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Effectiveness of two and three doses of COVID-19 mRNA vaccines against infection, symptoms, and severity in the pre-omicron era: A time-dependent gradient

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ABSTRACT

Background: Vaccines were developed and deployed to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study aimed to characterize patterns in the protection provided by the BNT162b2 and mRNA-1273 mRNA vaccines against a spectrum of SARS-CoV-2 infection symptoms and severities.
Methods: A national, matched, test-negative, case-control study was conducted in Qatar between January 1 and December 18, 2021, utilizing a sample of 238,896 PCR-positive tests and 6,533,739 PCR-negative tests. Vaccine effectiveness was estimated against asymptomatic, symptomatic, severe coronavirus disease 2019 (COVID-19), critical COVID-19, and fatal COVID-19 infections. Data sources included Qatar's national databases for COVID-19 laboratory testing, vaccination, hospitalization, and death.
Results: Effectiveness of two-dose BNT162b2 vaccination was 75.6% (95% CI: 73.6–77.5) against asymptomatic infection and 76.5% (95% CI: 75.1–77.9) against symptomatic infection. Effectiveness against each of severe, critical, and fatal COVID-19 infections surpassed 90%. Immediately after the second dose, all categories—namely, asymptomatic, symptomatic, severe, critical, and fatal COVID-19—exhibited similarly high effectiveness. However, from 181 to 270 days post-second dose, effectiveness against asymptomatic and symptomatic infections declined to below 40%, while effectiveness against each of severe, critical, and fatal COVID-19

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infections remained consistently high. However, estimates against fatal COVID-19 often had wide 95% confidence intervals. Analogous patterns were observed in three-dose BNT162b2 vaccination and two- and three-dose mRNA-1273 vaccination. Sensitivity analyses confirmed the results.

Conclusion: A gradient in vaccine effectiveness exists and is linked to the symptoms and severity of infection, providing higher protection against more symptomatic and severe cases. This gradient intensifies over time as vaccine immunity wanes after the last vaccine dose. These patterns appear consistent irrespective of the vaccine type or whether the vaccination involves the primary series or a booster.

1. Introduction

While the immune protection provided by the primary-series of coronavirus disease 2019 (COVID-19) mRNA vaccines is high against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection immediately after the second dose [1,2], this protection wanes over time and may not last beyond one year after the second dose [3–6]. Booster vaccination restores vaccine protection to the levels observed immediately after the second dose [7,8], but this boosted protection also experiences a gradual waning over time [7–11]. Notably, the degree of vaccine protection and the rate of its decline appear to vary based on whether the infection is symptomatic and the severity of the symptoms [3–5].

In December 2020, Qatar initiated its COVID-19 immunization program, deploying the mRNA vaccines BNT162b2 (Pfizer-BioNTech) [12,13] and mRNA-1273 (Moderna) [13,14]. The objective of this study was to estimate and characterize the protection patterns provided by the BNT162b2 and mRNA-1273 vaccines against a spectrum of five SARS-CoV-2 infection symptoms and severities, including asymptomatic infection, symptomatic infection, severe (acute-care hospitalization) COVID-19 [15] infection, critical (intensive-care-unit hospitalization) COVID-19 [15] infection, and fatal COVID-19 [16] infection. The assessment covered both the two-dose primary-series and the third-dose booster vaccination. The study also investigated vaccine effectiveness at 3-month intervals post-vaccination to describe the impact of waning vaccine protection on the effectiveness patterns against these five forms of infection.

2. Methods

2.1. Study population and data sources

This study was conducted on the resident population of Qatar from January 1, 2021, marking the initiation of COVID-19 primary-series vaccination [1,2], until December 18, 2021, immediately preceding the onset of the Omicron wave on December 19, 2021 [17]. Over the course of this study, Qatar encountered two waves of SARS-CoV-2 infection successively dominated by the Alpha [18] and Beta [19] variants, alongside an extended low incidence phase dominated by the Delta [20] variant (Fig. 1 and Supplementary Section S1). Additional information on the viral genome sequencing and variant genotyping throughout the SARS-CoV-2 waves are available in previous publications [2,3,7,20–23] (Supplementary Section S2). Data on COVID-19 laboratory testing, vaccination, hospitalization, and mortality were extracted from the integrated nationwide digital-health information platforms (Supplementary Section S3), capturing all SARS-CoV-2-related data and associated demographic information since the onset of the pandemic.

These national databases provide results of all SARS-CoV-2 polymerase chain reaction (PCR) tests conducted in Qatar, ensuring completeness of information across all locations and facilities (Supplementary Section S3). Until October 31, 2022, SARS-CoV-2 testing was conducted on a large scale, primarily for routine purposes such as screening or travel-related requirements, resulting in the diagnosis of infections predominantly through routine testing rather than symptom manifestation [3,24]. Qatar's population is characterized by a distinctive demographic composition, with only 9% aged 50 years or older, and 89% consisting of expatriates from over 150 countries [25]. Additional details about the study population and national databases have been previously published [3,7,11,24–27].

2.2. Study design

This study estimated and characterized the effectiveness patterns of BNT162b2 and mRNA-1273 vaccination against a spectrum of SARS-CoV-2 infection symptoms and severities: asymptomatic infection, symptomatic infection, severe COVID-19 infection, critical COVID-19 infection, and fatal COVID-19 infection. Vaccine effectiveness was defined as the proportional reduction in susceptibility to infection among the vaccinated compared to the unvaccinated, i.e., the reduction in the likelihood of being infected for those vaccinated compared to those unvaccinated [3,28–30]. Vaccine effectiveness was estimated for the two-dose primary-series vaccination as well as for three-dose (primary series followed by first booster) vaccination.

The study implemented a matched, test-negative, case-control

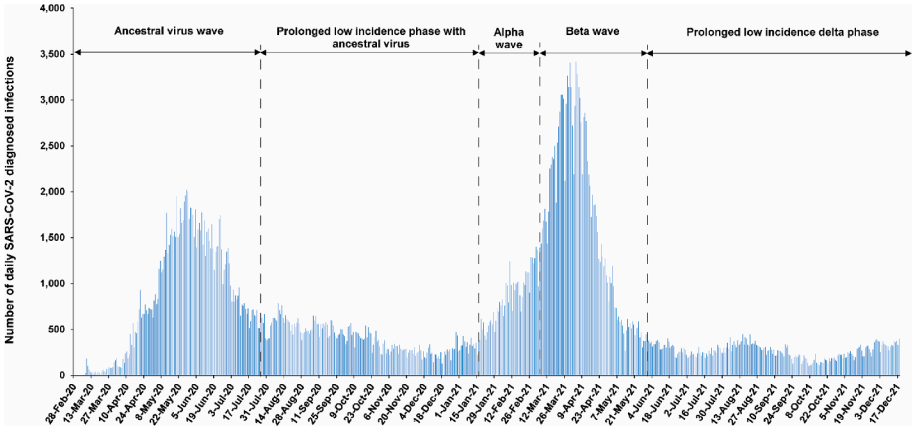

Fig. 1. Daily count of newly diagnosed SARS-CoV-2 infections up to the end of the study, between February 28, 2020 and December 18, 2021. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.

design, a standard design for assessing immune protection of vaccination [3,28,29]. The reference group for comparing effectiveness consisted of PCR-negative tests for individuals with no COVID-19 vaccination since the onset of the pandemic. Effectiveness estimates were derived by comparing the odds of vaccination among cases (PCR-positive tests) with those among controls (PCR-negative tests) [3,28,29].

Only the first PCR-positive test identified during the study period was included in the study, but all PCR-negative tests were included. Tests preceded by a PCR-positive test before the study's test (prior infections) were excluded. A study's test refers to a test conducted within the study duration and thus used in the study's analyses. Tests for individuals who received vaccines other than BNT162b2 or mRNA-1273 or who received mixed vaccines were also excluded from the study.

In the two-dose analysis, the vaccinated group included individuals who had received only the primary-series vaccination before the study's test, while in the third-dose analysis, the vaccinated group included individuals who had received only three vaccine doses before the study's test. Tests conducted within 14 days after the second dose or 7 days after the third dose were excluded from these analyses, respectively.

These inclusion and exclusion criteria were employed to allow for the build-up of immunity post-vaccination [1,7] and to minimize different types of potential biases, as investigated in previous analyses in the same population [3,4,31]. All cases and controls that fulfilled the inclusion criteria and that could be matched were included in the analyses. Therefore, no sample size calculation was necessary.

Cases and controls were exactly matched on a one-to-one ratio for each of the asymptomatic and symptomatic infection analyses, and on a one-to-five ratio for each of the severe, critical, and fatal COVID-19 infection analyses. The latter was implemented to improve the statistical precision of the estimates with the smaller number of cases with severe forms of infection.

Exact matching was done according to sex, 10-year age group, nationality, calendar week of PCR test, number of coexisting conditions (1, 2, 3, 4, 5, or $\geq$6), and reason for PCR testing. The term "coexisting conditions" describes comorbidities determined by ICD-10 codes documented in the electronic health records of each individual (Supplementary Section S4). Exact matching here refers to the pairing of cases and controls based on identical values of the matching factors—the matched pairs shared precisely the same characteristics.

Matching was done to balance observed confounders between exposure groups that are related to risk of infection in Qatar [25,32–35]. Matching by the considered factors was informed by results of prior studies that used matching to control for differences in infection risk in Qatar, including test-negative, case-control studies [2–4,13,36].

All PCR tests conducted in Qatar are classified according to symptoms and the reason for testing including clinical symptoms, contact tracing, surveys, individual requests, routine healthcare testing, pre-travel, port of entry, post-antibody, or other. This categorization allowed us to distinguish tests performed due to asymptomatic or symptomatic infection. Asymptomatic infection was defined as a PCR-positive test conducted as part of a survey; that is with no reported presence of symptoms compatible with a respiratory tract infection. Symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection. Accordingly, in the asymptomatic and symptomatic infection analyses, only PCR tests conducted as part of a survey or because of clinical symptoms, respectively, were included in the analyses. In the analyses of severe, critical, and fatal COVID-19, all reasons for testing were included. For example, an individual testing PCR-positive during routine healthcare testing (or for any other reason) and later developing severe COVID-19 would be included in the analysis.

Classification of severe [15], critical [15], and fatal [16] COVID-19 followed the World Health Organization (WHO) guidelines (Supplementary Section S5). The assessments were made by trained medical personnel independent of study investigators and using individual chart reviews. As part of the national protocol, each individual who had a SARS-CoV-2-positive test and concurrent COVID-19 hospital admission was subject to an infection severity assessment every 3 days until discharge or death, irrespective of hospital length of stay or the time between the SARS-CoV-2-positive test and the final disease outcome. Individuals who progressed to severe, critical, or fatal COVID-19 between the SARS-CoV-2-positive test and the end of this study were classified based on their worst outcome, starting with death, followed by critical disease, and then severe disease.

To assess the impact of waning vaccine protection over time on the patterns of vaccine effectiveness, additional analyses were conducted by examining vaccine effectiveness at 3-month intervals post-vaccination: 14–90 days (for two doses) or 7–90 days (for three doses), 91–180 days, and 181–270 days. These analyses were performed applying the same methods as for the main analysis, but with the study samples restricted to vaccinated cases and controls within these time-interval categories. The analysis for third-dose vaccination could not be conducted for the 91–180 and 181–270 day intervals because no individuals reached these periods within the study duration.

2.3. Statistical analysis

All PCR testing records were reviewed for the selection of cases and controls, but only matched samples were included in the analyses. Cases and controls were described using frequency distributions and measures of central tendency and compared using standardized mean differences (SMDs). An SMD that is $\leq$0.1 indicated adequate balance across groups [37]. The "stddiff" command in STATA was used to calculate the SMDs [38]. The median and interquartile range (IQR) of the duration between vaccination and study PCR test were calculated for cases and controls in each analysis.

Conditional logistic regression was used to derive the odds ratios (ORs) and associated 95% confidence intervals (CIs). The OR compared the odds of vaccination among cases with that among controls. The study analytical approach, which involved matching by calendar week of PCR testing, was implemented to reduce potential bias due to variation in the epidemic phase and gradual vaccination rollout during the study period [28,39], besides other confounders [40]. CIs did not factor multiplicity and interactions were not examined.

Based on the test-negative design methodology, effectiveness and 95% CIs were estimated as 1 - OR of vaccination among cases versus controls if the OR was $\leq$1 [28], and as (1/OR) − 1 if the OR was >1 [11,41]. The latter convention was implemented to guarantee a symmetric scale for both negative and positive effectiveness, ranging from −100% to 100% [11,41].

When conditional logistic regression failed to converge because of zero events among exposed cases, the 95% CI was obtained using McNemar's test. When McNemar's test and 1:n matching were employed, the number of pairs was considered as 'n', with this approach providing only an approximate estimate of the 95% CI in these specific situations, following an approach that was applied in an earlier study [42].

Five sensitivity and supplementary analyses were conducted to explore the impacts of alterations in study inclusion and exclusion criteria, changes in study matching, and to present additional pertinent results. The first analysis involved adjusting the inclusion and exclusion criteria to include cases and controls with a prior SARS-CoV-2 infection. In the second analysis, the inclusion and exclusion criteria were modified to include cases and controls with a prior SARS-CoV-2 infection, and matching was additionally performed based on prior SARS-CoV-2 infection status. The third analysis involved matching by exact age instead of the original design of matching by 10-year age groups. For the fourth analysis, matching was based on exact coexisting condition status rather than the original design of matching by the number of coexisting conditions. Finally, vaccine effectiveness was evaluated for any mRNA vaccination, as opposed to assessing effectiveness separately for each of the BNT162b2 or mRNA-1273 vaccines.

Table 1
Characteristics of cases and controls in the BNT162b2 vaccine analyses.

Characteristics	Two-dose analyses						Three-dose analyses					
	Unmatched sample			Matched sample			Unmatched sample			Matched sample		
	Cases* N = 218,153	Controls* N = 4,935,088	SMD‡	Cases*† N = 200,481	Controls*† N = 200,481	SMD‡	Cases* N = 202,882	Controls* N = 3,538,642	SMD‡	Cases*† N = 184,243	Controls*† N = 184,243	SMD‡
Median age (IQR) - years	32 (24–40)	32 (24–41)	0.03§	32 (24–39)	32 (24–39)	0.00§	32 (24–39)	30 (21–38)	0.08§	31 (23–38)	31 (23–38)	0.00§
Age group - n (%)												
0–9 years	21,254 (9.7)	496,397 (10.1)	0.10	19,474 (9.7)	19,474 (9.7)	0.00	21,254 (10.5)	496,392 (14.0)	0.15	19,470 (10.6)	19,470 (10.6)	0.00
10–19 years	19,557 (9.0)	419,171 (8.5)		17,740 (8.8)	17,740 (8.8)		18,507 (9.1)	301,623 (8.5)		16,630 (9.0)	16,630 (9.0)	
20–29 years	47,613 (21.8)	1,118,903 (22.7)		45,934 (22.9)	45,934 (22.9)		45,369 (22.4)	861,642 (24.3)		43,609 (23.7)	43,609 (23.7)	
30–39 years	73,814 (33.8)	1,547,470 (31.4)		70,449 (35.1)	70,449 (35.1)		68,791 (33.9)	1,082,576 (30.6)		64,997 (35.3)	64,997 (35.3)	
40–49 years	38,258 (17.5)	824,613 (16.7)		33,984 (17.0)	33,984 (17.0)		34,590 (17.0)	517,024 (14.6)		29,915 (16.2)	29,915 (16.2)	
50–59 years	12,989 (6.0)	373,131 (7.6)		10,132 (5.1)	10,132 (5.1)		11,089 (5.5)	201,321 (5.7)		8,094 (4.4)	8,094 (4.4)	
60–69 years	3,521 (1.6)	122,997 (2.5)		2,221 (1.1)	2,221 (1.1)		2,499 (1.2)	61,266 (1.7)		1,268 (0.7)	1,268 (0.7)	
70 + years	1,147 (0.5)	32,406 (0.7)		547 (0.3)	547 (0.3)		783 (0.4)	16,798 (0.5)		260 (0.1)	260 (0.1)	
Sex												
Male	147,678 (67.7)	3,472,974 (70.4)	0.06	136,958 (68.3)	136,958 (68.3)	0.00	138,854 (68.4)	2,533,329 (71.6)	0.07	127,466 (69.2)	127,466 (69.2)	0.00
Female	70,475 (32.3)	1,462,114 (29.6)		63,523 (31.7)	63,523 (31.7)		64,028 (31.6)	1,005,313 (28.4)		56,777 (30.8)	56,777 (30.8)	
Nationality‖												
Bangladeshi	15,156 (6.9)	243,575 (4.9)	0.28	14,075 (7.0)	14,075 (7.0)	0.00	14,748 (7.3)	176,697 (5.0)	0.27	13,597 (7.4)	13,597 (7.4)	0.00
Egyptian	12,443 (5.7)	245,415 (5.0)		11,524 (5.7)	11,524 (5.7)		11,019 (5.4)	172,001 (4.9)		9,967 (5.4)	9,967 (5.4)	
Filipino	23,467 (10.8)	276,075 (5.6)		22,428 (11.2)	22,428 (11.2)		22,563 (11.1)	213,632 (6.0)		21,133 (11.5)	21,133 (11.5)	
Indian	58,924 (27.0)	1,427,122 (28.9)		57,108 (28.5)	57,108 (28.5)		56,495 (27.8)	1,141,915 (32.3)		54,233 (29.4)	54,233 (29.4)	
Nepalese	18,066 (8.3)	325,692 (6.6)		16,694 (8.3)	16,694 (8.3)		17,839 (8.8)	275,551 (7.8)		16,426 (8.9)	16,426 (8.9)	
Pakistani	10,684 (4.9)	241,719 (4.9)		9,752 (4.9)	9,752 (4.9)		10,155 (5.0)	199,073 (5.6)		9,184 (5.0)	9,184 (5.0)	
Qatari	26,244 (12.0)	808,445 (16.4)		25,815 (12.9)	25,815 (12.9)		21,459 (10.6)	373,880 (10.6)		20,831 (11.3)	20,831 (11.3)	
Sri Lankan	6,860 (3.1)	99,371 (2.0)		6,106 (3.0)	6,106 (3.0)		6,683 (3.3)	71,206 (2.0)		5,887 (3.2)	5,887 (3.2)	
Sudanese	5,647 (2.6)	96,897 (2.0)		4,957 (2.5)	4,957 (2.5)		5,201 (2.6)	69,065 (2.0)		4,508 (2.4)	4,508 (2.4)	
Other nationalities¶	40,662 (18.6)	1,170,777 (23.7)		32,022 (16.0)	32,022 (16.0)		36,720 (18.1)	845,622 (23.9)		28,477 (15.5)	28,477 (15.5)	
Coexisting conditions												
None	176,053 (80.7)	4,112,793 (83.3)	0.08	167,859 (83.7)	167,859 (83.7)	0.00	166,671 (82.2)	3,105,100 (87.7)	0.16	157,615 (85.5)	157,615 (85.5)	0.00
1	24,570 (11.3)	464,077 (9.4)		20,725 (10.3)	20,725 (10.3)		22,070 (10.9)	277,885 (7.9)		18,014 (9.8)	18,014 (9.8)	
2	9,797 (4.5)	181,571 (3.7)		7,241 (3.6)	7,241 (3.6)		8,412 (4.1)	89,261 (2.5)		5,785 (3.1)	5,785 (3.1)	
3	3,665 (1.7)	79,280 (1.6)		2,346 (1.2)	2,346 (1.2)		2,922 (1.4)	31,810 (0.9)		1,570 (0.9)	1,570 (0.9)	
4	1,907 (0.9)	44,826 (0.9)		1,079 (0.5)	1,079 (0.5)		1,389 (0.7)	16,108 (0.5)		635 (0.3)	635 (0.3)	
5	1,105 (0.5)	25,773 (0.5)		578 (0.3)	578 (0.3)		770 (0.4)	9,019 (0.3)		295 (0.2)	295 (0.2)	
6+	1,056 (0.5)	26,768 (0.5)		653 (0.3)	653 (0.3)		648 (0.3)	9,459 (0.3)		329 (0.2)	329 (0.2)	
Reason for PCR testing												
Clinical suspicion**	64,976 (29.8)	282,084 (5.7)	1.10	55,304 (27.6)	55,304 (27.6)	0.00	60,266 (29.7)	196,616 (5.6)	1.08	49,743 (27.0)	49,743 (27.0)	0.00
Contact tracing	26,159 (12.0)	157,789 (3.2)		23,277 (11.6)	23,277 (11.6)		24,927 (12.3)	140,264 (4.0)		22,105 (12.0)	22,105 (12.0)	
Port of entry	46,469 (21.3)	2,140,889 (43.4)		45,879 (22.9)	45,879 (22.9)		43,677 (21.5)	1,769,278 (50.0)		43,095 (23.4)	43,095 (23.4)	
Individual request	15,759 (7.2)	245,712 (5.0)		14,901 (7.4)	14,901 (7.4)		14,723 (7.3)	172,968 (4.9)		13,841 (7.5)	13,841 (7.5)	
Survey††	36,470 (16.7)	735,965 (14.9)		34,618 (17.3)	34,618 (17.3)		33,753 (16.6)	519,072 (14.7)		31,841 (17.3)	31,841 (17.3)	
Healthcare routine testing	18,806 (8.6)	158,803 (3.2)		17,800 (8.9)	17,800 (8.9)		18,415 (9.1)	120,685 (3.4)		17,297 (9.4)	17,297 (9.4)	
Pre-travel	8,812 (4.0)	1,200,358 (24.3)		8,425 (4.2)	8,425 (4.2)		6,466 (3.2)	611,262 (17.3)		6,089 (3.3)	6,089 (3.3)	
Post-antibody	8 (0.0)	599 (0.0)		–	–		1 (0.0)	316 (0.0)		–	–	
Other	694 (0.3)	12,889 (0.3)		277 (0.1)	277 (0.1)		654 (0.3)	8,181 (0.2)		232 (0.1)	232 (0.1)	

IQR denotes interquartile range, PCR polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and SMD standardized mean difference.

* Cases represent PCR-positive SARS-CoV-2 tests, while controls represent PCR-negative SARS-CoV-2 tests.

† Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡ SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD $\leq$ 0.1 indicates adequate matching.

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

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

¶ These comprise up to 183 other nationalities in Qatar among cases and controls in the unmatched two-dose and three-dose analyses, 125 other nationalities in the matched analysis with two doses, and 122 other nationalities in the matched analysis with three doses.

** The tests used to define symptomatic infection.

†† The tests used to define asymptomatic infection.

Statistical analyses were conducted with the use of STATA/SE software version 18.0 (Stata Corporation, College Station, TX, USA).

2.4. Ethical approval and oversight

This retrospective study was approved by the institutional review boards at Hamad Medical Corporation and Weill Cornell Medicine-Qatar, with a waiver of informed consent. The reporting of this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary Table S1).

3. Results

3.1. Study population

Between December 23, 2020 (date of first vaccination in Qatar) [42] and December 18, 2021 (end of study), 1,286,978 individuals received a minimum of two doses of BNT162b2, with 152,324 among them receiving a third/booster dose. The median dates for the first, second, and third doses were May 2, 2021, May 23, 2021, and November 25, 2021, respectively. The median time between the first and second doses was 21 days (IQR, 21–22 days). The median time between the second and third doses was 247 days (IQR, 238–258 days).

During the same timeframe, 888,043 individuals received a minimum of two doses of mRNA-1273, with 26,606 among them receiving a third/booster dose. The median dates for the first, second, and third doses were May 27, 2021, June 27, 2021, and December 6, 2021, respectively. The median time between the first and second doses was 28 days (IQR, 28–30 days). The median time between the second and third doses was 216 days (IQR, 207–225).

This study was carried out on Qatar's entire population, and therefore, the study population is representative of the internationally diverse, but predominantly young and male demographic of the country.

3.2. BNT162b2 effectiveness

Supplementary Figure S1 shows the study population selection process for the BNT162b2 analyses. Characteristics of the unmatched and matched samples in both the two-dose and three-dose analyses are presented in Table 1.

The effectiveness of two-dose BNT162b2 vaccination against asymptomatic and symptomatic infections was 75.6% (95% CI: 73.6–77.5) and 76.5% (95% CI: 75.1–77.9), respectively (Table 2 and Fig. 2A). The median time between the second dose and PCR test was 69 days (IQR, 32–159 days) for asymptomatic infection and 71 days (IQR, 33–157 days) for symptomatic infection. Vaccination against each of severe, critical, and fatal COVID-19 infections all showed very high effectiveness at 90% or higher (Table 2 and Fig. 2A).

The effectiveness of three-dose BNT162b2 vaccination against asymptomatic and symptomatic infections was 77.8% (95% CI: 55.9–88.8) and 82.9% (95% CI: 69.2–90.5), respectively (Table 2 and Fig. 2B). The median time between the third dose and PCR test was 18 days (IQR, 10–38 days) for asymptomatic infection and 26 days (IQR, 15–43 days) for symptomatic infection. Vaccination against each of severe, critical, and fatal COVID-19 infections all showed 100% effectiveness as no cases of severe disease were observed among those vaccinated (Table 2 and Fig. 2B). However, the majority of the 95% CIs lacked adequate statistical precision with the small number of cases.

The analyses aiming at assessing the impact of waning vaccine protection over time on the BNT162b2 vaccine effectiveness patterns indicated a widening gradient with time after the second dose (Table 3). Initially, the differences in protection were small immediately following the second dose, with effectiveness against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections all suggesting largely similar levels of effectiveness.

However, the gradient between asymptomatic and symptomatic infections (non-severe outcomes) on one side and severe, critical, and fatal COVID-19 infections (severe outcomes) on the other side substantially increased over time after the second dose (Table 3). Between 181 and 270 days post-second dose, effectiveness against asymptomatic and symptomatic infections dropped below 40%, while effectiveness against severe, critical, or fatal COVID-19 infections largely remained at their very high values observed right after the second dose. Supplementary Table S2 provides the analysis for BNT162b2 effectiveness at 7–90 days after the third dose.

3.3. mRNA-1273 effectiveness

Supplementary Figure S2 shows the study population selection process for the mRNA-1273 analyses. Characteristics of the unmatched and matched samples in both the two-dose and three-dose analyses are presented in Table 4.

The effectiveness of two-dose mRNA-1273 vaccination against asymptomatic and symptomatic infections was 69.6% (95% CI: 64.2–74.1) and 75.2% (95% CI: 71.3–78.6), respectively (Table 2 and Fig. 2C). The median time between the second dose and PCR test was 91 days (IQR, 37–152 days) for asymptomatic infection and 100 days (IQR, 42–162 days) for symptomatic infection. Vaccination against each of severe, critical, and fatal COVID-19 infections all showed very high effectiveness at 99% or higher (Table 2 and Fig. 2C). However, some of the 95% CIs lacked adequate statistical precision with the small number of cases.

The effectiveness of a three-dose mRNA-1273 vaccination exhibited comparable patterns to both two-dose mRNA-1273 and three-dose BNT162b2 vaccinations (Table 2 and Fig. 2D). However, all effectiveness measures lacked sufficient statistical precision due to the limited number of individuals who received a third mRNA-1273 dose within the study duration.

The analyses aimed at evaluating the impact of waning vaccine protection over time on the mRNA-1273 vaccine effectiveness patterns yielded results akin to those observed with the BNT162b2 vaccine (Table 3). The results indicated an expanding gradient between non-severe and severe outcomes with time after the second vaccine dose. Supplementary Table S2 provides the analysis for mRNA-1273 effectiveness at 7–90 days after the third dose.

3.4. Sensitivity and supplementary analyses

The four sensitivity analyses, conducted to examine the effects of modifications in study inclusion and exclusion criteria, as well as changes in study matching, consistently demonstrated results similar to the main analysis (Supplementary Table S3-S6). This indicates that these alterations to the study methodology had no discernible impact on the study results.

The analysis for vaccine effectiveness of any mRNA vaccination, irrespective of whether it is BNT162b2 or mRNA-1273, also showed results similar to those observed in the main analysis for each of the BNT162b2 and mRNA-1273 vaccines individually (Supplementary Table S7).

4. Discussion

The study's results indicate two patterns for COVID-19 vaccine effectiveness. Firstly, a gradient in effectiveness is observed based on the symptoms and severity of infection, with higher protection corresponding to more symptomatic and severe infections. Secondly, this gradient in vaccine protection becomes more pronounced over time after the last dose as vaccine immunity wanes. While protection against asymptomatic or symptomatic infections diminishes within months after vaccination, protection against severe forms of infection declines at a slower rate, remaining robust. These patterns appear consistent regardless of the vaccine type (BNT162b2 or mRNA-1273) or whether

Table 2
Effectiveness of BNT162b2 and mRNA-1273 vaccines against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections.

Analyses	BNT162b2 vaccine effectiveness				Effectiveness % (95 % CI)*	mRNA-1273 vaccine effectiveness				Effectiveness % (95 % CI)*
	Cases (PCR-positive tests)		Controls (PCR-negative tests)			Cases (PCR-positive tests)		Controls (PCR-negative tests)		
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Two-dose analysis										
Asymptomatic infection†‡	2,439	32,179	4,808	29,810	75.6 (73.6 to 77.5)	452	31,855	889	31,418	69.6 (64.2 to 74.1)
Symptomatic infection†§	3,946	51,358	8,310	46,994	76.5 (75.1 to 77.9)	466	49,817	1,145	49,138	75.2 (71.3 to 78.6)
Severe COVID-19 infection‖	94	4,142	2,964	15,031	96.9 (95.7 to 97.7)	3	3,936	411	16,157	98.9 (95.6 to 99.7)
Critical COVID-19 infection‖	10	505	416	1,542	97.0 (93.0 to 98.7)	0	468	30	1,705	100.0 (86.9 to 100.0)¶
Fatal COVID-19 infection‖	13	210	248	615	90.3 (81.1 to 95.0)	0	189	5	682	100.0 (-8.4 to 100.0)¶
Three-dose analysis										
Asymptomatic infection†‡	20	31,821	55	31,786	77.8 (55.9 to 88.8)	1	31,799	3	31,797	66.7 (-68.8 to 96.5)
Symptomatic infection†§	24	49,719	87	49,656	82.9 (69.2 to 90.5)	0	49,685	4	49,681	100.0 (-34.0 to 100.0)¶
Severe COVID-19 infection‖	0	3,914	53	16,378	100.0 (92.8 to 100.0)¶	0	3,906	5	16,390	100.0 (-8.4 to 100.0)¶
Critical COVID-19 infection‖	0	465	1	1,724	100.0 (-97.4 to 100.0)¶	0	465	0	1,725	Omitted**
Fatal COVID-19 infection‖	0	189	3	683	100.0 (-58.7 to 100.0)¶	0	188	0	684	Omitted**

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

* Effectiveness was estimated with the use of a test-negative, case-control study design.

† Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡ 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, PCR testing done as part of a survey.

§ A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖ Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶ The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

** Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

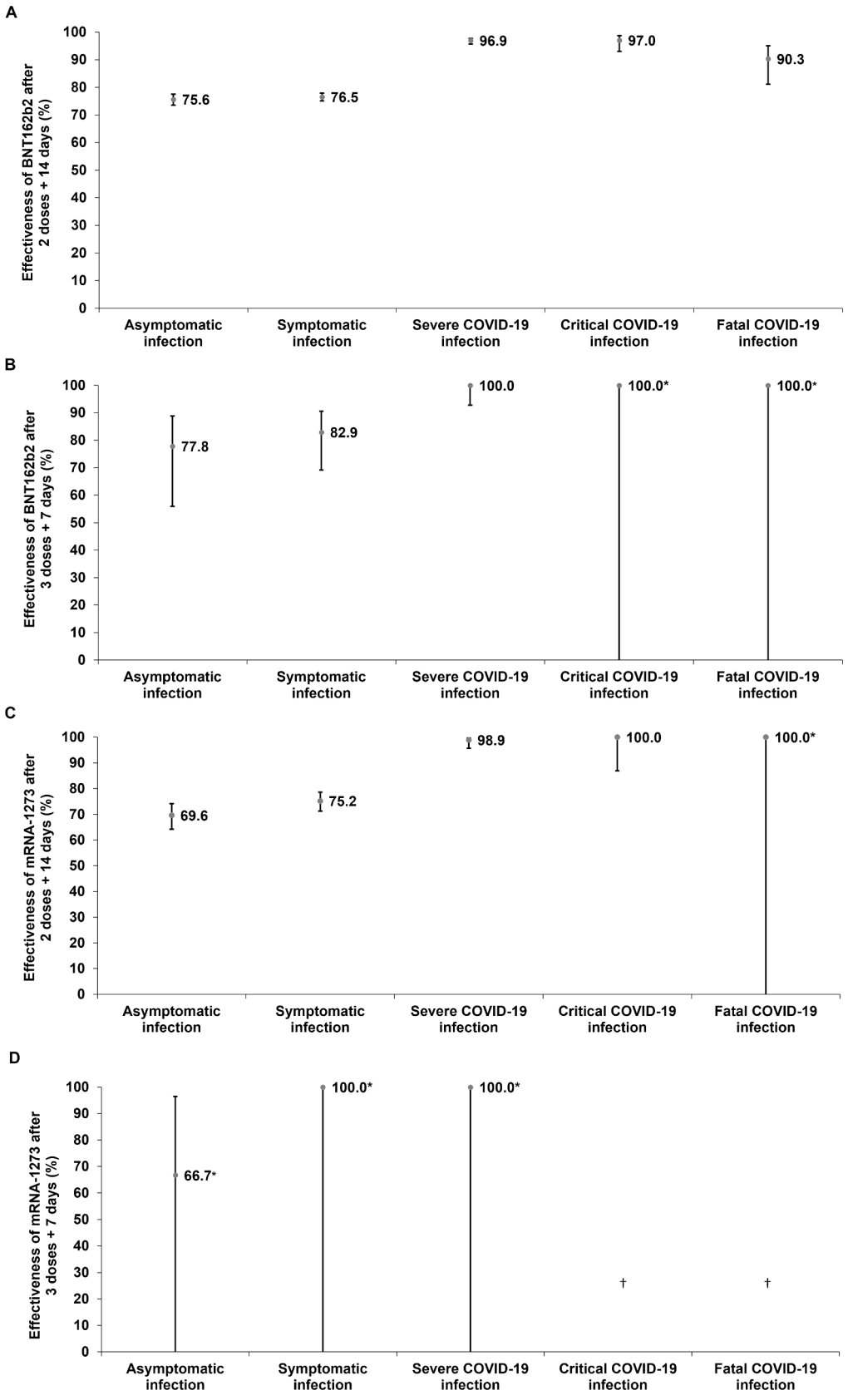

Fig. 2. Effectiveness of A) two-dose primary-series and B) third-dose booster BNT162b2 vaccination and C) two-dose primary-series and D) third-dose booster mRNA-1273 vaccination against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections. Data are presented as effectiveness point estimates. Error bars indicate the corresponding 95% confidence intervals. COVID-19 denotes coronavirus disease 2019. *The negative lower bound for the confidence interval was truncated because the confidence interval was too wide. †Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

Table 3
Effectiveness of the BNT162b2 and mRNA-1273 vaccines against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections at 3-month intervals after the second vaccine dose: A) 14–90 days, B) 91–180 days, and C) 181–270 days.

Analyses	BNT162b2 vaccine effectiveness				Effectiveness % (95 % CI)*	mRNA-1273 vaccine effectiveness				Effectiveness % (95 % CI)*
	Cases (PCR-positive tests)		Controls (PCR-negative tests)			Cases (PCR-positive tests)		Controls (PCR-negative tests)		
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
A) 14–90 days after second dose										
Asymptomatic infection†‡	1,029	32,116	3,243	29,902	81.1 (79.3 to 82.8)	162	31,846	492	31,516	76.4 (70.7 to 81.0)
Symptomatic infection†§	1,522	51,164	5,527	47,159	81.6 (80.3 to 82.9)	114	49,780	630	49,264	85.7 (82.1 to 88.6)
Severe COVID-19 infection‖	24	4,088	2,338	15,142	98.5 (97.5 to 99.1)	0	3,926	237	16,242	100.0 (98.4 to 100.0)¶
Critical COVID-19 infection‖	6	501	358	1,549	97.5 (93.2 to 99.1)	0	467	22	1,707	100.0 (81.7 to 100.0)¶
Fatal COVID-19 infection‖	8	207	215	616	94.5 (86.3 to 97.8)	0	188	5	681	100.0 (-8.4 to 100.0)¶
B) 91–180 days after second dose										
Asymptomatic infection†‡	749	31,870	1,071	31,548	53.5 (46.4 to 59.6)	168	31,834	257	31,745	53.0 (38.6 to 64.0)
Symptomatic infection†§	1,249	49,878	1,809	49,318	54.5 (49.2 to 59.2)	185	49,736	340	49,581	59.4 (49.1 to 67.6)
Severe COVID-19 infection‖	25	3,957	456	16,221	94.2 (89.8 to 96.8)	3	3,916	131	16,324	96.4 (85.0 to 99.1)
Critical COVID-19 infection‖	3	471	60	1,707	93.2 (69.8 to 98.5)	0	466	6	1,723	100.0 (15.1 to 100.0)¶
Fatal COVID-19 infection‖	3	189	10	688	18.1 (-74.5 to 82.9)	0	189	1	683	100.0 (-97.4 to 100.0)¶
C) 181–270 days after second dose										
Asymptomatic infection†‡	544	31,849	605	31,788	26.4 (10.3 to 39.6)	107	31,817	120	31,804	17.3 (-13.6 to 40.9)
Symptomatic infection†§	961	49,816	1,139	49,638	36.6 (26.8 to 45.0)	144	49,719	182	49,681	33.3 (10.9 to 50.1)
Severe COVID-19 infection‖	38	3,939	345	16,328	90.5 (83.5 to 94.5)	0	3,911	60	16,356	100.0 (93.7 to 100.0)¶
Critical COVID-19 infection‖	1	467	17	1,720	89.1 (2.7 to 98.8)	0	465	1	1,722	100.0 (-97.4 to 100.0)¶
Fatal COVID-19 infection‖	2	190	12	686	67.4 (-52.8 to 95.0)	0	188	0	683	Omitted**

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

* Effectiveness was estimated with the use of a test-negative, case-control study design.

† Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡ 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, PCR testing done as part of a survey.

§ A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖ Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶ The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

** Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

Table 4
Characteristics of cases and controls in the mRNA-1273 vaccine analyses.

Characteristics	Two-dose analyses						Three-dose analyses					
	Unmatched sample			Matched sample			Unmatched sample			Matched sample		
	Cases*	Controls*	SMD‡	Cases*†	Controls*†	SMD‡	Cases*	Controls*	SMD‡	Cases*†	Controls*†	SMD‡
	N = 205,702	N = 4,052,275		N = 186,912	N = 186,912		N = 202,739	N = 3,501,428		N = 184,052	N = 184,052	
Median age (IQR) - years	32 (24–39)	31 (23–39)	0.03§	31 (24–38)	31 (24–38)	0.00§	32 (24–39)	30 (21–38)	0.09§	31 (23–38)	31 (23–38)	0.00§
Age group - n (%)												
0–9 years	21,254 (10.3)	496,394 (12.2)	0.10	19,465 (10.4)	19,465 (10.4)	0.00	21,254 (10.5)	496,392 (14.2)	0.15	19,470 (10.6)	19,470 (10.6)	0.00
10–19 years	18,557 (9.0)	307,229 (7.6)		16,680 (8.9)	16,680 (8.9)		18,504 (9.1)	301,263 (8.6)		16,626 (9.0)	16,626 (9.0)	
20–29 years	45,946 (22.3)	978,894 (24.2)		44,162 (23.6)	44,162 (23.6)		45,359 (22.4)	859,225 (24.5)		43,592 (23.7)	43,592 (23.7)	
30–39 years	70,034 (34.0)	1,311,610 (32.4)		66,199 (35.4)	66,199 (35.4)		68,754 (33.9)	1,073,964 (30.7)		64,944 (35.3)	64,944 (35.3)	
40–49 years	35,301 (17.2)	642,691 (15.9)		30,600 (16.4)	30,600 (16.4)		34,557 (17.0)	508,770 (14.5)		29,865 (16.2)	29,865 (16.2)	
50–59 years	11,287 (5.5)	236,428 (5.8)		8,271 (4.4)	8,271 (4.4)		11,056 (5.5)	192,010 (5.5)		8,061 (4.4)	8,061 (4.4)	
60–69 years	2,539 (1.2)	62,663 (1.5)		1,274 (0.7)	1,274 (0.7)		2,484 (1.2)	54,931 (1.6)		1,243 (0.7)	1,243 (0.7)	
70 + years	784 (0.4)	16,366 (0.4)		261 (0.1)	261 (0.1)		771 (0.4)	14,873 (0.4)		251 (0.1)	251 (0.1)	
Sex												
Male	140,462 (68.3)	2,932,341 (72.4)	0.09	129,000 (69.0)	129,000 (69.0)	0.00	138,767 (68.4)	2,509,603 (71.7)	0.07	127,351 (69.2)	127,351 (69.2)	0.00
Female	65,240 (31.7)	1,119,934 (27.6)		57,912 (31.0)	57,912 (31.0)		63,972 (31.6)	991,825 (28.3)		56,701 (30.8)	56,701 (30.8)	
Nationality‖												
Bangladeshi	14,939 (7.3)	242,392 (6.0)	0.25	13,793 (7.4)	13,793 (7.4)	0.00	14,747 (7.3)	176,338 (5.0)	0.27	13,596 (7.4)	13,596 (7.4)	0.00
Egyptian	11,306 (5.5)	196,218 (4.8)		10,233 (5.5)	10,233 (5.5)		11,012 (5.4)	170,572 (4.9)		9,954 (5.4)	9,954 (5.4)	
Filipino	22,845 (11.1)	239,737 (5.9)		21,443 (11.5)	21,443 (11.5)		22,553 (11.1)	210,207 (6.0)		21,121 (11.5)	21,121 (11.5)	
Indian	57,202 (27.8)	1,317,033 (32.5)		54,937 (29.4)	54,937 (29.4)		56,476 (27.9)	1,134,874 (32.4)		54,198 (29.4)	54,198 (29.4)	
Nepalese	17,957 (8.7)	329,901 (8.1)		16,551 (8.9)	16,551 (8.9)		17,837 (8.8)	275,421 (7.9)		16,421 (8.9)	16,421 (8.9)	
Pakistani	10,297 (5.0)	224,071 (5.5)		9,313 (5.0)	9,313 (5.0)		10,149 (5.0)	198,200 (5.7)		9,186 (5.0)	9,186 (5.0)	
Qatari	21,666 (10.5)	394,304 (9.7)		21,025 (11.2)	21,025 (11.2)		21,414 (10.6)	362,792 (10.4)		20,761 (11.3)	20,761 (11.3)	
Sri Lankan	6,767 (3.3)	93,826 (2.3)		5,987 (3.2)	5,987 (3.2)		6,680 (3.3)	70,844 (2.0)		5,884 (3.2)	5,884 (3.2)	
Sudanese	5,295 (2.6)	79,370 (2.0)		4,588 (2.5)	4,588 (2.5)		5,200 (2.6)	68,422 (2.0)		4,503 (2.4)	4,503 (2.4)	
Other nationalities¶	37,428 (18.2)	935,423 (23.1)		29,042 (15.5)	29,042 (15.5)		36,671 (18.1)	833,758 (23.8)		28,428 (15.4)	28,428 (15.4)	
Coexisting conditions												
None	168,884 (82.1)	3,564,874 (88.0)	0.17	159,793 (85.5)	159,793 (85.5)	0.00	166,604 (82.2)	3,085,370 (88.1)	0.17	157,514 (85.6)	157,514 (85.6)	0.00
1	22,403 (10.9)	311,245 (7.7)		18,315 (9.8)	18,315 (9.8)		22,050 (10.9)	272,138 (7.8)		17,972 (9.8)	17,972 (9.8)	
2	8,561 (4.2)	103,010 (2.5)		5,913 (3.2)	5,913 (3.2)		8,390 (4.1)	85,173 (2.4)		5,759 (3.1)	5,759 (3.1)	
3	2,973 (1.4)	36,521 (0.9)		1,599 (0.9)	1,599 (0.9)		2,912 (1.4)	29,076 (0.8)		1,562 (0.8)	1,562 (0.8)	
4	1,429 (0.7)	17,805 (0.4)		650 (0.3)	650 (0.3)		1,384 (0.7)	14,133 (0.4)		630 (0.3)	630 (0.3)	
5	787 (0.4)	9,473 (0.2)		307 (0.2)	307 (0.2)		762 (0.4)	7,615 (0.2)		294 (0.2)	294 (0.2)	
6+	665 (0.3)	9,347 (0.2)		335 (0.2)	335 (0.2)		637 (0.3)	7,923 (0.2)		321 (0.2)	321 (0.2)	
Reason for PCR testing												
Clinical suspicion**	60,837 (29.6)	222,485 (5.5)	1.10	50,283 (26.9)	50,283 (26.9)	0.00	60,231 (29.7)	194,530 (5.6)	1.07	49,685 (27.0)	49,685 (27.0)	0.00
Contact tracing	25,109 (12.2)	143,983 (3.6)		22,267 (11.9)	22,267 (11.9)		24,915 (12.3)	139,782 (4.0)		22,081 (12.0)	22,081 (12.0)	
Port of entry	44,433 (21.6)	1,901,633 (46.9)		43,828 (23.4)	43,828 (23.4)		43,650 (21.5)	1,762,224 (50.3)		43,074 (23.4)	43,074 (23.4)	
Individual request	14,883 (7.2)	206,864 (5.1)		13,984 (7.5)	13,984 (7.5)		14,718 (7.3)	172,043 (4.9)		13,836 (7.5)	13,836 (7.5)	
Survey††	34,265 (16.7)	590,420 (14.6)		32,307 (17.3)	32,307 (17.3)		33,727 (16.6)	515,573 (14.7)		31,800 (17.3)	31,800 (17.3)	
Healthcare routine testing	18,452 (9.0)	128,547 (3.2)		17,328 (9.3)	17,328 (9.3)		18,414 (9.1)	120,075 (3.4)		17,294 (9.4)	17,294 (9.4)	

(*continued on next page*)

Table 4 (*continued*)

Characteristics	Two-dose analyses						Three-dose analyses					
	Unmatched sample			Matched sample			Unmatched sample			Matched sample		
	Cases*	Controls*	SMD‡	Cases*†	Controls*†	SMD‡	Cases*	Controls*	SMD‡	Cases*†	Controls*†	SMD‡
	N = 205,702	N = 4,052,275		N = 186,912	N = 186,912		N = 202,739	N = 3,501,428		N = 184,052	N = 184,052	
Pre-travel	7,066 (3.4)	848,875 (20.9)		6,680 (3.6)	6,680 (3.6)		6,429 (3.2)	588,805 (16.8)		6,050 (3.3)	6,050 (3.3)	
Post-antibody	2 (0.0)	322 (0.0)		–	–		1 (0.0)	280 (0.0)		–	–	
Other	655 (0.3)	9,146 (0.2)		235 (0.1)	235 (0.1)		654 (0.3)	8,116 (0.2)		232 (0.1)	232 (0.1)	

IQR denotes interquartile range, PCR polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and SMD standardized mean difference.

* Cases represent PCR-positive SARS-CoV-2 tests, while controls represent PCR-negative SARS-CoV-2 tests.

† Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡ SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD $\leq$ 0.1 indicates adequate matching.

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

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

¶ These comprise up to 183 other nationalities in Qatar among cases and controls in the unmatched two-dose and three-dose analyses, 121 other nationalities in the matched analysis with two doses, and 122 other nationalities in the matched analysis with three doses.

** The tests used to define symptomatic infection.

†† The tests used to define asymptomatic infection.

vaccination was for the primary series or a booster. An illustrative schematic in Fig. 3 shows the concept depicted in these findings.

The results also indicate the presence of two smaller gradients within two infection groups, which are nested within the identified large gradient across all infections. The first group consists of asymptomatic and symptomatic infections (non-severe outcomes), where the differences in vaccine protection within this group are relatively small, but this type of protection diminishes rapidly. In contrast, the second group comprises severe, critical, and fatal COVID-19 infections, where the distinctions in vaccine protection are also modest, but this category of protection wanes at a slower pace.

These observed patterns may be attributed to distinct components of the immune system playing pivotal roles in vaccine protection against each group of infections. The protection against asymptomatic or symptomatic infections appears to be primarily driven by humoral immunity, specifically the presence of neutralizing antibodies that impede the virus from entering cells [12,14,43,44]. However, these antibodies exhibit rapid waning over time [43,45,46], potentially explaining the swift decline in vaccine protection against asymptomatic and symptomatic infections.

Conversely, cellular immunity [47] generates memory T cells that appear to provide the more enduring protection against severe outcomes [48,49]. Although these cells may not prevent the establishment of infection, they can swiftly respond to it, substantially mitigating the likelihood of a severe infection [48,49].

This study has limitations. While a discernible gradient in vaccine protection against severe, critical, and fatal COVID-19 infections could exist, with the highest protection against fatal COVID-19 and the lowest protection against severe COVID-19, the relatively small number of severe, critical, and fatal cases hindered the ability to distinguish minor variations in vaccine effectiveness against each category of severe outcomes. Due to the recent introduction of booster vaccination within the study duration, assessing the long-term effectiveness of boosters was not feasible. Some of the booster effectiveness measures also exhibited wide 95% CIs, given the small number of vaccinations administered within the study timeframe.

Vaccination in Qatar was implemented adhering strictly to the protocols approved by the United States Food and Drug Administration for the BNT162b2 and mRNA-1273 vaccines [12,14]. Accordingly, the median time between the first and second doses for BNT162b2 was only 21 days, and for mRNA-1273, it was 28 days. Thus, individuals spent only a brief period in a one-dose status, leading to a limited number of positive tests while in this status. This limitation precluded the inclusion of one-dose effectiveness estimates alongside the two- and three-dose estimates presented in this study.

The investigation of vaccine effectiveness patterns was limited to the pre-Omicron era, as the same analyses could not be extended to include the Omicron era. The onset of the large Omicron wave in Qatar on December 19, 2021 [17], prompted the introduction of rapid antigen testing alongside PCR testing. However, this shift in testing protocols was rapid and did not include the reason for testing for a large proportion of the rapid antigen tests [17,24]. Different reasons for testing were affected differently by the use of rapid antigen versus PCR testing, and the inclusion of the reason for testing was not consistent among the testing indications [17,24]. This complicated the ability to distinguish between asymptomatic and symptomatic infections and to conduct analyses at comparable time intervals since the last vaccine dose for each type of infection. The number of cases of severe, critical, and fatal COVID-19 was substantially lower in the Omicron era compared to the pre-Omicron era [50], potentially leading to estimates that lack adequate statistical precision.

Furthermore, the known modest-to-moderate effectiveness of first-generation COVID-19 vaccines against Omicron infections [7,10,41,51], attributed to an inferior match between circulating Omicron subvariants and pre-Omicron immunity [7,10,41,51], in addition to other potential effects such as immune imprinting [11,52], renders

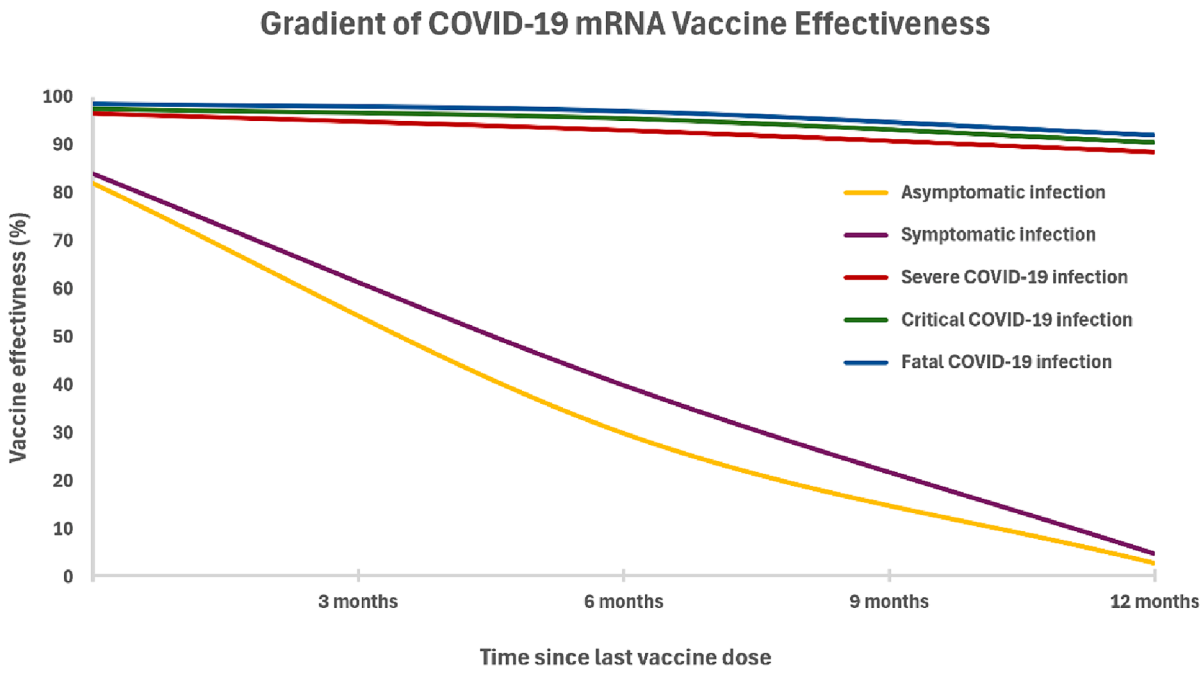

Fig. 3. An illustrative schematic highlighting the concept of the observed gradient effect in COVID-19 mRNA vaccine effectiveness, following primary-series or booster vaccination, against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections. The figure is informed by the study's results, with modifications applied to ensure it visually and succinctly conveys the core concept of the study. The curves are not entirely and strictly based on the quantitative estimates presented in this study. COVID-19 denotes coronavirus disease 2019.

the Omicron era less pertinent for investigating generic patterns in vaccine protection, as was undertaken in the present study. However, the evidence on vaccine effectiveness from the Omicron era, albeit indirectly, suggests a similar gradient in vaccine effectiveness [7,8,10,24,53]. This implies that the pattern identified in our study might also be generalizable to the Omicron era.

The results indicate minor differences in effectiveness between BNT162b2 and mRNA-1273, aligning with our earlier analysis, which demonstrated only a slightly higher effectiveness for mRNA-1273 [13], likely due to its larger antigen dose [12–14]. However, this study, unlike our earlier one [13], did not directly compare the effectiveness of BNT162b2 to that of mRNA-1273, thus caution is advised in comparing the effectiveness of these two vaccines. Qatar began administering BNT162b2 before introducing mRNA-1273 several months later [1,2]. Consequently, the time interval between vaccine doses and tests might vary between the BNT162b2 and mRNA-1273 analyses, and the variant distribution associated with the positive tests could also differ between these two vaccines.

Given the small proportion of individuals aged 50 years or older in Qatar [25,54], caution is warranted in generalizing the findings to regions where the elderly constitute a larger demographic proportion. Qatar's socio-demographic composition is distinct and not reflective of a typical national demographic structure. Households comprising single units and families with children, adults, and/or the elderly constitute only 40% of the total population [55,56]. The remainder is made up of migrant workers engaged in manual and craft-related occupations [34,35]. Originating from countries such as India, Nepal, and Bangladesh, these workers are predominantly single men aged between 20 and 49, employed in construction projects, and living in large shared accommodations [34,35,56,57]. Females account for only about one-fourth of Qatar's total population [58]. The majority of the population resides in urban settings, particularly in the capital city of Doha, while a very small fraction lives in non-urban areas [58].

While data capture was primarily conducted through electronic scanning methods for most measured variables, the potential for misclassification bias in studies utilizing real-world data cannot be overlooked. Misclassification bias may manifest in several forms, such as inaccuracies in exposure data (e.g., missing vaccination records), errors in covariate information (e.g., comorbidities), and inaccuracies in outcome reporting (e.g., hospitalizations outside Qatar). Misclassification bias can also be non-differential across the different study groups, thereby increasing the likelihood of a bias effect. If substantial, these misclassifications can distort the outcomes of real-world analyses.

As an observational study, one cannot rule out other biases that may emerge in real-world data unexpectedly or from unknown sources, such as subtle differences in test-seeking behavior. The depletion of individuals at risk may introduce bias, potentially leading to an underestimation of vaccine protection [59], even within the test-negative study design, which is typically considered less susceptible to such biases [3,31].

While matching in case-control studies aims to address confounding, it does not ensure the complete elimination of potential biases and may introduce selection bias [60]. Although our matching included various factors, certain variables like geographic location or occupation could not be considered due to data unavailability. However, Qatar, as a city-state, experiences a relatively uniform distribution of infection incidence across neighborhoods. Notably, nationality, age, and sex serve as robust proxies for socio-economic status in this specific population [25,32–34]. Matching based on these factors may have partially mitigated differences in infection exposure related to other variables, such as occupation. This matching approach has been explored in previous studies with different epidemiologic designs that utilized control groups to test for null effects [2–4,13,36], with the results supporting its reliability in controlling for differences in infection exposure.

This study has strengths. It was conducted on the entire population of Qatar during a period of widespread PCR testing [3], potentially minimizing bias. The population is also diverse, with nearly 89% being expatriates from over 150 countries [25], making it more representative of the global population. Thorough sensitivity and additional analyses were undertaken to explore the effects of potential biases, both in this study and in our previous studies [3,4]. These analyses involved different study inclusion and exclusion criteria, different prescriptions

for matching, various adjustments in the analyses, and different approaches for factoring prior SARS-CoV-2 infections. The consistent findings from these analyses support the reliability of the approach in this study. Lastly, the findings align with previous studies employing different epidemiologic study designs, including those within the same population, collectively pointing towards the observed vaccine effectiveness patterns [2–5,9,10,20].

In conclusion, the effectiveness of mRNA COVID-19 vaccines exhibits discernible patterns. There is a gradient in effectiveness linked to the symptoms and severity of infection, offering higher protection against more symptomatic and severe cases. This gradient intensifies over time as vaccine immunity wanes after the last vaccine dose. These patterns appear consistent irrespective of the vaccine type or whether the vaccination involves the primary series or a booster. The observed patterns may be attributed to distinct roles played by different components of the immune system, specifically humoral immunity versus cellular immunity.

Author contributions

All authors have read and approved the final manuscript. All authors attest they meet the ICMJE criteria for authorship.

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CRediT authorship contribution statement

Layan Sukik: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Hiam Chemaitelly:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Houssein H. Ayoub:** Writing – review & editing, Resources, Data curation. **Peter Coyle:** Writing – review & editing, Resources, Data curation. **Patrick Tang:** Writing – review & editing, Resources, Data curation. **Hadi M. Yassine:** Writing – review & editing, Resources, Data curation. **Asmaa A. Al Thani:** Writing – review & editing, Resources, Data curation. **Mohammad R. Hasan:** Writing – review & editing, Resources, Data curation. **Zaina Al-Kanaani:** Writing – review & editing, Resources, Data curation. **Einas Al-Kuwari:** Writing – review & editing, Resources, Data curation. **Andrew Jeremijenko:** Writing – review & editing, Resources, Data curation. **Anvar Hassan Kaleeckal:** Writing – review & editing, Resources, Data curation. **Ali Nizar Latif:** Writing – review & editing, Resources, Data curation. **Riyazuddin Mohammad Shaik:** Writing – review & editing, Resources, Data curation. **Hanan F. Abdul-Rahim:** Writing – review & editing, Resources, Data curation. **Gheyath K. Nasrallah:** Writing – review & editing, Resources, Data curation. **Mohamed Ghaith Al-Kuwari:** Writing – review & editing, Resources, Data curation. **Adeel A. Butt:** Writing – review & editing, Resources, Data curation. **Hamad Eid Al-Romaihi:** Writing – review & editing, Resources, Data curation. **Mohamed H. Al-Thani:** Writing – review & editing, Resources, Data curation. **Abdullatif Al-Khal:** Writing – review & editing, Resources, Data curation. **Roberto Bertollini:** Writing – review & editing, Resources, Data curation. **Manar E. Abdel-Rahman:** Writing – review & editing, Supervision. **Laith J. Abu-Raddad:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The study dataset belongs to the Qatar Ministry of Public Health and was made available to the researchers under a restricted-access agreement that prohibits sharing the dataset with a third party or publicly. The data can be accessed under restricted conditions to maintain patient data confidentiality. Access can be granted through a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-Health-Communication-Center.aspx). The raw data are protected and are not available due to data privacy laws.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.04.026.

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