



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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The SARS-CoV-2 pandemic continues to be a global health concern. The mRNA-1273 (Moderna) vaccine was reported to have an 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, 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 2 weeks after the first dose, but increased rapidly in the third and fourth weeks immediately before administration of a second dose. Effectiveness against B.1.1.7 infection was 88.1% (95% confidence interval (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 dose, respectively. The mRNA-1273 vaccine is highly effective against B.1.1.7 and B.1.351 infections, whether symptomatic or asymptomatic, and against any COVID-19 hospitalization and death, even after a single dose.

In a randomized clinical trial, the mRNA-1273 (Moderna) vaccine had a reported efficacy of 94.1% in preventing symptomatic coronavirus disease 2019 (COVID-19) due to infection with wild-type variants¹. The first immunization using this vaccine in Qatar was recorded on 28 December 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 the introduction and expansion of the B.1.1.7 (Alpha²) and B.1.351 (Beta³) variants³. This created a unique epidemiological opportunity to assess the 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 28 December 2020 and 10 May 2021, 256,037 individuals in Qatar 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 dates at first and second dose were 5 and 29 April 2021, respectively. The median time elapsing between the first and second doses was 28 days (interquartile range (IQR): 28–29 days), with 94.6% of individuals receiving their second dose ≤ 30 days after the first dose.

Flowcharts describing the population selection process for investigation and estimation of vaccine effectiveness are presented in Extended Data Figs. 1–3, and the demographic characteristics of the sample for each outcome of vaccine effectiveness are presented in Table 1. Median age in the study sample for estimation of 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 is that Qatar has a young and diverse demographic, where only 9% of its resident population are >50 years of age and 89% are expatriates from >150 countries^{4,5}.

Weekly rounds of viral genome sequencing from 8 March to 10 May 2021 identified B.1.351 ($n=369$; 64.4%), B.1.1.7 ($n=58$;

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Table 1 | Demographic characteristics of (1) B.1.1.7 cases (PCR-positive) and controls (PCR-negative), (2) B.1.351 cases (PCR-positive) and controls (PCR-negative) and (3) severe, critical or fatal COVID-19 disease cases (any PCR-positive case) and controls (PCR-negative)

Sample type	(1) Any infection with the B.1.1.7 variant between 1 February and 10 May 2021		(2) Any infection with the B.1.351 variant between 8 March and 10 May 2021		(3) Any severe, critical or fatal disease with any SARS-CoV-2 infection between 1 February and 10 May 2021	
Characteristics ^a	Cases ^b (PCR-positive)	Controls ^b (PCR-negative)	Cases ^b (PCR-positive)	Controls ^b (PCR-negative)	Cases ^b (PCR-positive)	Controls ^b (PCR-negative)
Median age, years (IQR)	31 (19–38)	31 (19–38)	32 (25–39)	32 (25–39)	43 (37–51)	43 (37–51)
Age group, <i>n</i> (%)						
<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 ^c						
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 ^d	4,523 (21.2)	4,523 (21.2)	5,491 (12.3)	5,491 (12.3)	428 (12.6)	428 (12.6)

^aThese demographic characteristics are for samples used in the ≥ 14 -days-after-second-dose analyses, but are essentially identical to those in the other analyses. ^bCases and controls were matched one-to-one by sex, age, nationality and reason for PCR testing. ^cNationalities were chosen to represent the most populous groups in Qatar. ^dThese comprise 80 other nationalities in Qatar among sample 1, 78 other nationalities among sample 2 and 41 other nationalities among sample 3.

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 PCR with reverse transcription (RT-qPCR)-based variant screening⁶ from 23 March to 10 May 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, three were B.1-like and three were undetermined.

As of 10 May 2021, 1,558 and 243 breakthrough infections were recorded among those who had received 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.

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 the B.1.1.7 variant, regardless of the reason for PCR testing or presence of symptoms (Methods), was negligible for 2 weeks after the first dose (Table 2 and Fig. 1), but increased rapidly in the third week reaching 81.6% (95% 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 the B.1.351 variant regardless of the reason for PCR testing or presence of symptoms (Methods), was negligible for 2 weeks after the first dose (Table 2 and Fig. 1) but increased rapidly in the third week to reach 47.9% (95% CI: 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 (ref. 7);

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 6 weeks after the first dose

	Cases, <i>n</i> (PCR-positive)		Controls, <i>n</i> (PCR-negative)		Effectiveness, % (95% CI) ^a		Cases, <i>n</i> (PCR-positive)		Controls, <i>n</i> (PCR-negative)		Effectiveness, % (95% CI) ^a	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
0–6 days after first dose												
Effectiveness against infection												
Any infection with the B.1.1.7 variant ^b	166	23,661	170	23,657	2.4 (0–21.7)	202	23,681	187	23,696	0.0 (0.0–11.9)		
Any infection with the B.1.351 variant ^c	535	47,359	558	47,336	4.2 (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 ^d	53	4,012	65	4,000	18.7 (0–44.7)	85	4,016	68	4,033	0.0 (0.0–10.1)		
14–20 days after first dose												
Effectiveness against infection												
Any infection with the B.1.1.7 variant ^b	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 ^c	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 ^d	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												
Effectiveness against infection												
Any infection with the B.1.1.7 variant ^b	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 ^c	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 ^d	0	3,432	62	3,370	100.0 (93.9–100.0)	0	3,399	29	3,370	100.0 (86.9–100.0)		

^aVaccine effectiveness was estimated using the test-negative, case-control study design²⁸. ^bAny 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 Scientific²⁹), applying the criterion of PCR cycle threshold value ≤ 30 for both the N and ORF1ab genes but a negative outcome for the S-gene^{30,32}. The median date of vaccination with first dose was 8 April for cases and 2 April for their matched controls. ^cAny 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 multiplex RT-qPCR variant screening between 8 March and 10 May 2021 (ref. 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 the above dates. The median date of vaccination with first dose was 4 April for cases and 3 April for their matched controls. ^dAny 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 classification of SARS-CoV-2 infection severity²³ and COVID-19-related death²⁴.

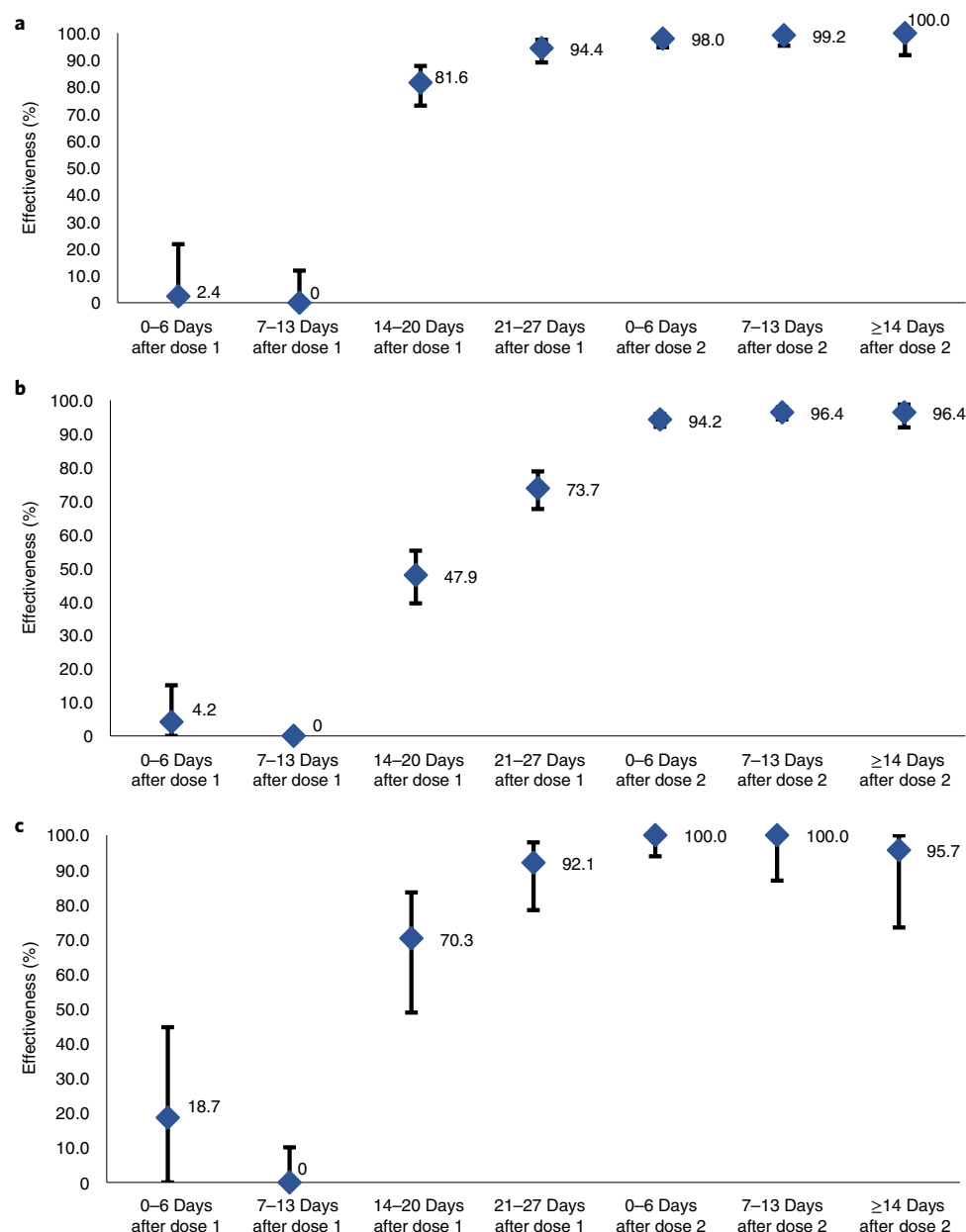


Fig. 1 | Effectiveness of the mRNA-1273 vaccine. a–c, Effectiveness of the mRNA-1273 vaccine against B.1.1.7 infections (**a**), B.1.351 infections (**b**) and severe, critical or fatal COVID-19 disease (**c**) after the first and second doses. Analyses were performed on independent samples of $n = 25,034$ PCR-positive cases and $n = 25,034$ PCR-negative controls examined between 1 February and 10 May 2021 for B.1.1.7, $n = 52,442$ PCR-positive cases and $n = 52,442$ PCR-negative controls examined between 8 March and 10 May 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 1 February and 10 May 2021. Data are presented as effectiveness point estimates, with error bars indicating the corresponding 95% CIs.

Methods) was negligible for 2 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 the main analysis results (Table 4).

An additional analysis estimated vaccine effectiveness against symptomatic infection (predominantly B.1.1.7 and B.1.351 (ref. 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 the 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.1.351⁷) at 92.5% (95% CI: 84.8–96.9%) 14 or more days after the second dose

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, <i>n</i> (PCR-positive)		Controls, <i>n</i> (PCR-negative)		Cases, <i>n</i> (PCR-positive)		Controls, <i>n</i> (PCR-negative)	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Effectiveness against infection								
Any infection with the B.1.1.7 variant ^b	44	23,860	365	23,539	0	21,305	47	21,258
Any infection with the B.1.351 variant ^c	419	47,872	1,067	47,224	6	44,731	165	44,572
Effectiveness against disease								
Any severe, critical or fatal disease with any SARS-CoV-2 infection ^d	23	4,067	122	3,968	1	3,393	23	3,371

^aVaccine effectiveness was estimated using the test-negative, case-control study design³⁸. ^bAny B.1.1.7 PCR-confirmed infection. ^cA 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[®]), applying the criterion of PCR cycle threshold value ≤ 30 for both the N and ORF1ab genes but a negative outcome for the S-gene^{39–42}. The median date of vaccination with first dose was 8 April for cases and 2 April for their matched controls. ^dAny 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 RT-qPCR variant screening between 8 March and 10 May 2021 (ref. 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 the above dates. The median date of vaccination with first dose was 4 April for cases and 3 April for their matched controls. ^eAny 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 classification of SARS-CoV-2 infection severity⁴³ and COVID-19-related death⁴⁴.

(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, PCR testing was done as part of a survey, for pretravel requirements or at a port of entry following arrival in 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 that in the national cohort of persons who were antibody negative (Methods, Supplementary Table 2 and Extended Data Fig. 4). Incidence rates among those vaccinated were estimated at 0 (95% CI: 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 person-weeks in a total follow-up time of 10,282.86 person-weeks. The 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 person-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 the results from the main analysis.

Discussion

Our analysis demonstrates that the effectiveness of the mRNA-1273 vaccine is high, regardless of variant, against both symptomatic 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 4 weeks after the first dose, these findings might suggest that most of the protection from 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 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 that, 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, 1 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 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–May 2021. Those vaccinated with the mRNA-1273 vaccine

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 (1) matching by sex, age, nationality, reason for PCR testing and PCR test date, (2) adjusting for calendar week in logistic regression analysis and (3) 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, n (PCR-positive)		Controls, n (PCR-negative)		Cases, n (PCR-positive)		Controls, n (PCR-negative)	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
(1) 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 ^b	14	12,828	97	12,745	0	11,689	6	11,683
								100.0 (36.0–100.0)
Any infection with the B.1.351 variant ^c	158	29,153	404	28,907	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 ^d	6	1,799	30	1,775	0	1,580	0	1,580
								Omitted ^e
(2) Adjusting for calendar week in regression analysis								
Effectiveness against infection								
Any infection with the B.1.1.7 variant ^b	44	23,860	365	23,539	0	21,305	47	21,258
								100.0 (Omitted ^f)
Any infection with the B.1.351 variant ^c	419	47,872	1,067	47,224	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 ^d	23	4,067	122	3,968	1	3,393	23	3,371
								89.0 (15.2–98.6)
(3) Adjusting for sex, age, nationality ^g , reason for PCR testing and calendar week in regression analysis								
Effectiveness against infection								
Any infection with the B.1.1.7 variant ^b	44	23,860	365	23,539	0	21,305	47	21,258
								100.0 (Omitted ^f)
Any infection with the B.1.351 variant ^c	419	47,872	1,067	47,224	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 ^d	23	4,067	122	3,968	1	3,393	23	3,371
								89.5 (18.8–98.7)

^aVaccine effectiveness was estimated using the test-negative, case-control study design⁷⁰⁸. ^bAny 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 Scientific⁷⁰⁹), applying the criterion of PCR cycle threshold value ≤30 for both the N and ORF1ab genes but a negative outcome for the S-gene^{60,72}. ^cAny 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 RT-qPCR variant screening between 8 March and 10 May 2021 (ref.⁷¹), 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 the above dates. ^dAny 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 severity⁷¹⁰ and COVID-19-related death⁷¹¹. ^eThere were no vaccinated persons among cases and controls, and thus estimates could not be obtained. ^fThere were no events among individuals vaccinated. ^gNationality was included in the regression analysis as a categorical variable comprising the most populous nationalities in Qatar: Bangladeshi, Filipino, Egyptian, Indian, Nepalese, Pakistani, Qatari, Sudanese, Sri Lankan and other nationalities.

(Table 1) tend to be slightly younger than those vaccinated with the BNT162b2 vaccine³.

Effectiveness in our study was assessed based on documented infections, but other infections may 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 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 certain limitations. Estimated effectiveness against severe, critical or fatal COVID-19 disease had somewhat wider 95% confidence intervals as a consequence of (1) the relatively lower severity of COVID-19 in the young population of Qatar compared to populations where the median age is higher^{4,12}, (2) the younger cohort of those vaccinated with mRNA-1273 and (3) the majority of vaccinated persons having had their second dose after the B.1.1.7 and B.1.351 waves peaked in early March and early April 2021, respectively. The median date of receiving the second dose in our study population was 29 April 2021. For the same reasons, we could not precisely estimate effectiveness against severe, critical or fatal COVID-19 disease attributable individually to the B.1.1.7 and B.1.351 variants.

Severe, critical or fatal COVID-19 disease was assessed up to the end of the study (10 May 2021), and it is possible that cases confirmed as PCR positive immediately before the end of the study may have progressed to a severe outcome only after the end of the study and were thus not included in our sample. This, however, should not affect our estimates because the study, by design, contrasts confirmed COVID-19 disease cases with PCR-negative cases. For reasons that remain unclear, among persons 7–13 days after the first dose the 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 vaccines¹⁶. 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 effect¹⁶ or an artifact of the estimation method, possibly because the first vaccine dose frequently coincided 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 comorbid conditions were not available and hence could not be factored explicitly in our analysis. However, adjustment for age may have served as a proxy given that comorbidities are associated with old age. Furthermore, given the young population structure in Qatar^{4,5} we anticipate that only a small proportion of the study population may have had serious comorbid conditions. However, our findings might not be entirely generalizable to other settings where the elderly constitute 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 intervals.

In conclusion, in the population of Qatar the mRNA-1273 vaccine is very effective against both B.1.1.7 and B.1.351 infection, whether symptomatic or asymptomatic, and against COVID-19 hospitalization and death. 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 substantially 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.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-021-01446-y>.

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References

- Baden, L. R. et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* **384**, 403–416 (2021).
- Tracking SARS-CoV-2 variants (World Health Organization, accessed 5 June 2021); <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
- 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.* <https://pubmed.ncbi.nlm.nih.gov/33951357/> (2021).
- Abu-Raddad, L. J. et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. *Sci. Rep.* **11**, 6233 (2021).
- Qatar Monthly Statistics (Planning and Statistics Authority, accessed 26 May 2020); <https://www.psa.gov.qa/en/pages/default.aspx>
- 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. <https://doi.org/10.17504/protocols.io.br9vm966> (2021).
- 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 (Ministry of Public Health, 2021).
- 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* <https://pubmed.ncbi.nlm.nih.gov/34106201/> (2021).
- 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. *Brit. Med. J.* **373**, n1088 (2021).
- 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).
- 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.* <https://pubmed.ncbi.nlm.nih.gov/34050372/> (2021).
- Seedat, S. et al. SARS-CoV-2 infection hospitalization, severity, criticality, and fatality rates. Preprint at <https://www.medrxiv.org/content/10.1101/2020.11.29.20240416v1.full> (2020).
- 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. Preprint at <https://www.medrxiv.org/content/10.1101/2021.04.07.21255081v1> (2021).
- 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. Preprint at <https://www.medrxiv.org/content/10.1101/2021.02.01.21250957v1> (2021).
- 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* **397**, 1725–1735 (2021).
- 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. *J. Infect. Dis.* **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 (Thermo Fisher Scientific, accessed 2 December 2020); https://assets.thermofisher.com/TFS-Assets/LSG/manuals/MAN0019215_TaqPathCOVID-19_CE-IVD_RT-PCR%20Kit_IFU.pdf
 20. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom (ECDC, accessed 10 February 2021); <https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf>
 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. *Brit. Med. J.* **372**, n579 (2021).
 23. COVID-19 clinical management: living guidance (WHO, accessed 15 May 2021); <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1>
 24. International guidelines for certification and classification (coding) of COVID-19 as cause of death (WHO, accessed 15 May 2021); https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19-20200420-EN.pdf?ua=1
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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 had received the mRNA-1273 COVID-19 vaccine outside Qatar, the individual's vaccination details were still recorded in the health system at the port of entry (airport) following their 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 assessment of vaccine effectiveness against influenza^{17,18}. Key to this design is the control of bias arising from misclassification of infection and differences in healthcare-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 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 variant, 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 (ref. 7)). Classification of COVID-19 case severity (acute care hospitalizations)²³, criticality (intensive care unit hospitalizations)²³ and fatality²⁴ 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 RT-qPCR variant screening⁶ of randomly collected clinical samples⁷, as well as by results of deep sequencing of wastewater samples⁷. 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 Scientific¹⁹; >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-gene²². Meanwhile, with essentially only B.1.351 and B.1.1.7 cases identified from 8 March 2021 until the end of the study (10 May 2021) in the viral genome sequencing and multiplex RT-qPCR variant screening⁷, 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 genes³.

With these considerations in regard to ascertaining infection by B.1.1.7 and B.1.351, the study extended from 1 February to 10 May 2021 for B.1.1.7, from 8 March to 10 May 2021 for B.1.351 and from 1 February to 10 May 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, 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 with a positive PCR test result and hospital admission was subject to an infection severity assessment every 3 days until discharge or death. Individuals who progressed to COVID-19 disease between the time of a positive PCR test result and the end of the study were classified based on their worst outcome, starting with death²⁴, followed by critical disease²³ and then severe disease²³.

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) were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were extracted on a QIAasympy platform (QIAGEN) and tested with RT-qPCR using TaqPath COVID-19 Combo Kits (100% sensitivity and specificity¹⁹; Thermo Fisher Scientific) on an ABI 7500 FAST (ThermoFisher), extracted using a custom protocol²⁸ on a Hamilton Microlab STAR (Hamilton) and tested using AccuPower SARS-CoV-2 Real-Time RT-PCR Kits (100% sensitivity and specificity²⁹; Bioneer) 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% specificity³⁰; Roche). The first assay targets the viral S, N and ORF1ab regions, the second targets the viral RdRp and E-gene regions while the third targets the ORF1ab and E-gene regions.

All tests were conducted at either 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 study samples. The odds ratios, 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}:

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 rollout 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 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; 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 the 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, PCR testing was done as part of a survey, for pretravel requirement or at the port of entry into the country (Supplementary Table 1).

Vaccine effectiveness was further assessed using a cohort study design^{3,34,35} by comparison of 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 (ref. 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:

Vaccine effectiveness

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

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 (ref. 36).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The dataset of this study is a property of the Qatar Ministry of Public Health and is provided to the researchers through a restricted-access agreement that prevents its sharing with a third party or publicly. Future access to this dataset can be considered through 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 (ref. 36). The commands/code are accessible using the following URL: <https://github.com/IDEGWCMQ/Vaccine-effectiveness-code>

References

- 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 Infect. Dis.* **May** 2, ofab221 (2021).
- 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).
- 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* **24**, 102646 (2021).
- Kaliki, M. K. R. et al. High-throughput extraction of SARS-CoV-2 RNA from nasopharyngeal swabs using solid-phase reverse immobilization beads. Preprint at <https://www.medrxiv.org/content/10.1101/2020.04.08.20055731v1> (2020).
- 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**, 434 (2020).
- Cobas® SARS-CoV-2: qualitative assay for use on the cobas® 6800/8800 Systems (US FDA, accessed 2 December 2020); <https://www.fda.gov/media/136049/download>
- 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, 2165–8. *Vaccine* **32**, 2942 (2014).

32. Pearce, N. Analysis of matched case-control studies. *Brit. Med. J.* **352**, i969 (2016).
33. Rothman, K. J., Greenland, S. & Lash, T. L. *Modern Epidemiology* (Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008).
34. Abu-Raddad, L. J. et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. *Clin. Infect. Dis.* <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1846/6033728> (2020).
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. Statistical Software: Release 16.1 (StataCorp, 2019); <https://www.stata.com>

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Author contributions

H.C. codesigned the study, performed statistical analyses and cowrote the first draft of the article. L.J.A.-R. conceived and codesigned the study, led the statistical analyses and cowrote the first draft of the article. A.A.B. and R.B. codesigned 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

A.A.B. received institutional grant funding from Gilead Sciences, unrelated to the work presented in this paper. Otherwise, the authors declare no competing interests.

Additional information

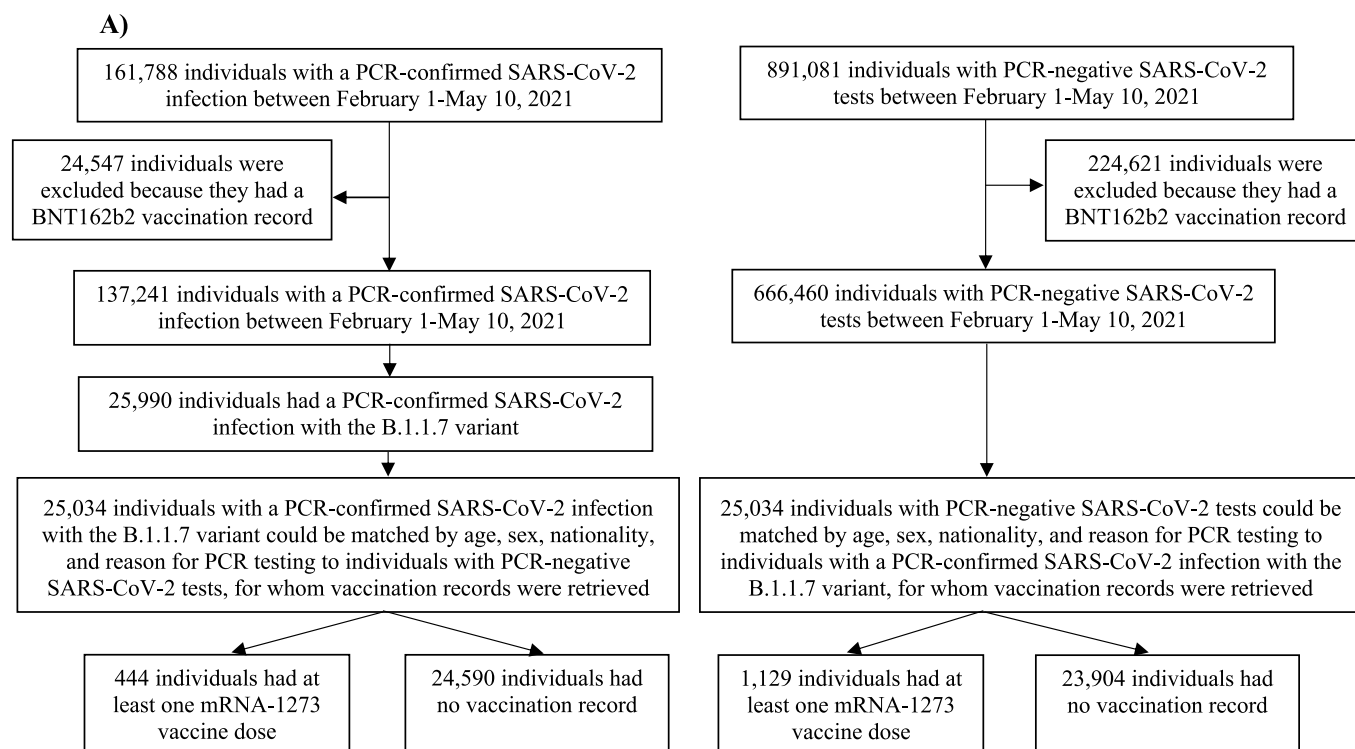
Extended data is available for this paper at <https://doi.org/10.1038/s41591-021-01446-y>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-021-01446-y>.

Correspondence and requests for materials should be addressed to L.J.A.-R.

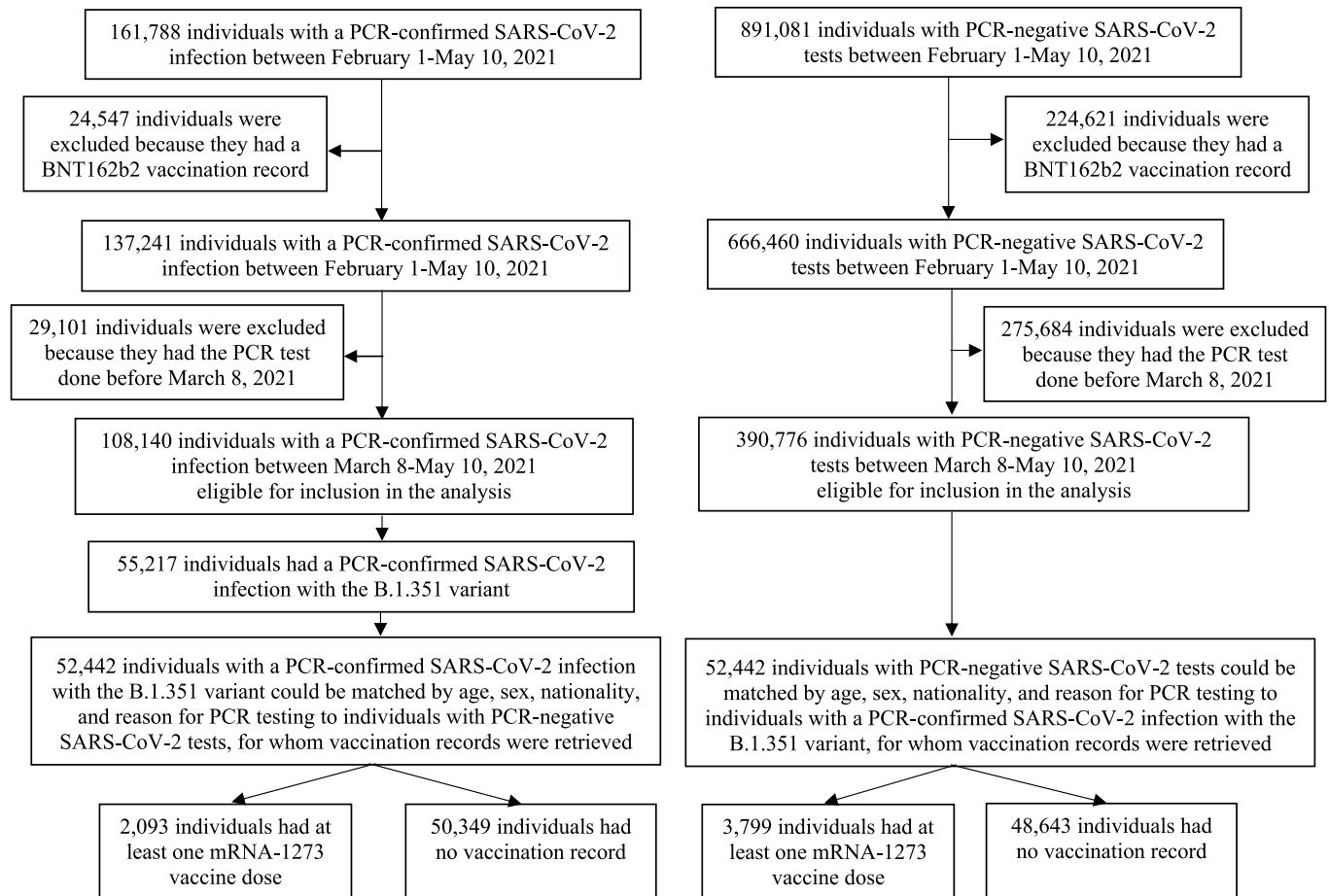
Peer review information *Nature Medicine* thanks Mark Tenforde and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Jennifer Sargent was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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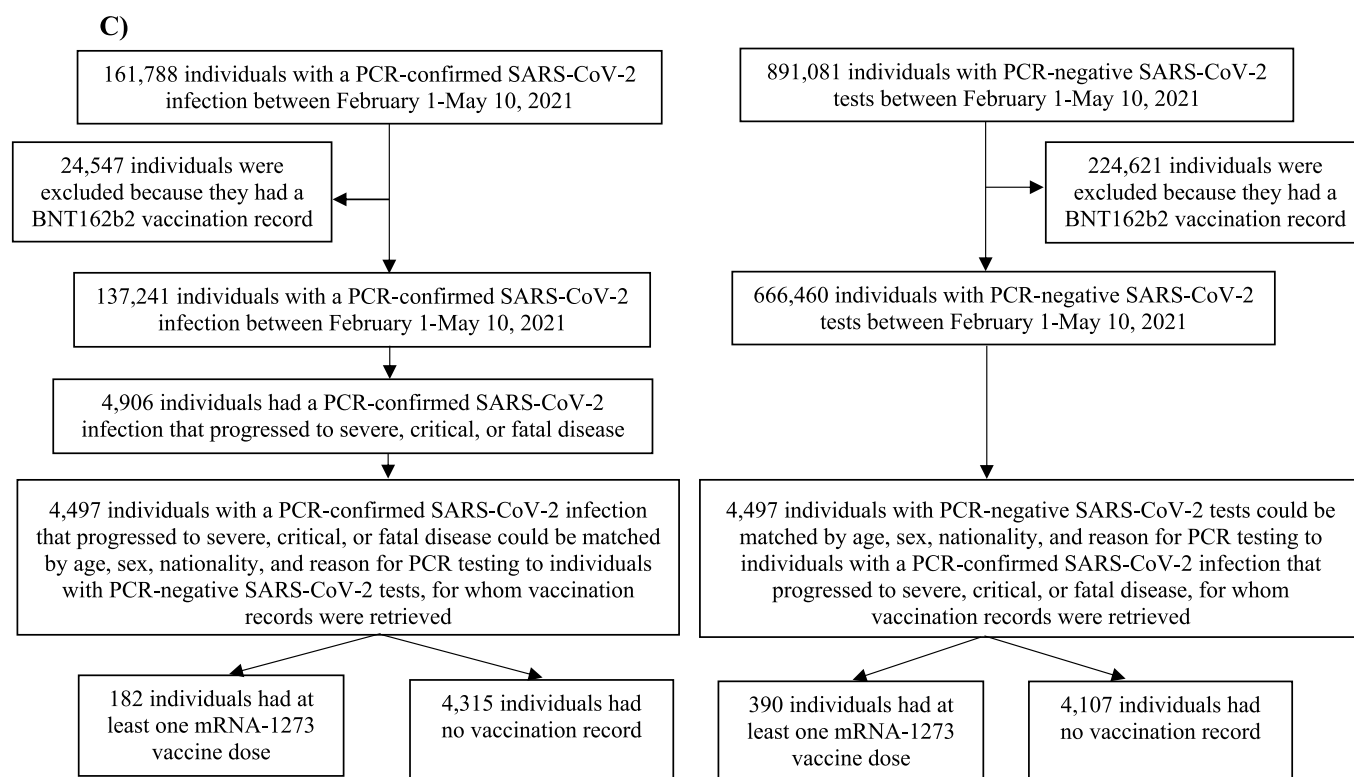


Extended Data Fig. 1 | Flowcharts describing the population selection process to assess vaccine effectiveness against B.1.1.7. Flowcharts describing the population selection process for investigating mRNA-1273 vaccine effectiveness against infection with the B.1.1.7 variant.

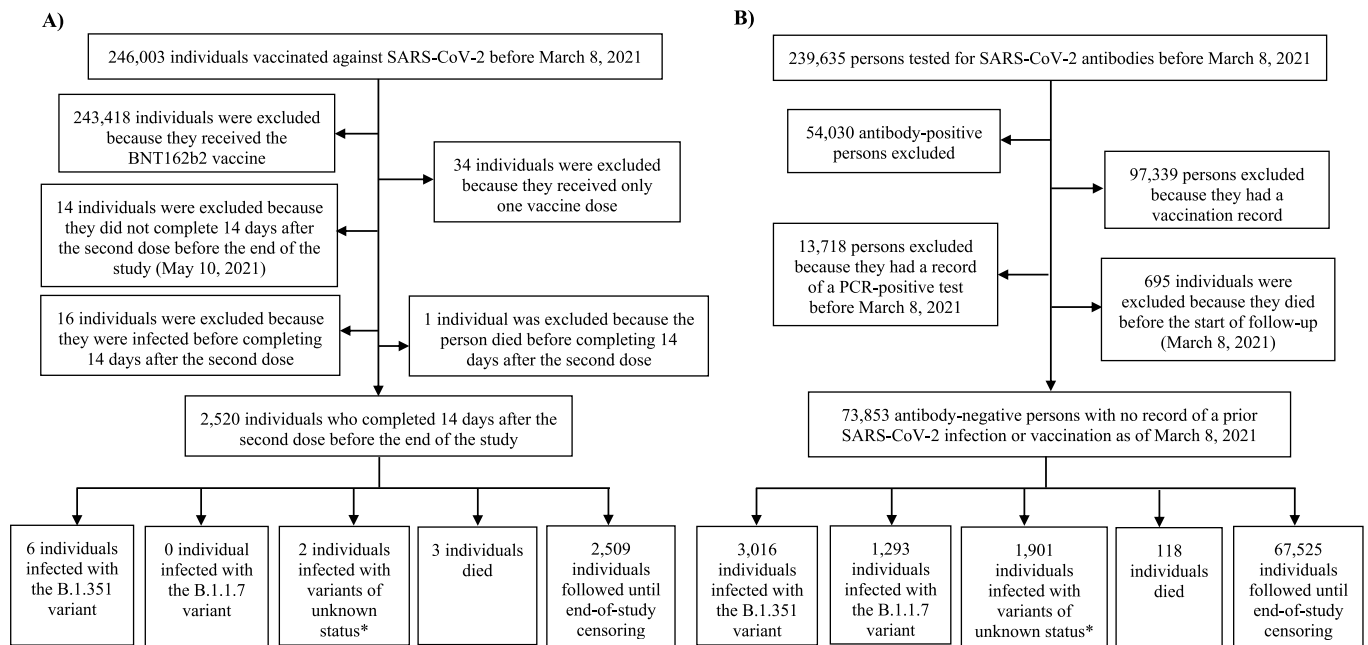
B)



Extended Data Fig. 2 | Flowcharts describing the population selection process to assess vaccine effectiveness against B.1.351. Flowcharts describing the population selection process for investigating mRNA-1273 vaccine effectiveness against infection with the B.1.351 variant.



Extended Data Fig. 3 | Flowcharts describing the population selection process to assess vaccine effectiveness against severe, critical, or fatal COVID-19 disease. Flowcharts describing the population selection process for investigating mRNA-1273 vaccine effectiveness against severe, critical, or fatal COVID-19 disease.



*These are likely B.1.351 cases as the B.1.351 variant dominated incidence during this period of follow-up.

Extended Data Fig. 4 | Occurrence of infection in vaccinated and unvaccinated persons. Occurrence of infection in the national cohort of persons vaccinated with the mRNA-1273 vaccine compared to occurrence of infection in the national cohort of those who were antibody-negative.

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Software and code

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Data collection Data were available to authors through .csv files

Data analysis Analyses were conducted in STATA/SE 16.1. The commands/code are accessible using URL: <https://github.com/IDEGWCMQ/Vaccine-effectiveness-code>

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	COVID-19 laboratory testing, vaccination, and clinical infection data were extracted from the national, federated SARS-CoV-2 databases that captured all SARS-CoV-2-related data since epidemic onset. The data is based on a national cohort that includes every single individual tested using PCR in Qatar. Sample size varied depending on the definition used for Cases (PCR-positive infected with B.1.1.7 variant, or infected with B.1.351 variant, or developing a severe, critical or fatal infection). Cases (PCR-positive infected with B.1.1.7 variant, or infected with B.1.351 variant, or developing a severe, critical or fatal infection) and controls (PCR-negative) were matched one-to-one by sex, age, nationality, and reason for SARS-CoV-2 polymerase chain reaction (PCR) testing. Only matched pairs were included in the analysis. Given that the sample sizes were based on national cohorts with only individuals that do not fit the eligibility criteria excluded, the sample size for each sub-study can be considered sufficient. Detailed sample sizes can be found in Extended Data 1-4.
Data exclusions	Exclusion criteria were specified a priori. For the case control study, these included having a BNT162b2 vaccination record or being tested using PCR outside the study period. For the cohort study, these included having a BNT162b2 vaccination record, being tested using PCR outside the study period, not completing 14 days after the second vaccine dose before the start of the study follow-up, or contracting the infection or dying before the start of the follow-up. Cases (PCR-positive infected with B.1.1.7 variant, or infected with B.1.351 variant, or developing a severe, critical or fatal infection) and controls (PCR-negative) were matched one-to-one by sex, age, nationality, and reason for SARS-CoV-2 PCR testing. Only matched pairs were included in the analysis and individuals not matched were excluded.
Replication	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 results
Randomization	Cases and controls were matched one-to-one by sex, age, nationality, and reason for SARS-CoV-2 polymerase chain reaction (PCR) testing. Additionally, 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 ^{16,30} . To further ensure control for confounding ^{31,32} , 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.
Blinding	Not applicable as this is an observational study and those vaccinated are aware of their vaccination status

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	The demographic characteristics of the different study populations can be found in Table 1 and Supplementary Table 2.
Recruitment	This is a retrospective study where 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.

Cases and controls were defined based on analysis for these data. 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. 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, or an artifact of the estimation method, possibly because the first vaccine dose coincided often with the peak of the B.1.351 wave.

Ethics oversight

The study was approved by the Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards.

Note that full information on the approval of the study protocol must also be provided in the manuscript.