Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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Author contributions

LJA conceived and co-designed the study, led the statistical analyses, and co-wrote the first draft of the article. HC co-designed the study, performed the statistical analyses, and co-wrote the first draft of the article. PT and MRH conducted the multiplex, RT-qPCR variant screening and viral genome sequencing. HY, FMB, and HAK conducted viral genome sequencing. 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.

Section S1. Study population, data sources, and study design

This study was conducted in the resident population of Qatar, applying the same methodology that was used recently to assess waning of BNT162b2[1] vaccine effectiveness in the same population.[2] A detailed description of this methodology can be found in Chemaitelly *et al*.[2]

COVID-19 laboratory testing, vaccination, clinical infection data, and related demographic details were extracted from the national, federated SARS-CoV-2 databases that include all polymerase chain reaction (PCR) testing, COVID-19 vaccinations, and COVID-19 hospitalizations and deaths in Qatar since the start of the pandemic.

Every PCR test conducted in Qatar is classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, at port of entry, or other). Qatar has unusually young, diverse demographics, in that only 9% of its residents are ≥50 years of age, and 89% are expatriates from over 150 countries.[3,4] Nearly all individuals were vaccinated in Qatar, but if vaccinated elsewhere, those vaccinations were still recorded in the health system at the port of entry upon return to Qatar.

Vaccine effectiveness was estimated using the test-negative, case-control study design, a standard design for assessing vaccine effectiveness.[5-13] Cases (PCR-positive persons) and controls (PCR-negative persons) were matched one-to-two by sex, 10-year age group, nationality, reason for SARS-CoV-2 PCR testing, and calendar week of PCR testing to estimate vaccine effectiveness against SARS-CoV-2 infection; and one-to-five to estimate vaccine effectiveness against any severe, critical, or fatal COVID-19 (to improve statistical precision given the relatively small number of severe forms of COVID-19). Matching was performed to control for known differences in the risk of exposure to SARS-CoV-2 infection in Qatar.[4,14-17]

Only the first PCR-positive test during the study was included for each case, and only the first PCR-negative test during the study was included for each control. PCR tests done for pre-travel or at the port of entry were excluded from analysis. For persons included as cases, we included only the first positive test and excluded from the analysis any other PCR-negative tests conducted during the study period. Therefore, controls included individuals with no record of a PCR-positive test during the study period. These inclusion and exclusion criteria were implemented to minimize different types of potential bias. Detailed discussion of these biases, inclusion and exclusion criteria, and related sensitivity analyses are found in our analysis for waning of BNT162b2 vaccine effectiveness in the same population.[2]

All persons who received mixed vaccines, or who received a vaccine other than mRNA-1273, or who were tested by PCR after receiving a booster dose were excluded. Every case that met the inclusion criteria 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.

Effectiveness was estimated against documented infection (defined as a PCR-positive swab, regardless of the reason for PCR testing or the presence of symptoms), as well as against any severe,[18] critical,[18] or fatal[19] COVID-19. Classification of COVID-19 case severity (acute-care hospitalizations),[18] criticality (ICU hospitalizations),[18] and fatality[19] followed World Health Organization (WHO) guidelines, and assessments were made by trained medical personnel using individual chart reviews (Section S2).

Each person who had a positive PCR test result and hospital admission was subject to an infection severity assessment every three days until discharge or death, regardless of the length of the hospital stay or the time between the PCR-positive test and the final disease outcome. Individuals who progressed to severe,[18] critical,[18] or fatal[19] COVID-19 between the PCR-positive

test result and the end of the study were classified based on their worst outcome, starting with death, followed by critical disease, and then severe disease.

Details of laboratory methods for real-time reverse-transcription PCR (RT-qPCR) testing are found in Section S3. All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or at Sidra Medicine Laboratory, following standardized protocols.

The study was approved by the Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards with a waiver of informed consent. Reporting of the study followed STROBE guidelines (Table S1).

Statistical analysis

All records of PCR testing in Qatar during the study were included, but only samples of matched cases and controls were included in the analysis. Demographic characteristics of study samples were described using frequency distributions and measures of central tendency. Study groups were compared using standardized mean differences (SMDs), defined as the difference in the mean of a covariate between groups divided by the pooled standard deviation. SMD <0.1 indicated adequate matching.

The odds ratio, comparing odds of vaccination among cases versus controls, and its associated 95% confidence interval (CI) were derived using conditional logistic regression, that is factoring the matching in the study design. This matching and analysis approach aims to minimize potential bias due to variation in epidemic phase,[5,20] gradual roll-out of vaccination during the study,[5,20] or other confounders.[21,22] CIs were not adjusted for multiplicity. Interactions were not investigated. Vaccine effectiveness at different time points and its associated 95% CI were then calculated by applying the following equation:[5,6]

$$\text{Vaccine effectiveness} = 1 - \text{odds ratio of vaccination among cases versus controls}.$$

In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in that specific time-since-vaccination stratum and those unvaccinated (our reference group). Only matched pairs of PCR-positive and PCR-negative persons, in which members of the pair were either unvaccinated or fell within each time-since-vaccination stratum were included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses. Effectiveness after the second dose was estimated month by month, where one month was defined as 30 days.

A sensitivity analysis was conducted by adjusting in the conditional logistic regression for prior infection and healthcare worker status, as healthcare workers were prioritized for vaccination and may have had a different risk of exposure to the infection. The analysis specifically adjusted for being a healthcare worker at Hamad Medical Corporation, the main public healthcare provider in Qatar and the nationally designated provider for all COVID-19 healthcare needs.

Vaccine effectiveness was also estimated 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. In the latter case, PCR testing was done strictly as part of a survey or a random testing campaign. Vaccine effectiveness was further estimated by age group and for severe forms of COVID-19.

Caveats and limitations

Since the immunization campaign prioritized vaccination of persons with severe or multiple chronic conditions and by age group, the observed pattern of waning of protection could

theoretically be confounded by effects of age and comorbidities. Individual-level data on co-morbid conditions were not available; therefore, they could not be explicitly factored into our analysis. However, only a small proportion of the study population may have had serious co-morbid conditions. Only 9% of the population of Qatar are ≥50 years of age,[3,4] and 60% are young, expatriate craft and manual workers working in mega-development projects.[16,17,23] The national list of persons prioritized to receive the vaccine during the first phase of vaccine roll-out included only 19,800 individuals of all age groups with serious co-morbid conditions. Old age may serve as a partial proxy for co-morbid conditions. A similar pattern of waning of protection was observed for younger and older persons (Tables S7). Notably, with the small proportion of Qatar's population being ≥50 years of age,[3,4] our findings may not be generalizable to other countries in which elderly citizens constitute a larger proportion of the total population.

Infection incidence was dominated sequentially by different variants;[2,10,11,24-27] thus, it is possible that waning of protection could be confounded by exposure to different variants at different times. However, this seems unlikely, as a similar pattern of waning was observed in our recent study of the BNT162b2 vaccine for the Alpha,[28] Beta,[28] and Delta[28] variants in the same population.[2] The gradual pattern of waning of mRNA-1273 protection observed in this study also does not seem to suggest a considerable impact for variant status.

Vaccinated persons presumably have a higher social contact rate than unvaccinated persons, and they may also adhere less strictly to safety measures.[29-31] This behavior could reduce real-world effectiveness of the vaccine compared to its biological effectiveness, possibly explaining the waning of protection. Public health restrictions have been easing gradually in Qatar, but differently for vaccinated and unvaccinated persons. Many social, work, and travel activities presently require evidence of vaccination (a "health pass") that is administered through a

mandatory mobile app (the Ehteraz app). However, risk compensation is perhaps more likely to affect the overall estimate of effectiveness, rather than the observed waning of protection over time, unless such risk compensation increases with time after the second dose.

PCR testing in Qatar is done on a mass scale, such that about 5% of the population are tested every week.[2] About 75% of those diagnosed at present are diagnosed not because of symptoms, but because of routine testing.[2] It is possible that many asymptomatic infections were diagnosed among vaccinated persons that otherwise would have been missed. The higher ascertainment of infection may have reduced the effectiveness estimates. This is supported by the observed lower effectiveness against asymptomatic infection (Table S8).

Effectiveness was assessed using an observational, test-negative, case-control study design,[5,6] rather than a randomized, clinical trial design, in which cohorts of vaccinated and unvaccinated individuals were followed up. We were unable to use a cohort study design due to depletion of unvaccinated cohorts by the high vaccine coverage. However, the cohort study design applied earlier to the same population of Qatar yielded findings similar to those of the test-negative case-control design,[10-13] supporting the validity of this standard approach in assessing vaccine effectiveness for respiratory tract infections.[5-13] The results of this study are also consistent with our earlier effectiveness estimates immediately after the first and second doses,[11,13] noting that estimated measures largely reflected effectiveness against the Beta and Delta variants that dominated incidence during that study (Section S3).[2,10,11,24-27]

To rapidly scale up vaccination, some vaccination campaigns are conducted outside healthcare facilities; thus, records of vaccination are not immediately uploaded into the CERNER system, which tracks all vaccination records at the national level. This administrative time delay can introduce a misclassification bias of those vaccinated versus those unvaccinated. A sensitivity

analysis investigating the impact of such potential bias, by assuming a 10% misclassification bias of those vaccinated in Table S5, found a difference of only few percentage points in estimated effectiveness. A key strength of the test-negative, case-control study design is that it is less susceptible to this form of bias.[5,6]

Nonetheless, one cannot exclude the possibility that in real-world data, bias could arise in unexpected ways, or from unknown sources, such as subtle differences in test-seeking behavior or changes in the pattern of testing with introduction of other testing modalities, such as rapid antigen testing.

With the small number of vaccinated persons who completed 6 months or more after the second dose, the corresponding confidence intervals for vaccine effectiveness against hospitalization and death were very wide.

To improve precision of confidence intervals around estimates of vaccine effectiveness, cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test. Optimal balance was achieved across all matching factors (SMD <0.1), except for reason for PCR testing. This is because there were not enough controls tested for clinical suspicion and that could be matched to clinical suspicion cases. An exact ratio of one-to-two for cases-to-controls could not be reached. Actual ratio was around 1-to-1.4 for clinical suspicion cases leading to an SMD of 0.13 for reason for PCR testing (Tables S2-S4).

Notwithstanding these limitations, consistent findings were reached, indicating a large effect size for the waning of vaccine protection over time, regardless of the reason for PCR testing, and regardless of the presence or absence of symptoms. Moreover, with the mass scale of PCR testing in Qatar,[2] the likelihood of bias is perhaps minimized. Extensive sensitivity and

additional analyses were conducted to investigate effects of potential bias in our recent study for the BNT162b2 vaccine,[2] which used the same methodology as the present study. All analyses presented consistent findings of waning vaccine protection, broadly consistent with findings of other studies.[32-34]

Section S2. COVID-19 severity, criticality, and fatality classification

Severe Coronavirus Disease 2019 (COVID-19) disease was defined per the World health Organization (WHO) classification as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥60 breaths/minute in children <2 months old or ≥50 breaths/minute in children 2-11 months old or ≥40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)".[18] Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.[18]

Critical COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy".[18] Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.[18]

COVID-19 death was defined per WHO classification as "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19". Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.[19]

Section S3. Laboratory methods

Real-time reverse-transcription polymerase chain reaction testing

Nasopharyngeal and/or oropharyngeal swabs 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 (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher, USA); tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or loaded directly into a Roche cobas 6800 system and assayed with a cobas SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and the third targets the ORF1ab and E-gene regions.

All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Classification of infections by variant type

Between March 23, 2021 and November 6, 2021, RT-qPCR genotyping of 19,234 randomly collected SARS-CoV-2-positive specimens on a weekly basis identified 3,494 (18.2%) Alpha (B.1.1.7)-like cases, 5,768 (30.0%) Beta (B.1.351)-like cases, 9,914 (51.5%) “other” variant cases, and 58 (0.3%) B.1.375-like or B.1.258-like cases.[24,25]

The accuracy of the RT-qPCR genotyping was verified against either Sanger sequencing of the receptor-binding domain (RBD) of SARS-CoV-2 surface glycoprotein (S) gene, or by viral whole-genome sequencing on a Nanopore GridION sequencing device. From 236 random samples (27 Alpha-like, 186 Beta-like, and 23 “other” variants), PCR genotyping results for

Alpha-like, Beta-like, and 'other' variants were in 88.8% (23 out of 27), 99.5% (185 out of 186), and 100% (23 out of 23) agreement with the SARS-CoV-2 lineages assigned by sequencing.

Within the "other" variant category, Sanger sequencing and/or Illumina sequencing of the RBD of SARS-CoV-2 spike gene on 728 random samples confirmed that 701 (96.3%) were Delta cases and 17 (2.3%) were other variant cases, with 10 (1.4%) samples failing lineage assignment.[6,8] Accordingly, a Delta case was proxied as any "other" case identified through the RT-qPCR based variant screening.

All the variant RT-qPCR screening was conducted at the Sidra Medicine Laboratory following standardized protocols.

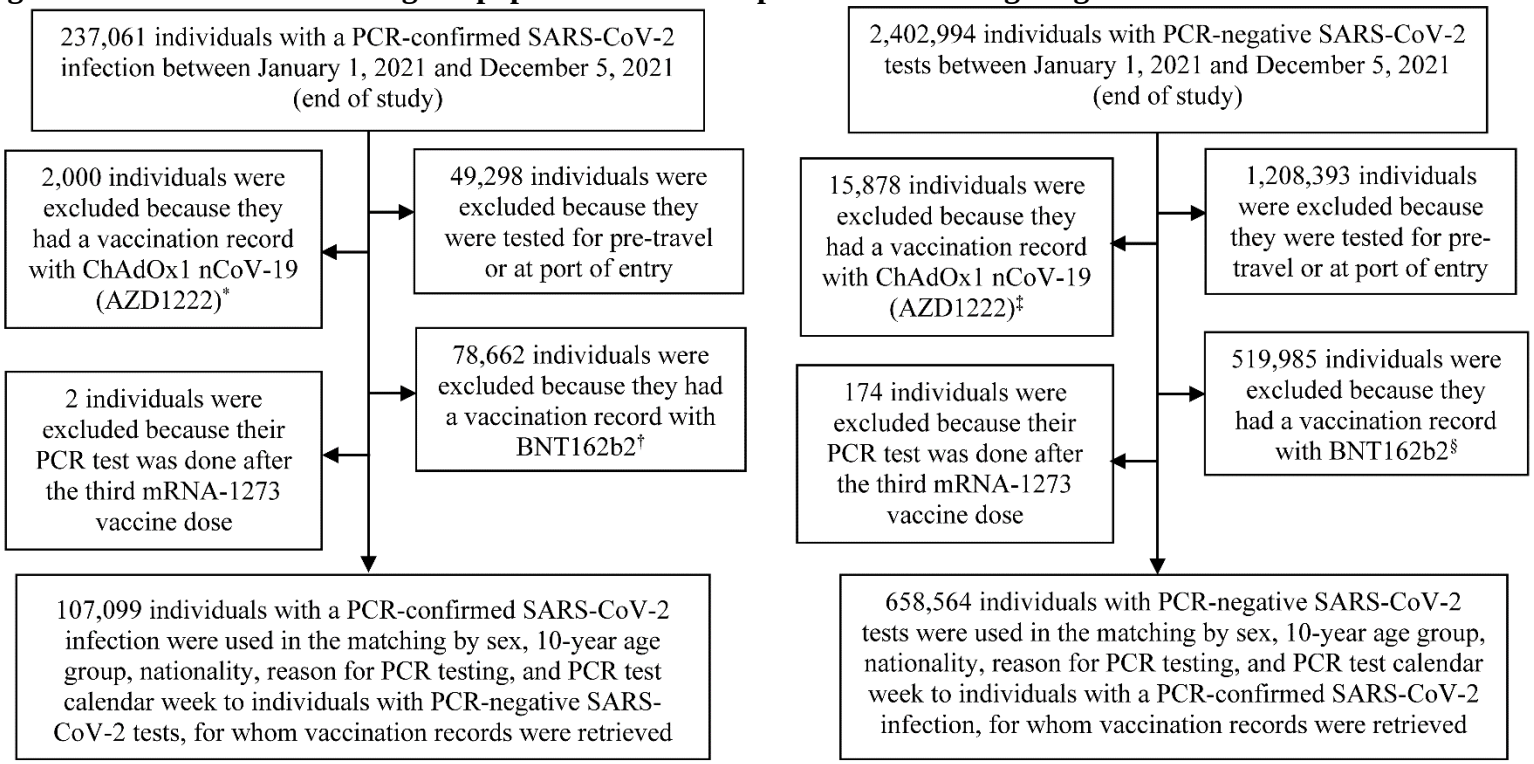
Table S1. STROBE checklist for case-control studies.

	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	Letter main text p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	NA
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Letter main text p.1
Objectives	3	State specific objectives, including any prespecified hypotheses	Letter main text p.1
Methods			
Study design	4	Present key elements of study design	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design')
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design') & Supp. Figure S1
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	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design') & Supp. Figure S1
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design' & 'Statistical analysis'), Supp. Sections S2 & S3, & Supp. Figure S1
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	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design' & 'Statistical analysis') & Supp. Tables S2-S4
Bias	9	Describe any efforts to address potential sources of bias	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design' & 'Statistical analysis')
Study size	10	Explain how the study size was arrived at	Supp. Figure S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Supp. Section S1 ('Study population, data sources, and study design' & 'Statistical analysis') & Supp. Tables S2-S4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Letter main text p.1 & Supp. Section S1 ('Statistical analysis') & Supp. Tables S2-S4
		(*b*) Describe any methods used to examine subgroups and interactions	Supp. Section S1 ('Statistical analysis')
		(*c*) Explain how missing data were addressed	NA, see Supp. Section S1 ('Study population, data sources, and study design')
		(*d*) If applicable, explain how matching of cases and controls was addressed	Letter main text p.1 & Supp. Section S1 ('Study population, data sources, and study design')
		(*e*) Describe any sensitivity analyses	Supp. Section S1 ('Statistical analysis')
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	Supp. Figure S1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supp. Tables S2-S4

		(b) Indicate number of participants with missing data for each variable of interest	NA, see Supp. Section S1 ('Study population, data sources, and study design')
Outcome data	15	Report numbers in each exposure category, or summary measures of exposure	Letter main text p.2, Figure 1, & Supp. Tables S5-S6
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	Letter main text p.2, Figure 1, & Supp. Tables S5-S6
		(*b*) Report category boundaries when continuous variables were categorized	Supp. Tables S2-S4
		(*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	Letter main text p.2 & Supp. Tables S7-S8
Discussion			
Key results	18	Summarise key results with reference to study objectives	Letter main text p.2
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	Supp. Section S1 ('Caveats and limitations')
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Letter main text p.2
Generalisability	21	Discuss the generalisability (external validity) of the study results	Supp. Section S1 ('Caveats and limitations')
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	Letter main text p.5

Abbreviations: NA, not applicable; p. page; Supp. Supplementary Appendix.

Figure S1. Flowchart describing the population selection process for investigating mRNA-1273 vaccine effectiveness.



*Sample includes 3 persons who had another vaccination with mRNA-1273 and 491 persons who had another vaccination with BNT162b2
†Sample includes 47 persons who had another vaccination with mRNA-1273
‡Sample includes 15 persons who had another vaccination with mRNA-1273 and 2,821 persons who had another vaccination with BNT162b2
§Sample includes 331 persons who had another vaccination with mRNA-1273

Note: In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Only matched pairs of PCR-positive and PCR-negative persons, in which both members of the pair were either unvaccinated or fell within each time-since-vaccination stratum have been included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

Table S2. Demographic characteristics of subjects and reasons for PCR testing among samples used to estimate mRNA-1273 vaccine effectiveness. The table includes samples used in the 0-13-days-after-first-dose analysis, ≥14-days-after-first-dose-and-no-second-dose analysis, and 1st-month-after-second-dose analysis.

Characteristics	0-13-days-after-first-dose			≥14-days-after-first-dose analyses			1st-month-after-second-dose		
	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§
	N=89,767	N=151,005		N=88,192	N=149,086		N=87,509	N=148,349	
Median age (IQR) — years	30 (16-38)	30 (12-38)	0.05¶	30 (15-38)	30 (12-37)	0.04¶	30 (14-38)	30 (11-37)	0.04¶
Age group — no. (%)									
<20 years	23,670 (26.4)	41,895 (27.7)		23,668 (26.8)	41,909 (28.1)		23,654 (27.0)	41,872 (28.2)	
20-29 years	18,567 (20.7)	31,719 (21.0)		18,230 (20.7)	31,284 (21.0)		18,146 (20.7)	31,186 (21.0)	
30-39 years	28,060 (31.3)	46,707 (30.9)		27,439 (31.1)	45,975 (30.8)		27,165 (31.0)	45,678 (30.8)	
40-49 years	14,264 (15.9)	22,752 (15.1)	0.04	13,771 (15.6)	22,144 (14.9)	0.04	13,570 (15.5)	21,936 (14.8)	0.04
50-59 years	4,221 (4.7)	6,508 (4.3)		4,117 (4.7)	6,379 (4.3)		4,022 (4.6)	6,282 (4.2)	
60-69 years	769 (0.9)	1,109 (0.7)		748 (0.9)	1,083 (0.7)		738 (0.8)	1,080 (0.7)	
70+ years	216 (0.2)	315 (0.2)		219 (0.3)	312 (0.2)		214 (0.2)	315 (0.2)	
Sex									
Male	61,688 (68.7)	104,433 (69.2)	0.01	60,377 (68.5)	102,808 (69.0)	0.01	59,947 (68.5)	102,396 (69.0)	0.01
Female	28,079 (31.3)	46,572 (30.8)		27,815 (31.5)	46,278 (31.0)		27,562 (31.5)	45,953 (31.0)	
Nationality†									
Bangladeshi	6,578 (7.3)	10,774 (7.1)		6,392 (7.3)	10,569 (7.1)		6,360 (7.3)	10,528 (7.1)	
Egyptian	5,677 (6.3)	9,271 (6.1)		5,592 (6.3)	9,197 (6.2)		5,550 (6.3)	9,162 (6.2)	
Filipino	8,532 (9.5)	13,684 (9.1)		8,277 (9.4)	13,298 (8.9)		8,147 (9.3)	13,123 (8.9)	
Indian	24,372 (27.2)	42,010 (27.8)		23,876 (27.1)	41,418 (27.8)		23,665 (27.0)	41,262 (27.8)	
Nepalese	7,735 (8.6)	13,248 (8.8)	0.04	7,567 (8.6)	13,024 (8.7)	0.04	7,531 (8.6)	12,958 (8.7)	0.04
Pakistani	4,960 (5.5)	8,592 (5.7)		4,908 (5.6)	8,529 (5.7)		4,881 (5.6)	8,520 (5.7)	
Qatari	11,961 (13.3)	21,413 (14.2)		11,968 (13.6)	21,437 (14.4)		11,912 (13.6)	21,364 (14.4)	
Sri Lankan	3,059 (3.4)	4,926 (3.3)		2,992 (3.4)	4,814 (3.2)		2,968 (3.4)	4,799 (3.2)	
Sudanese	2,408 (2.7)	3,875 (2.6)		2,363 (2.7)	3,823 (2.6)		2,325 (2.7)	3,777 (2.6)	
Other nationalities‡	14,485 (16.1)	23,212 (15.4)		14,257 (16.2)	22,977 (15.4)		14,170 (16.2)	22,856 (15.4)	
Reason for PCR testing									
Clinical suspicion	31,238 (34.8)	43,476 (28.8)		30,736 (34.9)	43,165 (29.0)		30,381 (34.7)	42,973 (29.0)	
Contact tracing	15,077 (16.8)	26,243 (17.4)		14,834 (16.8)	26,008 (17.4)		14,663 (16.8)	25,650 (17.3)	
Healthcare routine testing	10,999 (12.3)	19,493 (12.9)	0.14	10,845 (12.3)	19,329 (13.0)	0.13	10,821 (12.4)	19,296 (13.0)	0.13
Survey	21,676 (24.2)	41,258 (27.3)		21,195 (24.0)	40,400 (27.1)		21,026 (24.0)	40,136 (27.1)	
Individual request	10,469 (11.7)	20,115 (13.3)		10,278 (11.7)	19,774 (13.3)		10,304 (11.8)	19,874 (13.4)	
Other	308 (0.3)	420 (0.3)		304 (0.3)	410 (0.3)		314 (0.4)	420 (0.3)	

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

*Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test.

†Nationalities were chosen to represent the most populous groups in Qatar.

‡These comprise 102 other nationalities in Qatar in the 0-13-days-after-first-dose analysis, 102 other nationalities in the ≥14-days-after-first-dose-and-no-second-dose analysis, and 102 other nationalities in the 1st-month-after-second-dose analysis.

§SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD<0.1 indicates adequate matching.

¶SMD is for the mean difference between groups divided by the pooled standard deviation.

Table S3. Demographic characteristics of subjects and reasons for PCR testing among samples used to estimate mRNA-1273 vaccine effectiveness. The table includes samples used in the 2nd-month-after-second-dose analysis, 3rd-month-after-second-dose analysis, and 4th-month-after-second-dose analysis.

Characteristics	2nd-month-after-second-dose			3rd-month-after-second-dose			4th-month-after-second-dose		
	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§
	N=86,957	N=147,065		N=86,903	N=146,880		N=86,976	N=146,959	
Median age (IQR) — years	30 (14-38)	30 (11-37)	0.04¶	30 (11-37)	30 (14-38)	0.04¶	30 (14-38)	30 (11-37)	0.04¶
Age group — no. (%)									
<20 years	23,653 (27.2)	41,874 (28.5)		23,639 (27.2)	41,855 (28.5)		23,642 (27.2)	41,869 (28.5)	
20-29 years	18,051 (20.8)	30,884 (21.0)		18,023 (20.7)	30,861 (21.0)		18,032 (20.7)	30,869 (21.0)	
30-39 years	26,976 (31.0)	45,264 (30.8)		26,979 (31.0)	45,178 (30.8)		27,013 (31.1)	45,213 (30.8)	
40-49 years	13,408 (15.4)	21,557 (14.7)	0.04	13,415 (15.4)	21,543 (14.7)	0.04	13,426 (15.4)	21,555 (14.7)	0.04
50-59 years	3,935 (4.5)	6,129 (4.2)		3,917 (4.5)	6,093 (4.2)		3,931 (4.5)	6,101 (4.2)	
60-69 years	724 (0.8)	1,050 (0.7)		721 (0.8)	1,047 (0.7)		724 (0.8)	1,049 (0.7)	
70+ years	210 (0.2)	307 (0.2)		209 (0.2)	303 (0.2)		208 (0.2)	303 (0.2)	
Sex									
Male	59,526 (68.5)	101,364 (68.9)	0.01	59,479 (68.4)	101,225 (68.9)	0.01	59,513 (68.4)	101,223 (68.9)	0.01
Female	27,431 (31.6)	45,701 (31.1)		27,424 (31.6)	45,655 (31.1)		27,463 (31.6)	45,736 (31.1)	
Nationality†									
Bangladeshi	6,316 (7.3)	10,408 (7.1)		6,291 (7.2)	10,357 (7.1)		6,294 (7.2)	10,358 (7.1)	
Egyptian	5,507 (6.3)	9,070 (6.2)		5,505 (6.3)	9,063 (6.2)		5,512 (6.3)	9,079 (6.2)	
Filipino	8,126 (9.3)	13,065 (8.9)		8,111 (9.3)	13,022 (8.9)		8,128 (9.4)	13,080 (8.9)	
Indian	23,462 (27.0)	40,739 (27.7)		23,458 (27.0)	40,674 (27.7)		23,455 (27.0)	40,645 (27.7)	
Nepalese	7,507 (8.6)	12,914 (8.8)	0.04	7,497 (8.6)	12,882 (8.8)	0.04	7,481 (8.6)	12,856 (8.8)	0.04
Pakistani	4,857 (5.6)	8,440 (5.7)		4,859 (5.6)	8,469 (5.8)		4,859 (5.6)	8,444 (5.8)	
Qatari	11,839 (13.6)	21,224 (14.4)		11,823 (13.6)	21,191 (14.4)		11,861 (13.6)	21,254 (14.5)	
Sri Lankan	2,943 (3.4)	4,753 (3.2)		2,939 (3.4)	4,741 (3.2)		2,952 (3.4)	4,751 (3.2)	
Sudanese	2,313 (2.7)	3,752 (2.6)		2,317 (2.7)	3,753 (2.6)		2,318 (2.7)	3,762 (2.6)	
Other nationalities‡	14,087 (16.2)	22,700 (15.4)		14,103 (16.2)	22,728 (15.5)		14,116 (16.2)	22,730 (15.5)	
Reason for PCR testing									
Clinical suspicion	30,124 (34.6)	42,421 (28.9)		30,104 (34.6)	42,310 (28.8)		30,154 (34.7)	42,373 (28.8)	
Contact tracing	14,621 (16.8)	25,535 (17.4)		14,613 (16.8)	25,507 (17.4)		14,611 (16.8)	25,496 (17.4)	
Healthcare routine testing	10,802 (12.4)	19,252 (13.1)	0.13	10,798 (12.4)	19,245 (13.1)	0.13	10,801 (12.4)	19,248 (13.1)	0.13
Survey	20,927 (24.1)	39,894 (27.1)		20,921 (24.1)	39,867 (27.1)		20,932 (24.1)	39,892 (27.1)	
Individual request	10,176 (11.7)	19,554 (13.3)		10,164 (11.7)	19,544 (13.3)		10,175 (11.7)	19,546 (13.3)	
Other	307 (0.4)	409 (0.3)		303 (0.4)	407 (0.3)		303 (0.4)	404 (0.3)	

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction.

*Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test.

†Nationalities were chosen to represent the most populous groups in Qatar.

‡These comprise 102 other nationalities in Qatar in the 2nd-month-after-second-dose analysis, 102 other nationalities in the 3rd-month-after-second-dose analysis, and 102 other nationalities in the 4th-month-after-second-dose analysis.

§SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD<0.1 indicates adequate matching.

¶SMD is for the mean difference between groups divided by the pooled standard deviation.

Table S4. Demographic characteristics of subjects and reasons for PCR testing among samples used to estimate mRNA-1273 vaccine effectiveness. The table includes samples used in the 5th-month-after-second-dose analysis, 6th-month-after-second-dose analysis, 7th-month-after-second-dose, and 8th-month-after-second-dose analysis.

Characteristics	5th-month-after-second-dose			6th-month-after-second-dose			7th-month-after-second-dose			8th-month-after-second-dose		
	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§	Cases* (PCR-positive)	Controls* (PCR-negative)	SMD§
	N=86,962	N=146,870		N=86,814	N=146,576		N=86,843	N=146,628		N=86,754	N=146,435	
Median age (IQR) — years	30 (14-38)	30 (11-37)	0.04¶	30 (14-38)	30 (11-37)	0.05¶	30 (14-38)	30 (11-37)	0.04¶	30 (14-38)	30 (11-37)	0.04¶
Age group — no. (%)												
<20 years	23,647 (27.2)	41,862 (28.5)		23,638 (27.2)	41,840 (28.5)		23,645 (27.2)	41,864 (28.6)		23,644 (27.3)	41,853 (28.6)	
20-29 years	18,027 (20.7)	30,834 (21.0)		17,990 (20.7)	30,776 (21.0)		17,989 (20.7)	30,766 (21.0)		17,963 (20.7)	30,720 (21.0)	
30-39 years	26,990 (31.0)	45,138 (30.7)		26,924 (31.0)	45,030 (30.7)		26,965 (31.1)	45,085 (30.8)		26,917 (31.0)	44,983 (30.7)	
40-49 years	13,434 (15.5)	21,567 (14.7)	0.04	13,403 (15.4)	21,487 (14.7)	0.04	13,399 (15.4)	21,486 (14.7)	0.04	13,381 (15.4)	21,449 (14.7)	0.04
50-59 years	3,929 (4.5)	6,111 (4.2)		3,927 (4.5)	6,092 (4.2)		3,916 (4.5)	6,079 (4.2)		3,915 (4.5)	6,076 (4.2)	
60-69 years	727 (0.8)	1,055 (0.7)		724 (0.8)	1,049 (0.7)		720 (0.8)	1,044 (0.7)		724 (0.8)	1,049 (0.7)	
70+ years	208 (0.2)	303 (0.2)		208 (0.2)	302 (0.2)		209 (0.2)	304 (0.2)		210 (0.2)	305 (0.2)	
Sex												
Male	59,513 (68.4)	101,201 (68.9)	0.01	59,442 (68.5)	101,056 (68.9)	0.01	59,425 (68.4)	101,020 (68.9)	0.01	59,386 (68.5)	100,939 (68.9)	0.01
Female	27,449 (31.6)	45,669 (31.1)		27,372 (31.5)	45,520 (31.1)		27,418 (31.6)	45,608 (31.1)		27,368 (31.6)	45,496 (31.1)	
Nationality†												
Bangladeshi	6,287 (7.2)	10,347 (7.1)		6,280 (7.2)	10333 (7.1)		6,281 (7.2)	10,335 (7.1)		6,278 (7.2)	10,328 (7.1)	
Egyptian	5,526 (6.4)	9,099 (6.2)		5,516 (6.4)	9080 (6.2)		5,527 (6.4)	9,099 (6.2)		5,511 (6.4)	9,062 (6.2)	
Filipino	8,098 (9.3)	12,986 (8.8)		8,082 (9.3)	12953 (8.8)		8,088 (9.3)	12,962 (8.8)		8,062 (9.3)	12,901 (8.8)	
Indian	23,468 (27.0)	40,673 (27.7)		23,441 (27.0)	40608 (27.7)		23,467 (27.0)	40,657 (27.7)		23,439 (27.0)	40,602 (27.7)	
Nepalese	7,487 (8.6)	12,864 (8.8)		7,478 (8.6)	12842 (8.8)		7,471 (8.6)	12,818 (8.7)		7,468 (8.6)	12,810 (8.8)	
Pakistani	4,860 (5.6)	8,436 (5.7)	0.04	4,851 (5.6)	8422 (5.8)	0.04	4,845 (5.6)	8,405 (5.7)	0.04	4,845 (5.6)	8,404 (5.7)	0.04
Qatari	11,854 (13.6)	21,239 (14.5)		11,838 (13.6)	21182 (14.5)		11,827 (13.6)	21,187 (14.5)		11,829 (13.6)	21,191 (14.5)	
Sri Lankan	2,944 (3.4)	4,737 (3.2)		2,936 (3.4)	4728 (3.2)		2,929 (3.4)	4,717 (3.2)		2,929 (3.4)	4,717 (3.2)	
Sudanese	2,318 (2.7)	3,762 (2.6)		2,316 (2.7)	3754 (2.6)		2,319 (2.7)	3,762 (2.6)		2,313 (2.7)	3,750 (2.6)	
Other nationalities‡	14,120 (16.2)	22,727 (15.5)		14,076 (16.2)	22674 (15.5)		14,089 (16.2)	22,686 (15.5)		14,080 (16.2)	22,670 (15.5)	
Reason for PCR testing												
Clinical suspicion	30,153 (34.7)	42,336 (28.8)		30,084 (34.7)	42178 (28.78)		30,082 (34.6)	42,175 (28.8)		30,041 (34.6)	42,077 (28.7)	
Contact tracing	14,619 (16.8)	25,501 (17.4)		14,604 (16.8)	25485 (17.39)		14,603 (16.8)	25,481 (17.4)		14,599 (16.8)	25473 (17.4)	
Healthcare routine testing	10,801 (12.4)	19,251 (13.1)	0.13	10,800 (12.4)	19241 (13.13)	0.13	10,790 (12.4)	19,224 (13.1)	0.13	10,792 (12.4)	19226 (13.1)	0.13
Survey	20,927 (24.1)	39,865 (27.1)		20,884 (24.1)	39790 (27.15)		20,919 (24.1)	39,853 (27.2)		20,885 (24.1)	39780 (27.2)	
Individual request	10,156 (11.7)	19,509 (13.3)		10,143 (11.7)	19482 (13.29)		10,149 (11.7)	19,493 (13.3)		10,143 (11.7)	19484 (13.3)	
Other	306 (0.4)	408 (0.3)		299 (0.3)	400 (0.27)		300 (0.4)	402 (0.3)		294 (0.3)	395 (0.3)	

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction.

*Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test.

†Nationalities were chosen to represent the most populous groups in Qatar.

‡These comprise 102 other nationalities in Qatar in the 5th-month-after-second-dose analysis, 102 other nationalities in the 6th-month-after-second-dose analysis, 102 other nationalities in the 7th-month-after-second-dose analysis, and 102 other nationalities in the 8th-month-after-second-dose analysis.

§SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD<0.1 indicates adequate matching.

¶SMD is for the mean difference between groups divided by the pooled standard deviation.

Table S5. Effectiveness of the mRNA-1273 vaccine against any SARS-CoV-2 infection and against any severe, critical, or fatal COVID-19.

Sub-studies[*]	Effectiveness against infection					Effectiveness against hospitalization and death				
	Cases[†] (PCR-positive)		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]	Cases[†] (Severe, critical, or fatal disease)[§]		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
0-13 days after first dose	2,931	86,836	4,360	146,645	-2.2 (-7.6 to 2.9)	172	3,073	727	11,575	25.6 (10.6 to 38.1)
≥14 days after first dose and no second dose	962	87,230	3,891	145,195	65.5 (62.7 to 68.0)	28	3,066	464	11,379	83.1 (74.7 to 88.7)
1st month after the second dose	416	87,093	4,701	143,648	88.5 (87.2 to 89.7)	4	3,068	414	11,359	97.4 (93.0 to 99.0)
2nd month after the second dose	148	86,809	2,136	144,929	90.6 (88.7 to 92.1)	1	3,046	132	11,492	97.8 (83.7 to 99.7)
3rd month after the second dose	146	86,757	1,493	145,387	86.5 (83.8 to 88.8)	0	3,049	68	11,553	100.0 (55.0 to 100.0)[¶]
4th month after the second dose	186	86,790	1,221	145,738	80.7 (77.0 to 83.8)	2	3,043	52	11,556	91.5 (60.8 to 98.1)
5th month after the second dose	192	86,770	902	145,968	72.1 (66.7 to 76.7)	1	3,046	44	11,566	93.8 (53.6 to 99.2)
6th month after the second dose	105	86,709	494	146,082	70.6 (62.7 to 76.8)	1	3,042	10	11,583	67.6 (-165.6 to 96.0)
7th month after the second dose	168	86,675	376	146,252	29.9 (13.1 to 43.5)	0	3,041	13	11,571	100.0 (-146.7 to 100.0)[¶]
8th month or greater after the second dose	83	86,671	137	146,298	3.5 (-33.2 to 30.2)	0	3,043	11	11,581	100.0 (-194.4 to 100.0)[¶]

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[*]In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated. Only matched pairs of PCR-positive and PCR-negative persons, in which both members of the pair were either unvaccinated or fell within each time-since-vaccination stratum have been included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

[†]Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test in analysis of effectiveness against infection, and one-to-five in analysis of effectiveness against hospitalization and death.

[‡]Vaccine effectiveness was estimated using the test-negative, case-control study design.[5,6]

[§]Severity,[18] criticality,[18] and fatality[19] were defined as per World Health Organization guidelines.

[¶]Confidence interval could not be estimated using conditional logistic regression because of zero events among those vaccinated. Alternatively, the confidence interval was estimated using the standard error of the crude odds ratio after adding 0.5 to each of the number of vaccinated cases and number of unvaccinated cases.

Table S6. Effectiveness of the mRNA-1273 vaccine against any SARS-CoV-2 infection and against any severe, critical, or fatal COVID-19, after adjusting for prior infection and healthcare worker status.

Sub-studies[*]	Effectiveness against infection					Effectiveness against hospitalization and death				
	Cases[†] (PCR-positive)		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]	Cases[†] (Severe, critical, or fatal disease)[§]		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
0-13 days after first dose	2,931	86,836	4,360	146,645	-12.2 (-18.3 to -6.4)	172	3,073	727	11,575	22.1 (6.1 to 35.3)
≥14 days after first dose and no second dose	962	87,230	3,891	145,195	60.3 (57.0 to 63.3)	28	3,066	464	11,379	82.1 (73.1 to 88.1)
1st month after the second dose	416	87,093	4,701	143,648	85.3 (83.5 to 86.9)	4	3,068	414	11,359	97.2 (92.4 to 99.0)
2nd month after the second dose	148	86,809	2,136	144,929	84.7 (81.5 to 87.3)	1	3,046	132	11,492	97.4 (81.4 to 99.6)
3rd month after the second dose	146	86,757	1,493	145,387	75.7 (70.5 to 80.1)	0	3,049	68	11,553	100.0 (55.0 to 100.0)[¶]
4th month after the second dose	186	86,790	1,221	145,738	69.1 (62.5 to 74.5)	2	3,043	52	11,556	89.8 (51.9 to 97.8)
5th month after the second dose	192	86,770	902	145,968	53.6 (42.9 to 62.3)	1	3,046	44	11,566	94.2 (55.0 to 99.2)
6th month after the second dose	105	86,709	494	146,082	50.6 (34.5 to 62.8)	1	3,042	10	11,583	61.0 (-225.5 to 95.3)
7th month after the second dose	168	86,675	376	146,252	-3.5 (-32.3 to 19.1)	0	3,041	13	11,571	100.0 (-146.7 to 100.0)[¶]
8th month or greater after the second dose	83	86,671	137	146,298	-29.5 (-84.0 to 8.8)	0	3,043	11	11,581	100.0 (-194.4 to 100.0)[¶]

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[*]In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated. Only matched pairs of PCR-positive and PCR-negative persons, in which both members of the pair were either unvaccinated or fell within each time-since-vaccination stratum have been included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

[†]Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test in analysis of effectiveness against infection, and one-to-five in analysis of effectiveness against hospitalization and death.

[‡]Vaccine effectiveness was estimated using the test-negative, case-control study design.[5,6]

[§]Severity,[18] criticality,[18] and fatality[19] were defined as per World Health Organization guidelines.

[¶]Confidence interval could not be estimated using conditional logistic regression because of zero events among those vaccinated. Alternatively, the confidence interval was estimated using the standard error of the crude odds ratio after adding 0.5 to each of the number of vaccinated cases and number of unvaccinated cases.

Table S7. Effectiveness of the mRNA-1273 vaccine against any SARS-CoV-2 infection and against any severe, critical, or fatal COVID-19, stratified by age (<50 years or ≥50 years).

Sub-studies[*]	Effectiveness against infection					Effectiveness against hospitalization and death				
	Cases[†] (PCR-positive)		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]	Cases[†] (Severe, critical, or fatal disease)[§]		Controls[†] (PCR-negative)		Effectiveness in % (95% CI)[‡]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Age <50 years										
0-13 days after first dose	2,579	81,982	3,944	139,129	-0.2 (-5.7 to 5.1)	113	2,161	565	9,211	26.6 (8.4 to 41.2)
≥14 days after first dose and no second dose	807	82,301	3,500	137,812	67.1 (64.3 to 69.7)	12	2,162	350	9,066	89.4 (80.5 to 94.3)
1st month after the second dose	374	82,161	4,301	136,371	88.4 (87.0 to 89.7)	0	2,162	302	9,050	100.0 (88.9 to 100.0)[¶]
2nd month after the second dose	133	81,955	2,011	137,568	90.7 (88.8 to 92.3)	1	2,154	106	9,174	97.1 (79.1 to 99.6)
3rd month after the second dose	143	81,913	1,431	138,006	86.2 (83.4 to 88.6)	0	2,157	55	9,222	100.0 (37.1 to 100.0)[¶]
4th month after the second dose	173	81,940	1,146	138,360	80.6 (76.7 to 83.8)	2	2,153	43	9,231	89.6 (50.1 to 97.8)
5th month after the second dose	175	81,923	833	138,568	72.5 (66.8 to 77.2)	1	2,155	33	9,238	91.3 (33.9 to 98.8)
6th month after the second dose	94	81,861	456	138,677	70.9 (62.6 to 77.3)	1	2,153	9	9,250	64.5 (-196.1 to 95.8)
7th month after the second dose	155	81,843	353	138,848	31.1 (13.7 to 44.9)	0	2,152	12	9,237	100.0 (-202.8 to 100.0)[¶]
8th month or greater after the second dose	74	81,831	116	138,889	-5.3 (-48.7 to 25.4)	0	2,152	6	9,251	100.0 (-541.5 to 100.0)[¶]
Age ≥50 years										
0-13 days after first dose	352	4,854	416	7,516	-23.1 (-44.8 to -4.6)	59	912	162	2,364	23.3 (-6.9 to 45.0)
≥14 days after first dose and no second dose	155	4,929	391	7,383	51.0 (39.5 to 60.4)	16	904	114	2,313	69.6 (46.8 to 82.6)
1st month after the second dose	42	4,932	400	7,277	89.6 (84.8 to 92.9)	4	906	112	2,309	92.3 (78.6 to 97.2)
2nd month after the second dose	15	4,854	125	7,361	88.7 (77.5 to 94.4)	0	892	26	2,318	100.0 (17.9 to 100.0)[¶]
3rd month after the second dose	3	4,844	62	7,381	93.5 (78.9 to 98.0)	0	892	13	2,331	100.0 (-69.5 to 100.0)[¶]
4th month after the second dose	13	4,850	75	7,378	82.1 (63.2 to 91.3)	0	890	9	2,325	100.0 (-150.5 to 100.0)[¶]
5th month after the second dose	17	4,847	69	7,400	67.9 (41.2 to 82.4)	0	891	11	2,328	100.0 (-102.2 to 100.0)[¶]
6th month after the second dose	11	4,848	38	7,405	67.7 (27.5 to 85.6)	0	889	1	2,333	100.0 (-3,812.7 to 100.0)[¶]
7th month after the second dose	13	4,832	23	7,404	14.1 (-85.6 to 60.3)	0	889	1	2,334	100.0 (-3,814.3 to 100.0)[¶]
8th month or greater after the second dose	9	4,840	21	7,409	47.2 (-34.6 to 79.3)	0	891	5	2,330	100.0 (-378.9 to 100.0)[¶]

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

*In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated. Only matched pairs of PCR-positive and PCR-negative persons, in which both members of the pair were either unvaccinated or fell within each time-since-vaccination stratum have been included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

†Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test in analysis of effectiveness against infection, and one-to-five in analysis of effectiveness against hospitalization and death.

‡Vaccine effectiveness was estimated using the test-negative, case-control study design.[5,6]

§Severity,[18] criticality,[18] and fatality[19] were defined as per World Health Organization guidelines.

¶Confidence interval could not be estimated using conditional logistic regression because of zero events among those vaccinated. Alternatively, the confidence interval was estimated using the standard error of the crude odds ratio after adding 0.5 to each of the number of vaccinated cases and number of unvaccinated cases.

Table S8. Effectiveness of the mRNA-1273 vaccine against symptomatic and asymptomatic SARS-CoV-2 infection.

Sub-studies[*]	Effectiveness against symptomatic infection[†]					Effectiveness against asymptomatic infection[‡]				
	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	
0-13 days after first dose	1,170	30,068	1,562	41,914	11.0 (3.4 to 18.0)	788	20,888	1,379	39,879	-9.9 (-21.3 to 0.5)
≥14 days after first dose and no second dose	303	30,433	1,572	41,593	78.3 (75.2 to 81.1)	299	20,896	1,078	39,322	54.6 (47.7 to 60.6)
1st month after the second dose	79	30,302	1,720	41,253	94.4 (92.8 to 95.6)	139	20,887	1,022	39,114	79.9 (75.5 to 83.4)
2nd month after the second dose	44	30,080	1,033	41,388	94.0 (91.8 to 95.6)	59	20,868	432	39,462	81.8 (75.2 to 86.6)
3rd month after the second dose	52	30,052	814	41,496	91.2 (88.1 to 93.4)	56	20,865	241	39,626	66.1 (52.7 to 75.7)
4th month after the second dose	87	30,067	676	41,697	82.9 (78.1 to 86.7)	64	20,868	231	39,661	63.6 (48.8 to 74.2)
5th month after the second dose	94	30,059	552	41,784	76.7 (70.4 to 81.7)	63	20,864	148	39,717	33.7 (3.7 to 54.4)
6th month after the second dose	55	30,029	301	41,877	74.8 (65.3 to 81.7)	30	20,854	73	39,717	30.8 (-13.0 to 57.6)
7h month after the second dose	82	30,000	225	41,950	48.7 (30.3 to 62.2)	62	20,857	86	39,767	-46.6 (-115.6 to 0.2)
8th month or greater after the second dose	35	30,006	64	42,013	20.0 (-29.0 to 50.3)	29	20,856	42	39,738	-28.4 (-129.3 to 28.1)

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[*]In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated. Only matched pairs of PCR-positive and PCR-negative persons, in which both members of the pair were either unvaccinated or fell within each time-since-vaccination stratum have been included in the corresponding vaccine effectiveness estimate. Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

[†]A 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 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 or a random testing campaign.

[§]Cases and controls were matched one-to-two by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test in analysis of effectiveness against infection, and one-to-five in analysis of effectiveness against hospitalization and death.

[¶]Vaccine effectiveness was estimated using the test-negative, case-control study design.[5,6]

References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603-15.
2. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med 2021;385:e83.
3. 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.
4. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. Sci Rep 2021;11:6233.
5. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31:2165-8.
6. Verani JR, Baqui AH, Broome CV, et al. Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. Vaccine 2017;35:3295-302.
7. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet 2021;397:2461-2.
8. Nasreen S, He S, Chung H, et al. Effectiveness of COVID-19 vaccines against variants of concern, Canada. medRxiv 2021:2021.06.28.21259420.
9. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385:585-94.
10. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for Covid Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187-9.
11. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021;27:1614-21.
12. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest 2021;131.
13. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med 2021.
14. Ayoub HH, Chemaitelly H, Seedat S, et al. Mathematical modeling of the SARS-CoV-2 epidemic in Qatar and its impact on the national response to COVID-19. J Glob Health 2021;11:05005.
15. Coyle PV, Chemaitelly H, Ben Hadj Kacem MA, 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 2021;24:102646.
16. Al-Thani MH, Farag E, Bertollini R, et al. SARS-CoV-2 infection is at herd immunity in the majority segment of the population of Qatar. Open Forum Infect Dis 2021;8:ofab221.
17. Jeremijenko A, Chemaitelly H, Ayoub HH, et al. Herd Immunity against Severe Acute Respiratory Syndrome Coronavirus 2 Infection in 10 Communities, Qatar. Emerg Infect Dis 2021;27:1343-52.
18. 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 31, 2021. 2021.
19. 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 31, 2021. 2021.

20. 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 2014;32:2942.
21. Pearce N. Analysis of matched case-control studies. BMJ 2016;352:i969.
22. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
23. Planning and Statistics Authority- State of Qatar. Labor force sample survey. Available from: https://www.psa.gov.qa/en/statistics/Statistical%20Releases/Social/LaborForce/2017/statistical_analysis_labor_force_2017_En.pdf. Accessed on: May 01, 2020. 2017.
24. Qatar viral genome sequencing data. Data on randomly collected samples. https://www.gisaid.org/phylodynamics/global/nextstrain/. 2021. at https://www.gisaid.org/phylodynamics/global/nextstrain/.)
25. Hasan MR, Kalikiri MKR, Mirza F, et al. Real-Time SARS-CoV-2 Genotyping by High-Throughput Multiplex PCR Reveals the Epidemiology of the Variants of Concern in Qatar. Int J Infect Dis 2021;112:52-4.
26. Benslimane FM, Al Khatib HA, Al-Jamal O, et al. One Year of SARS-CoV-2: Genomic Characterization of COVID-19 Outbreak in Qatar. Front Cell Infect Microbiol 2021;11:768883.
27. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar. JAMA 2021;326:1930-9.
28. World Health Organization. Tracking SARS-CoV-2 variants. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. 2021.
29. Makhoul M., Ayoub H.H., Chemaitelly H., et al. Epidemiological impact of SARS-CoV-2 vaccination: Mathematical modeling analyses. Vaccines 2020;8.
30. Usherwood T, LaJoie Z, Srivastava V. A model and predictions for COVID-19 considering population behavior and vaccination. Scientific Reports 2021;11:12051.
31. Andersson O, Campos-Mercade P, Meier AN, Wengström E. Anticipation of COVID-19 Vaccines Reduces Social Distancing. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3765329. SSRN 2021.
32. Anderegg N, Althaus CL, Colin S, et al. Assessing real-world vaccine effectiveness against severe forms of SARS-CoV-2 infection from routine surveillance data in Switzerland. Preprint available from: 10.31219/osf.io/rxk9b. 2021.
33. Feikin D, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 Disease: results of a systematic review and meta-regression. Preprint available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3961378. 2021.
34. Skowronski DM, Setayeshgar S, Febriani Y, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. medRxiv 2021:2021.10.26.21265397.