

Supplemental Material

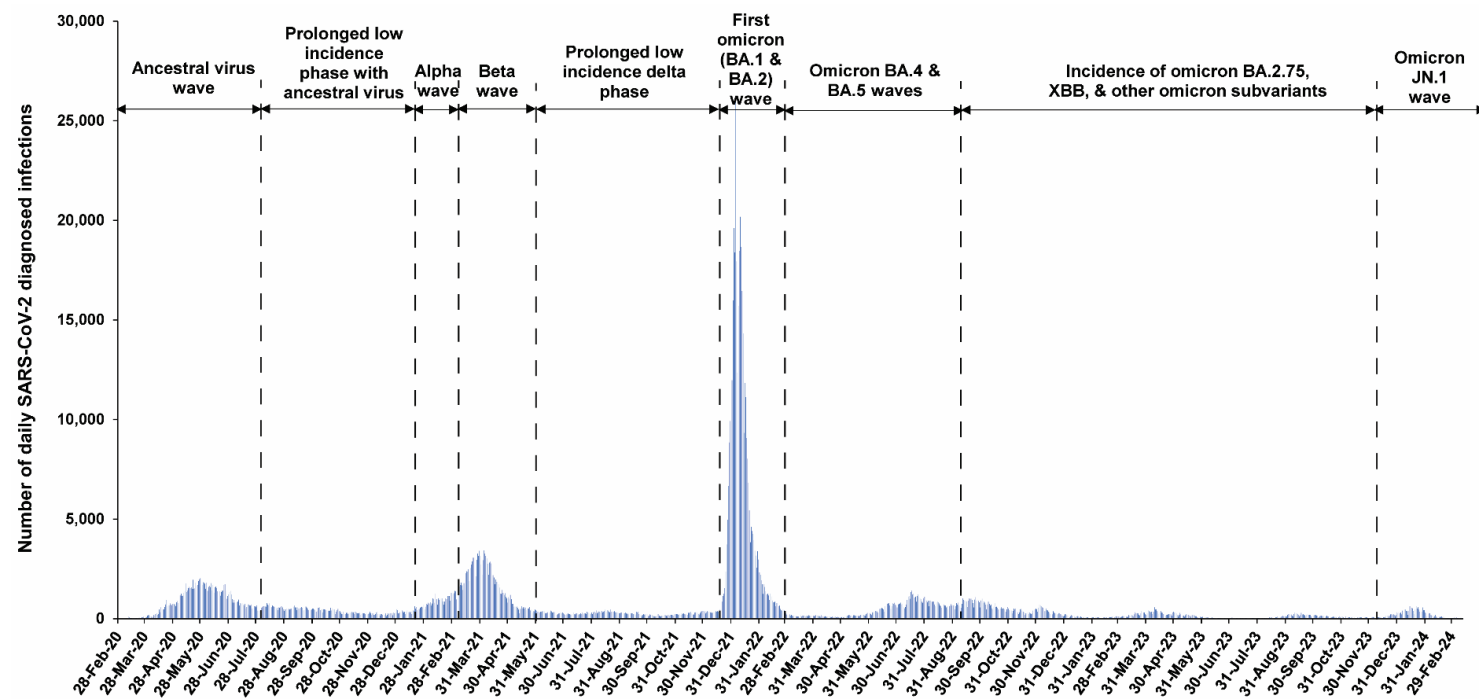
Table of Contents

Section S1. Phases of the COVID-19 pandemic	2
Figure S1. Daily count of newly diagnosed SARS-CoV-2 infections up to the end of the study, between February 5, 2020 and March 12, 2024.	3
Section S2. Study population and data sources	4
Section S3. Laboratory methods and variant ascertainment	7
Real-time reverse-transcription polymerase chain reaction testing	7
Rapid antigen testing	7
Classification of infections by variant type	8
Section S4. COVID-19 severity, criticality, and fatality classification	9
Section S5. Classification of coexisting conditions	11
Figure S2. Flowchart describing the population selection process for investigating the effectiveness of a pre-omicron infection in preventing reinfection with a pre-omicron virus.	12
Figure S3. Flowchart describing the population selection process for investigating the effectiveness of an omicron infection in preventing reinfection with an omicron virus.	13
Table S1. Characteristics of the unmatched and matched cases and controls in samples used to estimate the effectiveness of an omicron infection in preventing reinfection with an omicron virus.	14
Figure S4. Subgroup analysis by vaccination status. Effectiveness of A) a pre-omicron infection in preventing asymptomatic, symptomatic, severe, critical, and fatal COVID-19 reinfections with a pre-omicron virus among unvaccinated individuals, (B) a pre-omicron infection in preventing these outcomes among vaccinated individuals, (C) an omicron infection in preventing asymptomatic, symptomatic, severe, critical, and fatal COVID-19 reinfections with an omicron virus among unvaccinated individuals, and (D) an omicron infection in preventing these outcomes among vaccinated individuals. Data are presented as effectiveness point estimates. Error bars indicate the corresponding 95% confidence intervals.	15
Table S2. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies.	16
References	18

Section S1. Phases of the COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic in Qatar up to the end of the study duration was categorized into distinct phases based on the level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incidence and the predominant variant. The phases included the ancestral virus wave (February 28, 2020 - July 31, 2020),¹ a prolonged low incidence phase with the ancestral virus (August 1, 2020 - January 17, 2021),^{2 3} the alpha wave (January 18, 2021 - March 7, 2021),⁴ the beta wave (March 8, 2021 - May 31, 2021),⁵ a prolonged low incidence delta phase (June 1, 2021 - December 18, 2021),^{6 7} the first (BA.1 & BA.2) omicron wave (December 19, 2021 - February 28, 2022),⁸ the omicron BA.4 & BA.5 wave (March 1, 2022 - September 9, 2022), the omicron BA.2.75 & XBB waves (September 10, 2022 - December 3, 2023),⁹ and the omicron JN.1 wave (December 4, 2023 - March 12, 2024).¹⁰

Figure S1. Daily count of newly diagnosed SARS-CoV-2 infections up to the end of the study, between February 5, 2020 and March 12, 2024.



SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.

Section S2. Study population and data sources

Qatar's national and universal public healthcare system uses the Cerner-system advanced digital health platform to track all electronic health record encounters of each individual in the country, including all citizens and residents registered in the national and universal public healthcare system. Registration in the public healthcare system is mandatory for citizens and residents.

The databases analyzed in this study are data-extract downloads from the Cerner-system that have been implemented on a regular schedule since the onset of pandemic by the Business Intelligence Unit at Hamad Medical Corporation (HMC). HMC is the national public healthcare provider in Qatar. At every download, all SARS-CoV-2 tests, COVID-19 vaccinations, hospitalizations related to COVID-19, and all death records regardless of cause are provided to the authors through .csv files. These databases have been analyzed throughout the pandemic not only for study-related purposes, but also to provide policymakers with summary data and analytics to inform the national response.

Every health encounter in the Cerner-system is linked to a unique individual through the HMC Number that links all records for this individual at the national level. Databases were merged and analyzed using the HMC Number to link all records whether for testing, vaccinations, hospitalizations, and deaths. All COVID-19-related healthcare was provided in the public healthcare system. COVID-19 vaccination was also provided only through the public healthcare system. These health records were tracked throughout the COVID-19 pandemic using the Cerner system. This system has been implemented in 2013, before the onset of the pandemic. Therefore, we had the health records related to this study for all citizens and residents throughout the pandemic.

Demographic details for every HMC Number (individual) such as sex, age, and nationality are collected upon issuing of the universal health card, based on the Qatar Identity Card, which is a mandatory requirement by the Ministry of Interior to every citizen and resident in the country. Data extraction from the Qatar Identity Card to the digital health platform is performed electronically through scanning techniques.

All SARS-CoV-2 testing in any facility in Qatar is tracked nationally in one database, the national testing database. This database covers all testing in all locations and facilities throughout the country, whether public or private. Every polymerase chain reaction (PCR) test and a proportion of the facility-based rapid antigen tests conducted in Qatar, regardless of location or setting, are classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, at port of entry, post-antibody, or other).

Before November 1, 2022, SARS-CoV-2 testing in Qatar was done at a mass scale where about 5% of the population were tested every week.¹¹ As of October 31, 2022, the majority of SARS-CoV-2 tests conducted in Qatar were for routine purposes, such as travel-related requirements.^{2 11} Approximately 75% of cases were diagnosed not because symptoms prompted individuals to seek testing, but rather through routine testing, regardless of whether symptoms developed.^{2 11} Subsequently, testing rates decreased, with less than 1% of the population being tested per week.⁹ All testing results in the national testing database during the present study were factored in the analyses of this study.

The first large omicron wave that peaked in January of 2022 was massive and strained the testing capacity in the country.^{9 11-13} Accordingly, rapid antigen testing was introduced to relieve the pressure on PCR testing. Implementation of this change in testing policy occurred quickly

precluding incorporation of reason for testing in a large proportion of the rapid antigen tests.

While the reason for testing is available for all PCR tests, it is not available for all rapid antigen tests. Availability of reason for testing for the rapid antigen tests also varied with time.

Rapid antigen test kits are available for purchase in pharmacies in Qatar, but outcome of home-based testing is not reported nor documented in the national databases. Since SARS-CoV-2-test outcomes were linked to specific public health measures, restrictions, and privileges, testing policy and guidelines stress facility-based testing as the core testing mechanism in the population. While facility-based testing is provided free of charge or at low subsidized costs, depending on the reason for testing, home-based rapid antigen testing is de-emphasized and not supported as part of national policy.

Qatar launched its COVID-19 vaccination program in December 2020, employing mRNA vaccines and prioritizing individuals based on coexisting conditions and age criteria.^{2 14} COVID-19 vaccination was provided free of charge, regardless of citizenship or residency status, and was nationally tracked.^{2 14}

Qatar has unusually young, diverse demographics, in that only 9% of its residents are ≥ 50 years of age, and 89% are expatriates from over 150 countries.^{1 15} Further descriptions of the study population and these national databases were reported previously.^{1 2 5 11 13 16-18}

Section S3. Laboratory methods and variant ascertainment

Real-time reverse-transcription polymerase chain reaction testing

Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: 1) extracted on KingFisher Flex (Thermo Fisher Scientific, USA), MGISP-960 (MGI, China), or ExiPrep 96 Lite (Bioneer, South Korea) followed by testing with real-time reverse-transcription PCR (RT-qPCR) using TaqPath COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher Scientific, USA); 2) tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or 3) loaded directly into a Roche cobas 6800 system and assayed with the cobas SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and the third targets the ORF1ab and E-gene regions.

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

Rapid antigen testing

SARS-CoV-2 antigen tests were performed on nasopharyngeal swabs using one of the following lateral flow antigen tests: Panbio COVID-19 Ag Rapid Test Device (Abbott, USA); SARS-CoV-2 Rapid Antigen Test (Roche, Switzerland); Standard Q COVID-19 Antigen Test (SD Biosensor, Korea); or CareStart COVID-19 Antigen Test (Access Bio, USA). All antigen tests were performed point-of-care according to each manufacturer's instructions at public or private hospitals and clinics throughout Qatar with prior authorization and training by the Ministry of Public Health (MOPH). Antigen test results were electronically reported to the MOPH in real

time using the Antigen Test Management System which is integrated with the national COVID-19 database.

Classification of infections by variant type

Surveillance for SARS-CoV-2 variants in Qatar is based on viral genome sequencing and multiplex RT-qPCR variant screening¹⁹ of weekly collected random positive clinical samples,^{2 20-24} complemented by deep sequencing of wastewater samples.^{22 25 26} Further details on the viral genome sequencing and multiplex RT-qPCR variant screening throughout the SARS-CoV-2 waves in Qatar can be found in previous publications.^{2 6 11 12 16 20-24 27-30}

Section S4. COVID-19 severity, criticality, and fatality classification

Classification of COVID-19 case severity (acute-care hospitalizations),³¹ criticality (intensive-care-unit hospitalizations),³¹ and fatality³² followed World Health Organization (WHO) guidelines. Assessments were made by trained medical personnel independent of study investigators and using individual chart reviews, as part of a national protocol applied to every hospitalized COVID-19 patient. Each hospitalized COVID-19 patient underwent an infection severity assessment every three days until discharge or death. We classified individuals who progressed to severe, critical, or fatal COVID-19 between the time of the documented infection and the end of the study based on their worst outcome, starting with death,³² followed by critical disease,³¹ and then severe disease.³¹

Severe COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥ 60 breaths/minute in children <2 months old or ≥ 50 breaths/minute in children 2-11 months old or ≥ 40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)".³¹ Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.³¹

Critical COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy".³¹ Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.³¹

COVID-19 death was defined per WHO classification as "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19".³² Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.³²

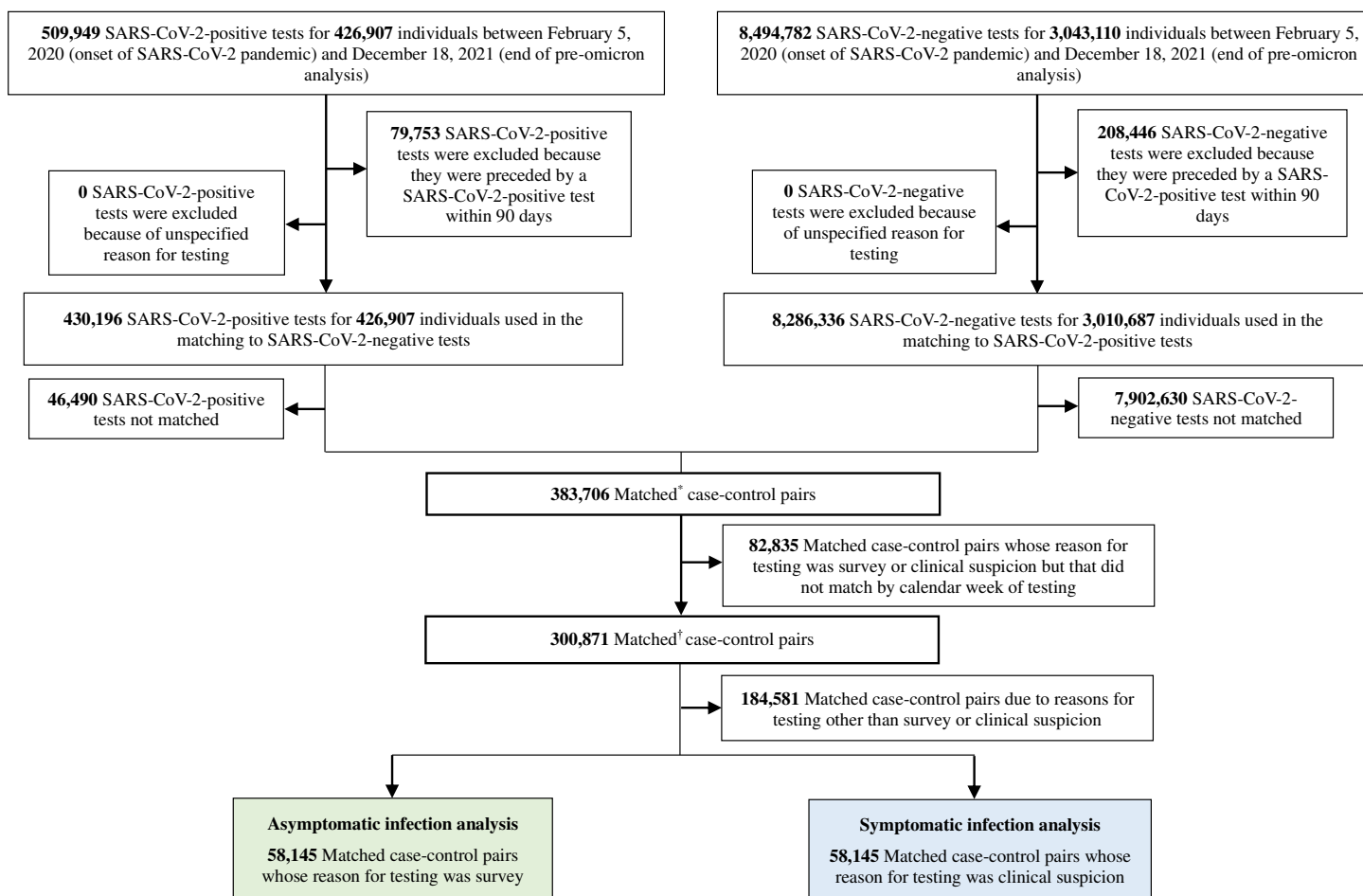
Section S5. Classification of coexisting conditions

Coexisting conditions were ascertained and classified based on the ICD-10 codes for the conditions as recorded in the electronic health record encounters of each individual in the Cerner-system national database that includes all citizens and residents registered in the national and universal public healthcare system. The public healthcare system provides healthcare to the entire resident population of Qatar free of charge or at heavily subsidized costs, including prescription drugs. With the mass expansion of this sector in recent years, facilities have been built to cater to specific needs of subpopulations. For example, tens of facilities have been built, including clinics and hospitals, in localities with high density of craft and manual workers.³³

All encounters for each individual were analyzed to determine the coexisting-condition classification for that individual, as part of a recent national analysis to assess healthcare needs and resource allocation. The Cerner-system national database includes encounters starting from 2013, after this system was launched in Qatar. As long as each individual had at least one encounter with a specific coexisting-condition diagnosis since 2013, this person was classified with this coexisting condition.

Individuals who have coexisting conditions but never sought care in the public healthcare system, or seek care exclusively in private healthcare facilities, were classified as individuals with no coexisting condition due to absence of recorded encounters for them.

Figure S2. Flowchart describing the population selection process for investigating the effectiveness of a pre-omicron infection in preventing reinfection with a pre-omicron virus.

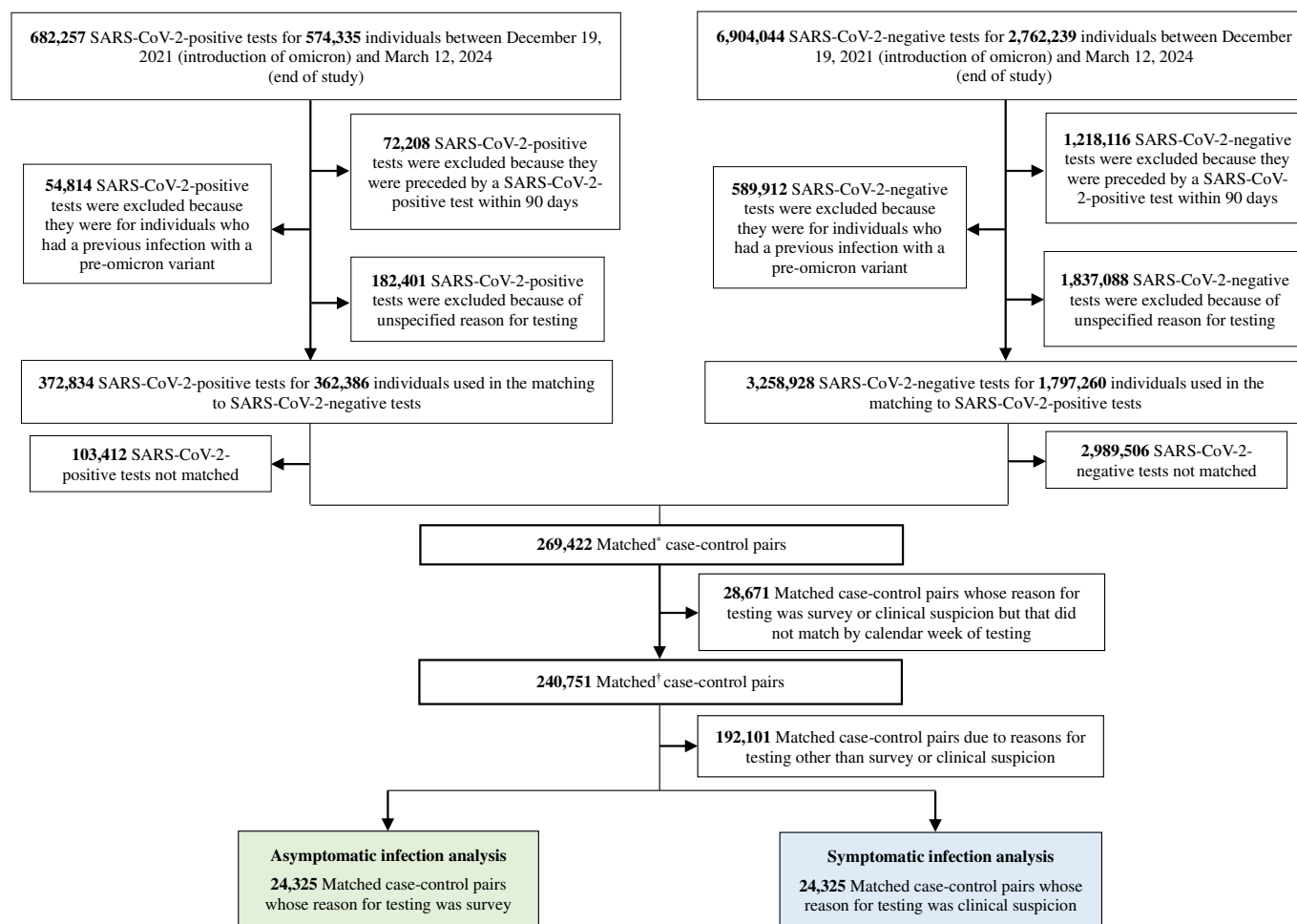


PCR denotes polymerase chain reaction, RA rapid antigen, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

[†]SARS-CoV-2-positive tests were matched exactly one-to-one to SARS-CoV-2-negative tests by sex, 10-year age group, nationality, number of coexisting conditions, number of vaccine doses at the time of the study test, calendar week of SARS-CoV-2 test, testing method (PCR or RA), and reason for testing.

[‡]Matched case-control pairs identified through surveys were subsequently matched by calendar week of testing to their counterparts identified through clinical suspicion.

Figure S3. Flowchart describing the population selection process for investigating the effectiveness of an omicron infection in preventing reinfection with an omicron virus.



PCR denotes polymerase chain reaction, RA rapid antigen, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

*SARS-CoV-2-positive tests were matched exactly one-to-one to SARS-CoV-2-negative tests by sex, 10-year age group, nationality, number of coexisting conditions, number of vaccine doses at the time of the study test, calendar week of SARS-CoV-2 test, testing method (PCR or RA), and reason for testing.

†Matched case-control pairs identified through surveys were subsequently matched by calendar week of testing to their counterparts identified through clinical suspicion.

Table S1. Characteristics of the unmatched and matched cases and controls in samples used to estimate the effectiveness of an omicron infection in preventing reinfection with an omicron virus.

Characteristics	Unmatched sample			Matched sample		
	Cases N=372,834	Controls N=3,258,928	SMD [†]	Cases* N=240,751	Controls* N=240,751	SMD [†]
Median age (IQR) - years	33 (25-42)	34 (25-42)	0.01 [‡]	32 (24-40)	32 (24-40)	0.00 [‡]
Age group - no. (%)						
<10 years	30,654 (8.2)	277,314 (8.5)		21,015 (8.7)	21,015 (8.7)	
10-19 years	34,510 (9.3)	289,671 (8.9)		22,651 (9.4)	22,651 (9.4)	
20-29 years	75,128 (20.2)	629,167 (19.3)		52,768 (21.9)	52,768 (21.9)	
30-39 years	118,278 (31.7)	1,010,417 (31.0)	0.06	80,382 (33.4)	80,382 (33.4)	0.00
40-49 years	66,909 (17.9)	632,110 (19.4)		42,338 (17.6)	42,338 (17.6)	
50-59 years	31,389 (8.4)	293,256 (9.0)		16,086 (6.7)	16,086 (6.7)	
60-69 years	11,333 (3.0)	97,845 (3.0)		4,353 (1.8)	4,353 (1.8)	
70+ years	4,633 (1.2)	29,148 (0.9)		1,158 (0.5)	1,158 (0.5)	
Sex						
Male	217,359 (58.3)	2,120,740 (65.1)	0.14	145,017 (60.2)	145,017 (60.2)	0.00
Female	155,475 (41.7)	1,138,188 (34.9)		95,734 (39.8)	95,734 (39.8)	
Nationality[§]						
Bangladeshi	12,793 (3.4)	158,622 (4.9)		9,149 (3.8)	9,149 (3.8)	
Egyptian	15,596 (4.2)	137,006 (4.2)		8,074 (3.4)	8,074 (3.4)	
Filipino	42,041 (11.3)	267,533 (8.2)		28,193 (11.7)	28,193 (11.7)	
Indian	76,985 (20.6)	745,940 (22.9)		58,533 (24.3)	58,533 (24.3)	
Nepalese	17,606 (4.7)	170,574 (5.2)	0.25	13,686 (5.7)	13,686 (5.7)	0.00
Pakistani	13,352 (3.6)	143,347 (4.4)		8,331 (3.5)	8,331 (3.5)	
Qatari	81,722 (21.9)	476,904 (14.6)		56,953 (23.7)	56,953 (23.7)	
Sri Lankan	9,168 (2.5)	87,757 (2.7)		5,798 (2.4)	5,798 (2.4)	
Sudanese	9,432 (2.5)	63,807 (2.0)		4,672 (1.9)	4,672 (1.9)	
Other nationalities	94,139 (25.2)	1,007,438 (30.9)		47,362 (19.7)	47,362 (19.7)	
Coexisting conditions						
0	294,981 (79.1)	2,766,330 (84.9)		203,188 (84.4)	203,188 (84.4)	
1	40,985 (11.0)	273,756 (8.4)		22,906 (9.5)	22,906 (9.5)	
2	17,410 (4.7)	111,749 (3.4)		8,226 (3.4)	8,226 (3.4)	
3	8,051 (2.2)	48,047 (1.5)	0.16	3,047 (1.3)	3,047 (1.3)	0.00
4	4,815 (1.3)	27,132 (0.8)		1,500 (0.6)	1,500 (0.6)	
5	3,102 (0.8)	15,443 (0.5)		873 (0.4)	873 (0.4)	
6+	3,490 (0.9)	16,471 (0.5)		1,011 (0.4)	1,011 (0.4)	
Vaccine doses[¶]						
0	123,250 (33.1)	1,222,108 (37.5)		84,372 (35.0)	84,372 (35.0)	
1	3,548 (1.0)	44,569 (1.4)		1,200 (0.5)	1,200 (0.5)	
2	190,673 (51.1)	1,266,290 (38.9)	0.27	123,425 (51.3)	123,425 (51.3)	0.00
3	54,709 (14.7)	717,661 (22.0)		31,712 (13.2)	31,712 (13.2)	
4+	654 (0.2)	8,300 (0.3)		42 (0.0)	42 (0.0)	
Method of testing						
PCR	293,024 (78.6)	1,667,037 (51.2)	0.60	202,474 (84.1)	202,474 (84.1)	0.00
RA	79,810 (21.4)	1,591,891 (48.8)		38,277 (15.9)	38,277 (15.9)	
Reason for testing						
Clinical suspicion	106,178 (28.5)	268,056 (8.2)		24,325 (10.1)	24,325 (10.1)	
Contact tracing	55,825 (15.0)	240,392 (7.4)		40,445 (16.8)	40,445 (16.8)	
Port of entry	44,468 (11.9)	1,187,859 (36.4)		41,712 (17.3)	41,712 (17.3)	
Individual request	39,862 (10.7)	441,020 (13.5)		28,972 (12.0)	28,972 (12.0)	
Survey	30,031 (8.1)	256,096 (7.9)	0.79	24,325 (10.1)	24,325 (10.1)	0.00
Healthcare routine testing	11,593 (3.1)	157,992 (4.8)		6,325 (2.6)	6,325 (2.6)	
Pre-travel	84,045 (22.5)	701,564 (21.5)		74,527 (31.0)	74,527 (31.0)	
Post-antibody	200 (0.1)	1,366 (0.0)		40 (0.0)	40 (0.0)	
Other	632 (0.2)	4,583 (0.1)		80 (0.0)	80 (0.0)	

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

*Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, number of vaccine doses at the time of the study test, calendar week of testing, method of testing (PCR or RA), and reason for testing. Matched case-control pairs identified through surveys were subsequently matched by calendar week of testing to their counterparts identified through clinical suspicion.

[†]SMD is the difference in the mean of a covariate between groups divided by the pooled standard deviation. An SMD of ≤ 0.1 indicates adequate matching.

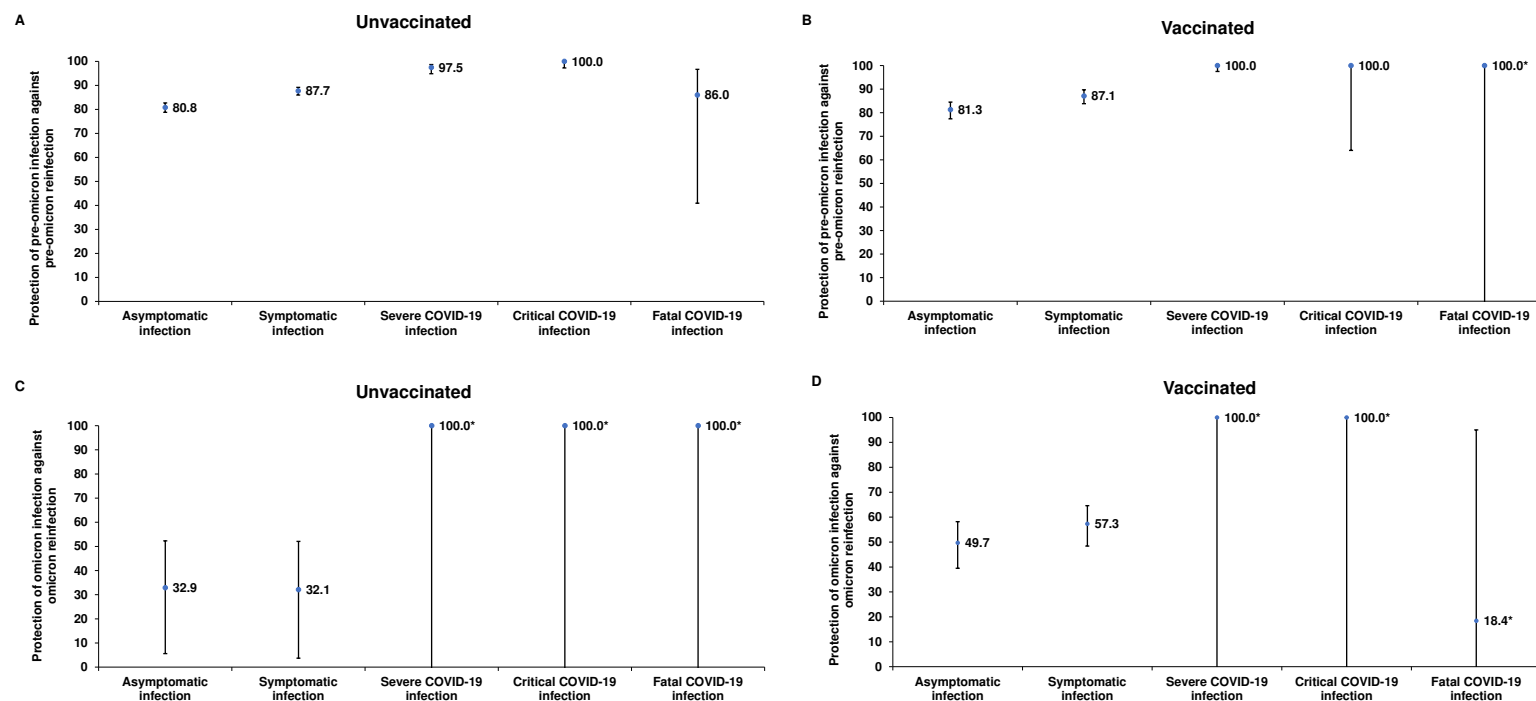
[‡]SMD is for the mean difference between groups divided by the pooled standard deviation.

[§]Nationalities were chosen to represent the most populous groups in Qatar.

^{||}These comprise up to 182 and 135 in the unmatched and matched samples, respectively.

[¶]Ascertained at the time of the SARS-CoV-2 test.

Figure S4. Subgroup analysis by vaccination status. Effectiveness of A) a pre-omicron infection in preventing asymptomatic, symptomatic, severe, critical, and fatal COVID-19 reinfections with a pre-omicron virus among unvaccinated individuals, (B) a pre-omicron infection in preventing these outcomes among vaccinated individuals, (C) an omicron infection in preventing asymptomatic, symptomatic, severe, critical, and fatal COVID-19 reinfections with an omicron virus among unvaccinated individuals, and (D) an omicron infection in preventing these outcomes among vaccinated individuals. 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.

Table S2. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies.

	Item No	Recommendation	Main text page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design	Methods ('Study design')
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods ('Study population and data sources' & 'Study design') & Sections S1-S3 in Supplementary Material
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (b) For matched studies, give matching criteria and the number of controls per case	Methods ('Study design') & Sections S1-S4 in Supplementary Material
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods ('Study design') & Sections S2-S5 in Supplementary Material
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods ('Study population and data sources', 'Study design' & 'Statistical analysis', paragraph 1) & Sections S2 & S3 in Supplementary Material
Bias	9	Describe any efforts to address potential sources of bias	Methods ('Study design' & 'Statistical analysis')
Study size	10	Explain how the study size was arrived at	Methods ('Study population and data sources' & 'Study design')
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods ('Study design' & 'Statistical analysis')
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods ('Statistical analysis')
		(b) Describe any methods used to examine subgroups and interactions	Methods ('Statistical analysis')
		(c) Explain how missing data were addressed	Not applicable, see Methods ('Study population and data sources')
		(d) If applicable, explain how matching of cases and controls was addressed	Methods ('Study design' & 'Statistical analysis')
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results & Figures S2 & S3 in Supplementary Material
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, Table 1 & Table S1 in Supplementary Material
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable, see Methods ('Study population and data sources')
Outcome data	15	Report numbers in each exposure category, or summary measures of exposure	Results, Tables 2, 3, & 4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, Tables 2, 3, & 4 & Figure S1 in Supplementary Material
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and	Results, Table 3 & 4 & Figure S4 in

		interactions, and sensitivity analyses	Supplementary Material
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, paragraphs 1-2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, paragraphs 3-6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, paragraphs 5-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, paragraph 5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding & Acknowledgements

References

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