted on a QIAsymphony platform (QIAGEN, USA) and tested with real-time reverse-transcription PCR (RT-qPCR) using TaqPath™ COVID-19 Combo Kits (100% sensitivity and specificity[19]; Thermo Fisher Scientific, USA) on an ABI 7500 FAST (ThermoFisher, USA); extracted using a custom protocol[28] on a Hamilton Microlab STAR (Hamilton, USA) and tested using AccuPower SARS-CoV-2 Real-Time RT-PCR Kits (100% sensitivity and specificity[29]; Bioneer, Korea) on an ABI 7500 FAST; or loaded directly into a Roche cobas® 6800 system and assayed with a cobas® SARS-CoV-2 Test (95% sensitivity, 100% specificity[30]; Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab regions. The second targets the viral RdRp and E-gene regions, and the third targets the ORF1ab and E-gene regions.

All tests were conducted at the HMC Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Statistical analysis

Descriptive statistics (frequency distributions and measures of central tendency) were used to characterize the study samples. The odds ratio, comparing odds of vaccination among cases to that among controls, and its associated 95% CI were calculated using the exact method. Confidence intervals were not adjusted for multiplicity. Interactions were not investigated. Vaccine effectiveness at different time frames and its associated 95% CI were then calculated by applying the following equation[17,18]:

$$\text{Vaccine effectiveness} = 1 - \frac{\text{vaccinated among cases} \times \text{unvaccinated among controls}}{\text{vaccinated among controls} \times \text{unvaccinated among cases}}$$

Additional analyses

To ensure that vaccine effectiveness estimates were not biased by epidemic phase and the gradual roll-out of vaccination during the study, two sensitivity analyses were conducted, first matching by the exact PCR testing date and second by logistic regression to adjust for calendar week[17,31]. To further ensure control for confounding[32,33], a third sensitivity analysis was conducted adjusting additionally for the matching factors in logistic regression, that is sex, age, reason for PCR testing, and nationality (grouping was based on the most populous nationality groups in Qatar, see Tables 1 and 4).

Additional analyses were conducted to estimate vaccine effectiveness against symptomatic infection, defined as a PCR-positive test conducted because of clinical suspicion due to presence of symptoms compatible with a respiratory tract infection, and against asymptomatic infection, defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection, that is the PCR testing was done as part of a survey, for pre-travel requirement, or at port of entry into the country (Supplementary Table 1).

Vaccine effectiveness was further assessed using a cohort study design[3,34,35] by comparing infection incidence in those who completed ≥14 days after the second dose with incidence in the national cohort of individuals who were antibody-negative. The incidence rate of infection was calculated for each of the variants using a Poisson log-likelihood regression model with the STATA 16.1[36] *stptime* command. The incidence rate ratio was calculated using the exact method. Vaccine effectiveness (with no adjustment for multiplicity) was estimated using the equation:

$$\text{Vaccine effectiveness} = 1 - \frac{\text{incidence rate of infection among the vaccinated individuals}}{\text{incidence rate of infection among the antibody-negative individuals}}.$$

Further details on this type of analysis and the antibody-negative cohort can be found in our previous studies of reinfection[34,35].

Analyses were conducted in STATA/SE 16.1[36].

Data availability

The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. Future access to this dataset can be considered through a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/Pages/default.aspx). Aggregate data are available within the manuscript and its Supplementary information.

Code availability

Standard epidemiological analyses were conducted using standard commands in STATA/SE 16.1[36]. The commands/code are accessible using URL: https://github.com/IDEGWCMQ/Vaccine-effectiveness-code

References

25. Al-Thani, M.H., *et al.* SARS-CoV-2 infection is at herd immunity in the majority segment of the population of Qatar. *Open Forum Infectious Diseases* (2021).
26. Jeremijenko, A., *et al.* Herd Immunity against Severe Acute Respiratory Syndrome Coronavirus 2 Infection in 10 Communities, Qatar. *Emerg Infect Dis* **27**, 1343-1352 (2021).
27. Coyle, P.V., *et al.* SARS-CoV-2 seroprevalence in the urban population of Qatar: An analysis of antibody testing on a sample of 112,941 individuals. *iScience*, 102646 (2021).
28. Kalikiri, M.K.R., *et al.* High-throughput extraction of SARS-CoV-2 RNA from nasopharyngeal swabs using solid-phase reverse immobilization beads. *medRxiv*, 2020.2004.2008.20055731 (2020).
29. Kubina, R. & Dziedzic, A. Molecular and Serological Tests for COVID-19 a Comparative Review of SARS-CoV-2 Coronavirus Laboratory and Point-of-Care Diagnostics. *Diagnostics (Basel)* **10**(2020).
30. US Food and Drug Administration. Cobas® SARS-CoV-2: Qualitative assay for use on the cobas® 6800/8800 Systems. Avilable from: https://www.fda.gov/media/136049/download. Accessed on: December 02, 2020. (2020).
31. Jacoby, P. & Kelly, H. Is it necessary to adjust for calendar time in a test negative design?: Responding to: Jackson ML, Nelson JC. The test negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31(April (17)):2165-8. *Vaccine* **32**, 2942 (2014).
32. Pearce, N. Analysis of matched case-control studies. *BMJ* **352**, i969 (2016).
33. Rothman, K.J., Greenland, S. & Lash, T.L. *Modern epidemiology*, (Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2008).
34. Abu-Raddad, L.J., *et al.* Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. *Clinical Infectious Diseases* (2020. ciaa1846. doi: 10.1093/cid/ciaa1846).
35. Abu-Raddad, L.J., *et al.* SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine* **35**, 100861 (2021).
36. StataCorp. Statistical Software: Release 16.1. *College Station, TX: Stata Corporation* (2019).

Supplementary Material

Table of Contents

Supplementary Table 1. Effectiveness of the mRNA-1273 vaccine against SARS-CoV-2 symptomatic infection and against SARS-CoV-2 asymptomatic infection, between February 1-May 10, 2021.

	≥14 days after first dose and no second dose					≥14 days after second dose				
	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*	Cases (PCR positive)		Controls (PCR negative)		Effectiveness in % (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against symptomatic infection†										
Any symptomatic infection with SARS-CoV-2	248	36,944	721	36,471	66.0 (60.6-70.7)	1	32,526	72	32,455	98.6 (92.0-100.0)
Effectiveness against asymptomatic infection‡										
Any asymptomatic infection with SARS-CoV-2	215	40,585	406	40,394	47.3 (37.6-55.5)	8	37,768	107	37,669	92.5 (84.8-96.9)

*Vaccine effectiveness was estimated using the test-negative, case-control study design.

†A symptomatic infection is defined as a PCR-positive test conducted because of clinical suspicion due to presence of symptoms compatible with a respiratory tract infection.

‡An asymptomatic infection is defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection, that is the PCR testing is done as part of a survey, for pre-travel requirement, or at port of entry into the country.

Supplementary Table 2. Demographic characteristics of the cohort of vaccinated persons who completed at least 14 days after the second vaccine dose and of the comparator cohort of antibody-negative controls.

Characteristics	Vaccinated persons	Antibody-negative controls
Median age (IQR) — years	40 (31-50)	32 (24-42)
Age group — no. (%)		
<30 years	511 (20.3)	30,023 (40.7)
30-39 years	745 (29.6)	21,502 (29.1)
40-49 years	623 (24.7)	11,570 (15.7)
50-59 years	378 (15.0)	6,222 (8.4)
60-69 years	109 (4.3)	2,761 (3.7)
70+ years	154 (6.1)	1,775 (2.4)
Sex		
Male	1,179 (46.8)	32,608 (44.2)
Female	1,341 (53.2)	41,245 (55.9)
Nationality[*]		
Bangladeshi	77 (3.1)	3,551 (4.8)
Egyptian	55 (2.2)	5,787 (7.8)
Filipino	377 (15.0)	4,327 (5.9)
Indian	392 (15.6)	11,133 (15.1)
Nepalese	8 (0.3)	2,573 (3.5)
Pakistani	82 (3.3)	3,807 (5.2)
Qatari	1,145 (45.4)	17,439 (23.6)
Sudanese	32 (1.3)	2,980 (4.0)
Sri Lankan	33 (1.3)	1,995 (2.7)
Other nationalities[†]	319 (12.7)	20,261 (27.4)

*Nationalities were chosen to represent the most populous groups in the population of Qatar.
[†]These comprise 32 other nationalities in Qatar among vaccinated persons and 148 other nationalities among antibody-negative controls.

Supplementary Table 3. STROBE checklist of items that should be included in reporting a case-control study

	Item No	Recommendation	Main text page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design	20-22
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	20-22, 24, Extended Data 1-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	20-24, Extended Data 1-4
		(*b*) For matched studies, give matching criteria and the number of controls per case	20, 23 & Extended Data 1-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	20-24
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	20-22
Bias	9	Describe any efforts to address potential sources of bias	23-24
Study size	10	Explain how the study size was arrived at	Extended Data 1-4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	23-24
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	23-24
		(*b*) Describe any methods used to examine subgroups and interactions	23-24
		(*c*) Explain how missing data were addressed	NA, see p. 20
		(*d*) If applicable, explain how matching of cases and controls was addressed	20
		(*e*) Describe any sensitivity analyses	23-24
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Extended Data 1-4
		(b) Give reasons for non-participation at each stage	Extended Data 1-4
		(c) Consider use of a flow diagram	Extended Data 1-4
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 & Supp. Table 2
		(b) Indicate number of participants with missing data for each variable of interest	NA, see p. 20
Outcome data	15	Report numbers in each exposure category, or summary measures of exposure	3-6, Tables 2-4, & Supp. Tables 1-2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4-7, Tables 2-4, & Supp. Table 1
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-7, Table 4, Supp. Table 1, & Extended Data 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	7-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

Abbreviations: NA, not applicable; Supp, Supplementary.