Supplementary Appendix

Supplement to: Chemaitelly H, Ayoub HH, Tang P, et al. Immune imprinting and protection against repeat reinfection with SARS-CoV-2. N Engl J Med. DOI: 10.1056/NEJMc2211055

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

Supplementary Appendix

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Acknowledgements

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Author contributions

HC co-designed the study, performed the statistical analyses, and co-wrote the first draft of the article. LJA conceived and co-designed the study, led the statistical analyses, and co-wrote the first draft of the article. PVC designed mass PCR testing to allow routine capture of SGTF variants. PT and MRH conducted the multiplex, RT-qPCR variant screening and viral genome sequencing. HY, HAK, and MKS conducted viral genome sequencing. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and to the writing of the manuscript. All authors have read and approved the final manuscript.

Competing interests

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

Section S1. Study population and data sources

This study was conducted in the population of Qatar and analyzed coronavirus disease 2019 (COVID-19) data for laboratory testing, vaccination, hospitalization, and death, retrieved from the national digital-health information platform. Databases include all severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related data, with no missing information since pandemic onset, such as all polymerase chain reaction (PCR) tests, and starting from January 5, 2022, rapid antigen tests conducted at healthcare facilities.

SARS-CoV-2 testing in the healthcare system in Qatar is done at a mass scale, and mostly for routine reasons, where about 5% of the population are tested every week.[1,2] Most infections are diagnosed not because of appearance of symptoms, but because of routine testing.[2] Every PCR test and an increasing 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, or other). All facility-based testing done during follow-up in the present study was factored in the analyses of this study.

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 are 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 testing is de-emphasized and not supported as part of national policy. There is no reason to believe that home-based testing could have differentially affected the followed matched cohorts in this study to affect our results.

Qatar has unusually young, diverse demographics, in that only 9% of its residents are ≥50 years of age, and 89% are expatriates from over 150 countries.[3,4] Qatar launched its COVID-19 vaccination program in December of 2020 using the BNT162b2 and mRNA-1273 vaccines.[5] Further descriptions of the study population and these national databases were reported previously.[1,2,4,6,7]

Study design

We conducted a national, matched, retrospective observational cohort study that used matching to balance observed confounders between two exposure groups. The study compared incidence of re-reinfection, irrespective of symptoms, in the national cohort of individuals with a documented Omicron (B.1.1.529)-subvariant (BA.1/BA.2[8]) SARS-CoV-2 reinfection after an earlier pre-Omicron primary infection (designated as the double-primed cohort), to incidence of reinfection in the national cohort of documented primary Omicron-subvariant (BA.1/BA.2[8]) infection (designated as the Omicron-primed cohort).

Previous infections were classified as pre-Omicron versus Omicron previous infections, based on whether they occurred before or after the Omicron wave that started in Qatar on December 19, 2021.[1] Incidence of non-Omicron variants has been limited since onset of the Omicron wave in Qatar.[1,7-10] December 19, 2021 was set as the cut-off date for labeling the variants.

Documentation of infection in all cohorts was based on positive PCR or rapid antigen tests. Laboratory methods are found in Section S2. Classification of COVID-19 case severity (acute-care hospitalizations),[11] criticality (intensive-care-unit hospitalizations),[11] and fatality[12] followed World Health Organization guidelines (Section S3).

Cohort eligibility, matching, and follow-up

Any individual with a documented reinfection between December 19, 2021 (onset of the Omicron wave in Qatar[1,7-10]) and August 15, 2022 was eligible for inclusion in the double-primed cohort, provided that the individual received no vaccination before the start of follow-up, set at 90 days after reinfection. Any individual with a documented primary infection between December 19, 2021 and August 15, 2022 was eligible for inclusion in the Omicron-primed cohort, provided that the individual received no vaccination before the start of follow-up. The primary study outcome was incidence of reinfection. The secondary outcome was incidence of severe, critical, or fatal COVID-19 following reinfection.

Individuals in the double-primed cohort were exact-matched in a one-to-three ratio by sex, 10-year age group, nationality, comorbidity count (none, 1 comorbidity, 2 comorbidities, 3 or more comorbidities), and calendar week of reinfection (double-primed cohort)/calendar week of primary infection (Omicron-primed cohort) to individuals in the Omicron-primed cohort, to control for differences in risk of SARS-CoV-2 infection in Qatar.[4,13-16] Matching was performed using an iterative process so that each individual in both cohorts was alive and unvaccinated at the start of follow-up.

SARS-CoV-2 reinfection is conventionally defined as a documented infection ≥90 days after an earlier infection, to avoid misclassification of prolonged PCR positivity as reinfection.[9,17,18] Therefore, matched pairs were followed from the calendar day the individual in the double-primed cohort completed 90 days after the documented Omicron-subvariant reinfection.

For exchangeability,[7,19] all members of matched pairs were censored on the earliest occurrence of first-dose vaccination of an individual in either cohorts. Individuals were followed up until the first of any of the following events: a documented SARS-CoV-2 reinfection, i.e., the first PCR-

positive or rapid-antigen-positive test after the start of follow-up, regardless of symptoms, or first-dose vaccination (with matched pair censoring), or death, or end of study censoring.

Statistical analysis

Eligible and matched cohorts were described using frequency distributions and measures of central tendency, and were compared using standardized mean differences (SMDs). An SMD ≤0.1 indicated adequate matching.[20] Cumulative incidence of reinfection (defined as the proportion of individuals at risk, whose primary endpoint during follow-up was a re-reinfection for the double-primed cohort, or a reinfection for the Omicron-primed cohort) was estimated using the Kaplan–Meier estimator method.[21] Incidence rate of reinfection in each cohort, defined as the number of identified reinfections divided by the number of person-weeks contributed by all individuals in the cohort, was estimated with its 95% confidence interval (CI) using a Poisson log-likelihood regression model with the Stata 17.0 *stptime* command.

The hazard ratio, comparing incidence of reinfection in both cohorts, and the corresponding 95% CI, were calculated using Cox regression adjusted for matching factors with the Stata 17.0 *stcox* command. Schoenfeld residuals and log-log plots for survival curves were used to test the proportional-hazards assumption and to investigate its adequacy. 95% CIs were not adjusted for multiplicity; thus, they should not be used to infer definitive differences between cohorts. Interactions were not considered. The E-value was calculated to assess how strong an unmeasured confounder would have to be to explain away the observed exposure–outcome relationship.[22]

A subgroup analysis was conducted to estimate adjusted hazard ratios by time since reinfection. This was done using separate Cox regressions with "failures" restricted to specific time intervals. Another subgroup analysis was conducted to investigate immune protection in the situation that

the primary infection in the double-primed cohort was restricted to only the index virus or the Alpha variant, out of specific relevance to effect of immune imprinting.[23] Sensitivity analysis adjusting the hazard ratio by the ratio of testing frequencies between cohorts was also performed. Statistical analyses were conducted using Stata/SE version 17.0 (Stata Corporation, College Station, TX, USA).

Oversight

Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards approved this retrospective study with a waiver of informed consent. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The STROBE checklist is found in Table S3.

Limitations

We investigated incidence of documented reinfections, but other reinfections may have occurred and gone undocumented. Undocumented reinfections confer immunity or boost existing immunity, thereby perhaps affecting the estimates. While protection against severe forms of COVID-19 was investigated (Section S3), none of the incident reinfections in both cohorts progressed to severe,[11] critical,[11] or fatal[12] COVID-19 (Figure S1). This is a consequence of the lower severity of SARS-CoV-2 reinfections[24,25] and the lower severity of Omicron infections.[26-28] This precluded the possibility of providing an effect size for the protection against severe forms of COVID-19.

Differences in testing frequency existed between the followed cohorts, but these were small. The proportion of individuals who had a SARS-CoV-2 test during follow-up was 45.3% for the double-primed cohort and 38.4% for the Omicron-primed cohort. The testing frequency was 0.79

and 0.64 tests per person, respectively. Adjusting the hazard ratio estimate in a sensitivity analysis by the ratio of testing frequencies between cohorts yielded an adjusted hazard ratio of 0.42 (95% CI: 0.32-0.55), confirming study results.

Depletion of the double-primed cohort by COVID-19 mortality at time of the primary infection may have biased this cohort towards healthier individuals with stronger immune responses. However, COVID-19 mortality has been low in Qatar's predominantly young population,[4,29] totaling 681 COVID-19 deaths (<0.1% of primary infections) up to August 15, 2022. A survival effect seems unlikely to explain or appreciably affect study findings.

Testing in Qatar is done for specific reasons including clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, or at port of entry.[1,2] Therefore, testing and probability of infection diagnosis can vary by socio-economic stratum or nationality. For example, travel-related testing affects specific socio-economic strata and nationalities more than others.[30] Infection incidence also varied by socio-economic stratum and nationality over time. For example, the first wave affected mainly the craft and manual workers who come from specific nationalities, while the Alpha wave affected primarily the urban population (other than craft and manual workers).[4,13-16,31,32]

Considering these differences in infection exposure, matching was implemented by sex, 10-year age group, nationality, comorbidity count, and calendar week of reinfection (double-primed cohort)/calendar week of primary infection (Omicron-primed cohort) to individuals in the Omicron-primed cohort, to control for these differences in risk of SARS-CoV-2 infection over time in Qatar.[4,13-16,31,32] These differences in infection exposure are thus not likely to affect our results.

December 19, 2021 was set as the cut-off date for labeling the variants. However, first detection of Omicron in Qatar was in early December of 2021.[1,7-9,33,34] The number of Omicron cases was small and sporadic till the onset of the Omicron wave on December 19, 2021.[1,7-9,33,34] Between December 1, 2021 and December 18, 2021, a period of mixed Delta and Omicron infections, infection incidence was low and the majority of cases were Delta infections.[1,7-9,33,34] The massive Omicron-wave exponential-growth phase started on December 19, 2021 and peaked in mid-January, 2022.[1,7-9,33,34] Therefore, adding a washout period to account for the transition from Delta to Omicron incidence is unlikely to affect the study estimates. Indeed, excluding any individual that had an infection diagnosed between December 1, 2021 and December 18, 2021, the period of mixed infections, did not appreciably affect the estimated adjusted hazard ratio for infection [0.51 (95% CI: 0.39-0.67) after including the washout period versus 0.52 (95% CI: 0.40-0.68) with no washout period].

COVID-19 vaccine coverage is high in Qatar and exceeds 90% among the adult population.[1,2,7] Nearly all individuals in the population were vaccinated free of charge in Qatar, rather than elsewhere. In rare situations in which an individual was vaccinated outside Qatar, that individual's vaccination details were still recorded in the health system at the port of entry upon return to Qatar, following national requirements and to benefit from privileges associated with vaccination, such as exemption from quarantine.[28]

By August 15, 2022, 2,241,937 individuals received two COVID-19 vaccine doses of either the BNT162b2 vaccine or the mRNA-1273 vaccine, and 711,470 individuals received a third (booster) mRNA dose. Median date of first mRNA vaccine dose was May 15, 2021, and of second dose was June 6, 2021. Median date of booster dose was Jan 23, 2022. Median time

between first and second doses was 27 days (interquartile range (IQR), 21-28 days) and between second and booster doses was 255 days (IQR, 229-289 days).

As a consequence of exclusion of vaccinated individuals, the cohorts of this study were young (Table S1). Nearly half of the members of these cohorts were <20 years of age (Table S1). With the young age of those that remained unvaccinated in our population, as well as Qatar's young population,[4] our findings may not be generalizable to older individuals or to other countries where older persons constitute a larger proportion of the total population.

As an observational study, investigated cohorts were neither blinded nor randomized, so unmeasured or uncontrolled confounding cannot be excluded. While matching was done for sex, age, nationality, comorbidity count, and calendar week of Omicron-subvariant infection, this was not possible for other factors such as geography or occupation, as such data were unavailable. However, Qatar is essentially a city state and infection incidence was broadly distributed across neighborhoods. Nearly 90% of Qatar's population are expatriates from over 150 countries, coming here because of employment.[4] Most are craft and manual workers working in development projects.[4] Nationality, age, and sex provide a powerful proxy for socio-economic status in this country.[4,13-16] Nationality alone is strongly associated with occupation.[4,14-16]

Matching was done to control for factors that affect infection exposure in Qatar.[4,13-16] The matching prescription had already been investigated in previous studies of different epidemiologic designs, and using control groups to test for null effects.[2,5,35-37] These control groups included unvaccinated cohorts versus vaccinated cohorts within two weeks of the first dose,[2,35-37] when vaccine protection is negligible,[38] and mRNA-1273- versus BNT162b2-vaccinated cohorts, also in the first two weeks after the first dose.[5] These studies have shown that this prescription provides adequate control of the differences in infection exposure.[2,5,35-37] The

present study analyses were implemented on Qatar's total population, thus perhaps minimizing the likelihood of bias.

In relation to potential for bias, the observed hazard ratio of 0.52 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a risk ratio of 3.3-fold each, above and beyond the measured confounders, but weaker confounding could not do so. The confidence interval could be moved to include the null by an unmeasured confounder that was associated with both the exposure and the outcome by a risk ratio of 2.3-fold each, above and beyond the measured confounders, but weaker confounding could not do so.

More than two years into the COVID-19 pandemic, the global population carries heterogenous immune histories derived from various exposures to infection, viral variants, and vaccination, and at different times and orders.[23] This study investigated immune imprinting for specific immune histories related to natural infection. While we did not find evidence for immune imprinting compromising protection against Omicron subvariants, immune imprinting could still occur in other immune histories, involving natural immunity, vaccine immunity, or combination of both. Further investigation is needed to explore effects of all different possible immune histories on subsequent infection acquisition.

Section S2. Laboratory methods

Real-time reverse-transcription polymerase chain reaction testing

Nasopharyngeal and/or oropharyngeal swabs were collected for polymerase chain reaction (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 Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Rapid antigen testing

Severe acute respiratory syndrome coronavirus 2 (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 Coronavirus Disease 2019 (COVID-19) database.

Viral genome sequencing and 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 screening[39] of random positive clinical samples,[2,33,36,40-42] complemented by deep sequencing of wastewater samples.[33,43,44] 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.[1,2,7,9,10,33,34,36,40-42,45,46]

Section S3. COVID-19 severity, criticality, and fatality classification

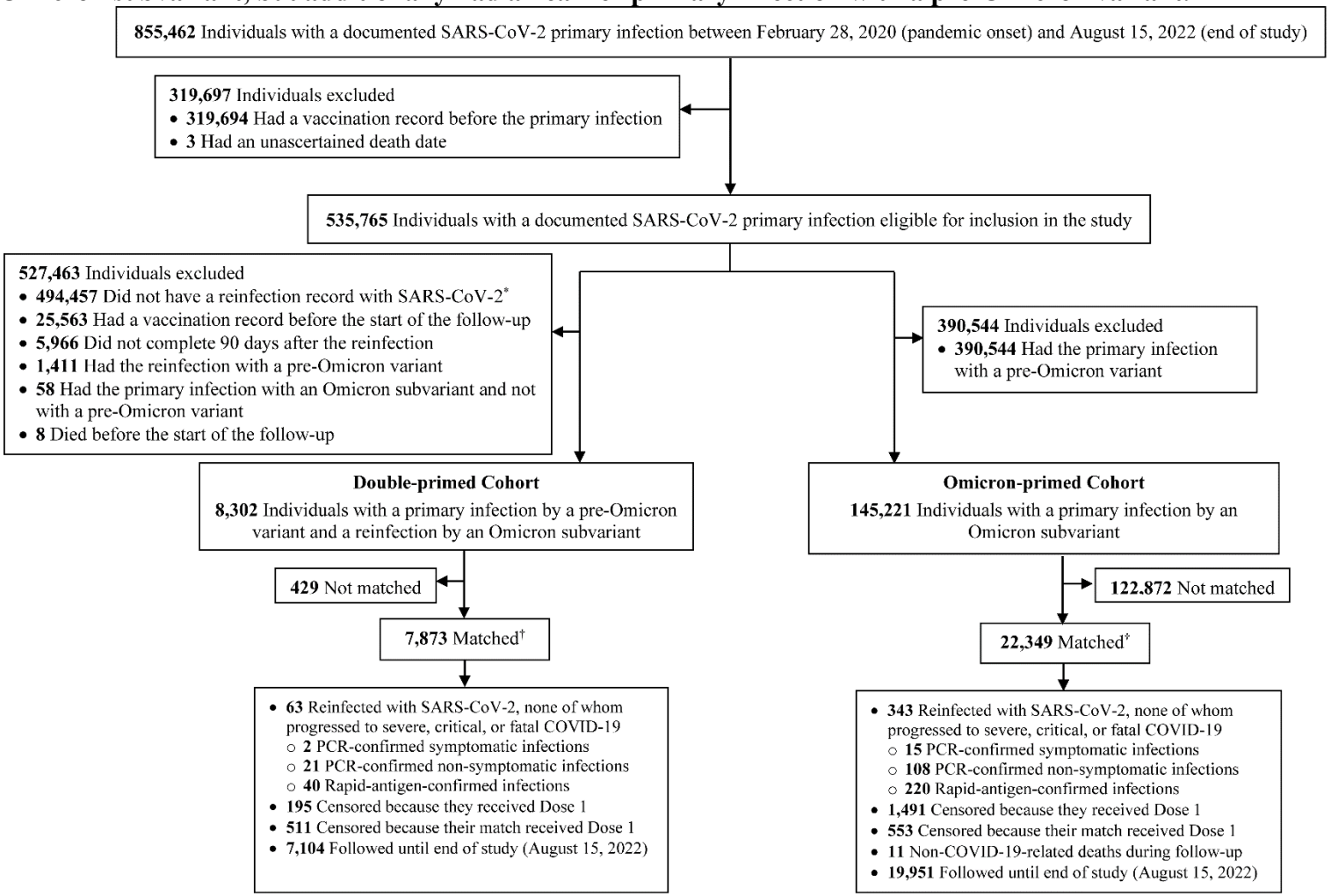
Classification of COVID-19 case severity (acute-care hospitalizations),[11] criticality (intensive-care-unit hospitalizations),[11] and fatality[12] followed World Health Organization (WHO) guidelines. Assessments were made by trained medical personnel independent of study investigators and using individual 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,[12] followed by critical disease,[11] and then severe disease.[11]

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)".[11] Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.[11]

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".[11] Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.[11]

COVID-19 death was defined per WHO classification as “a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19”. Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.[12]

Figure S1. Flowchart describing the population selection process for investigating immune protection against reinfection among those who were infected by an Omicron subvariant compared to protection among those who were infected by an Omicron subvariant, but additionally had an earlier primary infection with a pre-Omicron variant.



PCR denotes polymerase chain reaction and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
*A reinfection was defined as a positive SARS-CoV-2 test that is ≥90 days after the first positive test.
†Double-primed and Omicron-primed cohorts were exact-matched in a one-to-three ratio by sex, 10-year age group, nationality, and calendar week of reinfection (Double-primed cohort)/calendar week of primary infection (Omicron-primed cohort).

Table S1. Baseline characteristics of the eligible and matched cohorts.

Characteristics	Full eligible cohorts			Matched cohorts*		
	Double-primed cohort	Omicron-primed cohort	SMD†	Double-primed cohort	Omicron-primed cohort	SMD†
	N=8,302	N=145,221		N=7,873	N=22,349	
Median age (IQR)—years	23 (10-36)	22 (7-34)	0.14‡	21 (10-35)	19 (9-34)	0.07‡
Age group						
0-9 years	1,952 (23.5)	48,508 (33.4)		1,911 (24.3)	5,641 (25.2)	
10-19 years	1,972 (23.8)	20,908 (14.4)		1,910 (24.3)	5,549 (24.8)	
20-29 years	1,208 (14.6)	26,788 (18.5)		1,159 (14.7)	3,289 (14.7)	
30-39 years	1,651 (19.9)	27,960 (19.3)	0.32	1,574 (20.0)	4,423 (19.8)	0.04
40-49 years	892 (10.7)	12,954 (8.9)		811 (10.3)	2,185 (9.8)	
50-59 years	421 (5.1)	4,962 (3.4)		352 (4.5)	892 (4.0)	
60-69 years	149 (1.8)	2,070 (1.4)		113 (1.4)	261 (1.2)	
70+ years	57 (0.7)	1,071 (0.7)		43 (0.6)	109 (0.5)	
Sex						
Male	3,793 (45.7)	79,607 (54.8)	0.18	3,590 (45.6)	10,252 (45.9)	0.01
Female	4,509 (54.3)	65,614 (45.2)		4,283 (54.4)	12,097 (54.1)	
Nationality§						
Bangladeshi	78 (0.9)	2,722 (1.9)		71 (0.9)	189 (0.9)	
Egyptian	559 (6.7)	7,282 (5.0)		523 (6.6)	1,401 (6.3)	
Filipino	466 (5.6)	10,045 (6.9)		458 (5.8)	1,350 (6.0)	
Indian	703 (8.5)	29,726 (20.5)		700 (8.9)	2,050 (9.2)	
Nepalese	125 (1.5)	6,387 (4.4)	0.56	120 (1.5)	357 (1.6)	0.04
Pakistani	222 (2.7)	6,055 (4.2)		207 (2.6)	599 (2.7)	
Qatari	3,752 (45.2)	36,213 (24.9)		3,706 (47.1)	10,834 (48.5)	
Sri Lankan	57 (0.7)	2,415 (1.7)		53 (0.7)	146 (0.7)	
Sudanese	341 (4.1)	3,539 (2.4)		318 (4.0)	878 (3.9)	
Other nationalities¶	1,999 (24.1)	40,837 (28.1)		1,717 (21.8)	4,545 (20.3)	
Comorbidity count						
None	5,531 (66.6)	118,989 (81.9)		5,418 (68.8)	15,797 (70.7)	
1	1,788 (21.5)	18,869 (13.0)	0.37	1,648 (20.9)	4,559 (20.4)	0.05
2	579 (7.0)	4,804 (3.3)		494 (6.3)	1,242 (5.6)	
3+	404 (4.9)	2,559 (1.8)		313 (4.0)	751 (3.4)	

IQR denotes interquartile range and SMD standardized mean difference.

*Double-primed and Omicron-primed cohorts were exact-matched in a one-to-three ratio by sex, 10-year age group, nationality, and calendar week of reinfection (double-primed cohort)/calendar week of primary infection (Omicron-primed cohort).

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

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

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

¶These comprise up to 155 other nationalities in the unmatched cohorts and up to 56 other nationalities in the matched cohorts.

Table S2. Representativeness of study participants.

Category	
Disease, problem, or condition under investigation	Immune protection against reinfection among those who were reinfected by an Omicron-subvariant after an earlier pre-Omicron primary infection (double-primed cohort) versus protection among those infected with an Omicron-subvariant primary infection (Omicron-primed cohort).
Special considerations related to	
Sex and gender	A national, matched, retrospective cohort study was conducted to compare incidence of SARS-CoV-2 infection among individuals who were reinfected by an Omicron subvariant after an earlier pre-Omicron primary infection (double-primed cohort) to incidence among those who were infected by an Omicron-subvariant primary infection (Omicron-primed cohort). Cohorts were exact-matched in a one-to-three ratio by sex to control for potential differences in the risk of exposure to SARS-CoV-2 infection by sex.
Age	Cohorts were exact-matched in a one-to-three ratio by age to control for potential differences in the risk of exposure to SARS-CoV-2 infection by age.
Race or ethnicity group	Cohorts were exact-matched in a one-to-three ratio by nationality to control for potential differences in the risk of exposure to SARS-CoV-2 infection by nationality. Nationality is associated with race and ethnicity in the population of Qatar.
Geography	Individual-level data on geography were not available, but Qatar is essentially a city state and infection incidence was broadly distributed across the country's neighborhoods/areas. Cohorts were exact-matched by nationality to control for potential differences in the risk of exposure to SARS-CoV-2 infection by nationality. Qatar has unusually diverse demographics in that 89% of the population are international expatriate residents coming from over 150 countries from all world regions.
Other considerations	To ensure that matched individuals in both cohorts experience the same force of infection at all times, individuals who were reinfected by an Omicron subvariant in a specific week were matched to individuals who had a record of a primary infection with an Omicron subvariant in that same calendar week.
Overall representativeness of this study	The study was based on the total population of Qatar and thus the study population is broadly representative of the diverse, by national background, but young total population of Qatar. While there could be differences in the risk of exposure to SARS-CoV-2 infection by sex, age, nationality, and comorbidity count, cohorts were exact-matched by these factors to control for their potential impact on our estimates. With Qatar's young population and the young age of those that remained unvaccinated in our population, our findings may not be generalizable to older individuals or other countries where elderly citizens constitute a larger proportion of the total population.

Table S3. STROBE checklist for cohort studies.

	Item No	Recommendation	Main Text page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Letter page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Not applicable
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Letter page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Letter page 3 & Section S1 ('Study design')
Methods			
Study design	4	Present key elements of study design early in the paper	Letter page 3 & Section S1 ('Study design' & 'Cohort eligibility, matching, and follow-up')
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Letter page 3 & Section S1 ('Study design' & 'Cohort eligibility, matching, and follow-up')
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Section S1 ('Study design' & 'Cohort eligibility, matching, and follow-up') & Figure S1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Letter page 3 & Section S1 ('Study design' & 'Cohort eligibility, matching, and follow-up'), Figure 1, & Table S1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Sections S1-S3 & Table S1
Bias	9	Describe any efforts to address potential sources of bias	Letter page 3 & Section S1 ('Cohort eligibility, matching, and follow-up'& 'Statistical analysis', paragraph 2)
Study size	10	Explain how the study size was arrived at	Figure S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Section S1 ('Cohort eligibility, matching, and follow-up') & Table S1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Section S1 ('Statistical analysis')
		(*b*) Describe any methods used to examine subgroups and interactions	Section S1 ('Statistical analysis', paragraphs 2-3)
		(*c*) Explain how missing data were addressed	Not applicable, see Section S1 ('Study population and data sources')
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable, see Section S1 ('Study population and data sources')
		(*e*) Describe any sensitivity analyses	Section S1 ('Statistical analysis', paragraph 3)
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	Letter page 4 & Figure S1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table S1
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable, see Section S1 ('Study population and data sources')
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15	Report numbers of outcome events or summary measures over time	Letter page 4, Figure 1 & Figure S1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	Letter page 4 & Figure 1

		interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	Table S1
		(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 interactions, and sensitivity analyses	Letter page 4, Figure 1, & Section S1 ('Limitations' paragraphs 2, 6 and 12)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Letter page 4
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	Section S1 ('Limitations')
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Letter page 4
Generalisability	21	Discuss the generalisability (external validity) of the study results	Section S1 ('Limitations') & Table S2
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Letter page 7 & Acknowledgements in Supplementary Appendix

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