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Protection conferred by SARS-CoV-2 infection across a spectrum of reinfection symptoms and severities

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ABSTRACT

Background SARS-CoV-2 infection is associated with protection against reinfection. This study analysed this protection across different reinfection symptoms and severities, comparing the preomicron and omicron eras.

Methods A nationwide, matched, test-negative, case–control study was conducted in Qatar from 5 February 2020 to 12 March 2024. The preomicron analysis used a sample of 509 949 positive and 8 494 782 negative tests, while the omicron analysis included 682 257 positive and 6 904 044 negative tests. Data were sourced from Qatar's national databases for COVID-19 laboratory testing, vaccination, hospitalisation and death.

Results Effectiveness of preomicron infection against preomicron reinfection was estimated at 80.9% (95% CI: 79.1% to 82.6%) for asymptomatic reinfection, 87.5% (95% CI: 86.1% to 88.9%) for symptomatic reinfection, 97.8% (95% CI: 95.7% to 98.9%) for severe COVID-19 reinfection, 100.0% (95% CI: 97.5% to 100.0%) for critical COVID-19 reinfection and 88.1% (95% CI: 50.3% to 97.2%) for fatal COVID-19 reinfection. For omicron infection against omicron reinfection, the estimates were 46.4% (95% CI: 36.9% to 54.4%) for asymptomatic reinfection, 52.8% (95% CI: 44.4% to 60.0%) for symptomatic reinfection, 100.0% (95% CI: 55.4% to 100.0%) for severe COVID-19 reinfection, 100.0% (95% CI: 15.1% to 100.0%) for critical COVID-19 reinfection, and 75.2% (95% CI: −58.8% to 97.5%) for fatal COVID-19 reinfection. Effectiveness over time since previous infection showed no discernible decline in protection against all forms of reinfection in the preomicron era, but a rapid decline against asymptomatic and symptomatic reinfections in the omicron era.

Conclusions A gradient of protection against reinfection is evident, with the highest protection observed against severe forms of COVID-19. Over time, this gradient becomes more pronounced, as protection against asymptomatic and symptomatic reinfections decreases, while protection against severe outcomes remains strong.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vaccine-induced immunity offers varying degrees of protection against a spectrum of SARS-CoV-2 infection symptoms and severities. However, the extent to which this applies to natural immunity remains unclear.

WHAT THIS STUDY ADDS

⇒ A gradient in protection against SARS-CoV-2 reinfection is observed in Qatar's predominantly young population, with the lowest protection against asymptomatic reinfection and the highest against severe, critical and fatal reinfections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further clarification is needed on the roles of humoral and cellular immunity in driving observed protection patterns, with ongoing monitoring essential to adapt public health strategies to the evolving SARS-CoV-2 reinfection landscape.

INTRODUCTION

Reinfections have become a frequent occurrence in the epidemiology of SARS-CoV-2 infection.[1–3] This phenomenon resembles patterns observed for other respiratory infections, including common-cold coronaviruses[4 5] and influenza.[6–9] While a natural SARS-CoV-2 infection provides initially robust protection against reinfection,[10 11] this protection wanes over time.[1 3] The ongoing evolution of SARS-CoV-2 with immune evasion properties,[12–15] exemplified by the emergence of the omicron variant and its subvariants,[3 12–14 16–19] further contributes to the rising incidence of reinfections.[16 19–22]

We previously investigated the protection provided by COVID-19 mRNA vaccination

against a spectrum of SARS-CoV-2 infection symptoms and severities and also characterised the gradient in this protection over time.[23] Building on this work, the present study examines the protection conferred by natural immunity against a range of SARS-CoV-2 reinfection symptoms and severities. Natural immunity here refers to the protection acquired from a SARS-CoV-2 infection against reinfection, as well as against COVID-19-related hospitalisation and death on reinfection.

Specifically, the effectiveness of infection against reinfection was estimated for five outcomes: asymptomatic reinfection, symptomatic reinfection, severe[24] (acute care hospitalisation) COVID-19 at reinfection, critical[24] (intensive care unit hospitalisation) COVID-19 at reinfection and fatal[25] COVID-19 at reinfection. Given the major genomic changes in the virus between the preomicron and omicron eras, which led to substantial immune evasion and increased transmissibility,[12–14 16–18] the analysis was stratified by era. This stratification allowed us to estimate and compare the effectiveness of a preomicron infection in preventing reinfection with a preomicron virus versus the effectiveness of an omicron infection in preventing reinfection with an omicron virus.

METHODS

Study population and data sources

This study was conducted on Qatar's resident population before and after the emergence of the omicron variant on 19 December 2021[16] (online supplemental section S1 and online supplemental figure S1). The first analysis estimated the effectiveness of a preomicron infection in preventing reinfection with a preomicron virus from 5 February 2020 (start of the COVID-19 pandemic in Qatar)[26] until 18 December 2021 (end of the preomicron period). The second analysis estimated the effectiveness of an omicron infection in preventing reinfection with an omicron virus from 19 December 2021 (onset of the first omicron wave)[16] until 12 March 2024 (end of study).

Throughout the study period, Qatar experienced the circulation of SARS-CoV-2 alongside other respiratory viruses, such as influenza, with the patterns of these viruses changing substantially over time due to the non-pharmaceutical interventions implemented during the COVID-19 pandemic.[27 28]

Data were sourced from the integrated, nationwide, digital health information platforms, which include the national federated databases for COVID-19 laboratory testing, vaccination, hospitalisation and death (online supplemental section S2). These databases contain SARS-CoV-2-related data on testing, with no missing information since the beginning of the pandemic, encompassing all PCR tests regardless of location or facility (online supplemental section S3). Starting 5 January 2022, these databases also incorporated all medically supervised rapid antigen (RA) tests (online supplemental section S3).

Until 31 October 2022, SARS-CoV-2 testing in Qatar was conducted on a mass scale, with around 5% of the population being tested every week, primarily for routine purposes such as screening or meeting travel-related requirements.[29 30] Subsequently, testing rates decreased, with less than 1% of the population being tested per week.[31] Most infections detected throughout the pandemic were identified through routine testing rather than due to the presence of symptoms.[29 30]

In December 2020, Qatar initiated its COVID-19 vaccination campaign using mRNA vaccines, prioritising individuals based on coexisting health conditions and age.[29 32] Vaccination was tracked nationally and provided to all residents and citizens free of charge.[29 32] Demographic information, such as sex, age and nationality, was obtained from the national health registry records. Qatar has a unique demographic profile, with only 9% of its population aged 50 years or older and 89% of its residents being expatriates from more than 150 countries.[26] Detailed descriptions of Qatar's population and national databases have been reported previously.[26 29 30 33–36]

Study design

A matched, test-negative, case–control study design was employed to assess the effectiveness of SARS-CoV-2 infection against reinfection.[3 16 37–39] Cases and controls were identified based on SARS-CoV-2 testing within each analysis period. Individuals with positive tests were designated as cases, while those with negative tests were designated as controls. The odds of having a previous infection were then compared between cases and controls.[3 16 37–39]

The protection conferred by infection was estimated against five forms of reinfection: asymptomatic, symptomatic, severe[24] COVID-19, critical[24] COVID-19 and fatal[25] COVID-19. SARS-CoV-2 reinfection is conventionally defined as a documented infection occurring at least 90 days after a previous infection to distinguish true reinfections from potential cases of prolonged viral shedding.[40–42] Consistent with this definition, individuals with a positive SARS-CoV-2 test within the preceding 90 days were excluded from the analysis to avoid misclassifying cases of prolonged viral positivity as reinfections. The analysis was conducted over the entire study periods, as well as in 3-month intervals since the previous infection.

All PCR tests and a portion of the facility-based RA tests carried out in Qatar, irrespective of setting or location, are categorised based on symptoms and the reason for testing.[29 30] These categories include clinical suspicion, contact tracing, surveys or random testing campaigns, individual request, routine healthcare testing, pretravel, post-travel or other. This categorisation allowed differentiation between tests conducted due to asymptomatic or symptomatic infections.

Asymptomatic infection was defined as a positive PCR or RA test result obtained when the reason for testing was a survey, with no symptoms compatible with a respiratory tract infection reported. Conversely, symptomatic

infection was defined by a positive PCR or RA test prompted by the presence of symptoms consistent with a respiratory tract infection. Accordingly, only PCR or RA tests from surveys (asymptomatic) or those conducted due to clinical suspicion (symptomatic) were included in the respective analyses.

Classification of severe,[24] critical[24] and fatal[25] COVID-19 followed WHO guidelines (online supplemental section S4). Trained medical personnel, independent of the study investigators, reviewed individual medical records to determine severity.[43] As part of the national protocol, all individuals with a positive SARS-CoV-2 test and concurrent hospitalisation underwent infection severity assessments every 3 days until discharge or death, regardless of hospital stay duration or the time between the positive test and the final outcome.[43]

The severity assessment results were provided to the study investigators in the form of a database containing a categorical variable assessment. However, the database did not include detailed information used to determine severity, such as oxygen use and mechanical ventilation, which are available in the Cerner system that tracks all medical encounters within Qatar's public healthcare system but to which investigators do not have direct access. The categorical variable assessment is considered complete, as it was conducted in accordance with a national COVID-19 protocol for clinical assessment implemented across the entire public healthcare system.

Individuals experiencing progression to severe, critical or fatal COVID-19 during the follow-up period were classified based on their worst outcome, with death[25] being the highest severity, followed by critical[24] illness and then severe[24] illness.[43]

All cases and controls that met the inclusion criteria and could be matched were included in the analyses. The test-negative design helps mitigate potential confounding due to differential healthcare-seeking behaviour[3 37–39] by restricting the population to individuals who sought testing for documented reasons. This approach ensures comparability between cases and controls regarding their healthcare-seeking patterns. Consequently, only tests with a documented reason for testing were included in the analyses.

The test-negative design applied in this study is an extension of the original test-negative design commonly used in influenza vaccine effectiveness studies.[38 39] This extended design leverages the widespread testing conducted during the COVID-19 pandemic, where individuals were tested for various reasons, such as routine requirements, and has been thoroughly investigated and validated through numerous studies, sensitivity analyses, negative control outcomes and mathematical modelling simulations.[3 29 32 37 44–46] Importantly, cases and controls are exactly matched by the reason for testing and the testing method in this design. This exact matching minimises bias stemming from differential testing or healthcare-seeking behaviour.

For analyses specific to the omicron era, individuals with a documented preomicron infection were excluded to separately investigate the effects of preomicron and omicron immunities. For the analyses of asymptomatic and symptomatic reinfections, cases and controls were matched on a one-to-one ratio. In contrast, to enhance statistical precision due to the lower number of cases with severe outcomes, a one-to-five matching ratio was employed for analyses of severe,[24] critical[24] and fatal[25] COVID-19 reinfections.

Cases and controls were matched exactly on several factors to minimise the influence of confounding or mediating variables that might affect infection risk[26 47–50] and to ensure non-differential healthcare-seeking behaviour.[37–39] These factors, informed by our previous research in Qatar,[22 29 32 44 45 51] included sex, 10-year age group, nationality, the number of coexisting conditions (0 to ≥6; online supplemental section S5), the number of vaccine doses received by the time of the study (outcome) test (0 to ≥4), calendar week of testing, testing method (PCR or RA) and reason for testing. This exact matching approach ensured that each case–control pair shared identical values for all these variables and controlled for the effect of vaccination on infection risk between cases and controls.

This study aimed to compare the protective effect of infection against various forms of reinfection. However, waning immunity can bias such comparisons if the time between the previous infection and the study test differs across analyses. To address this potential bias, matched case–control pairs identified through surveys were subsequently matched by calendar week of testing to their counterparts identified through clinical suspicion. Only case–control pairs matched on both the initial criteria and this additional calendar week matching were included in the analyses. Consequently, the distributions of time from previous infection to the study test were similar in both asymptomatic and symptomatic reinfection analyses.

Statistical analysis

All SARS-CoV-2 testing records were reviewed to select cases and controls; however, only matched samples were analysed. Cases and controls were described using frequency distributions and measures of central tendency and compared using standardised mean differences (SMDs). An SMD of ≤0.1 indicated adequate matching.[52] The median and IQR for the time between the previous infection and the study test were calculated.

Conditional logistic regression was used to estimate ORs and their corresponding 95% CIs, comparing the odds of having a previous infection between cases and controls. The analysis considered the date of the most recent documented previous infection for each participant. Individuals with no documented previous infection served as the reference group for all comparisons. CIs were not adjusted for multiplicity, and interactions were not examined.

Table 1 Characteristics of the unmatched and matched cases and controls in samples used to estimate the effectiveness of a preomicron infection in preventing reinfection with a preomicron virus

	Unmatched sample			Matched sample		
	Cases	Controls		Cases†	Controls†	
Characteristics	N=430 196	N=8 286 336	SMD*	N=300 871	N=300 871	SMD*
Median age (IQR)—years	33 (25–41)	33 (25–41)	0.01‡	32 (25–39)	32 (25–39)	0.00‡
Age group—no. (%)						
<10 years	33 933 (7.9)	660 291 (8.0)	0.05	26 127 (8.7)	26 127 (8.7)	0.00
10–19 years	31 171 (7.2)	618 680 (7.5)		23 427 (7.8)	23 427 (7.8)	
20–29 years	96 989 (22.5)	1 881 353 (22.7)		71 434 (23.7)	71 434 (23.7)	
30–39 years	145 498 (33.8)	2 714 746 (32.8)		104 987 (34.9)	104 987 (34.9)	
40–49 years	79 480 (18.5)	1 471 382 (17.8)		52 451 (17.4)	52 451 (17.4)	
50–59 years	31 333 (7.3)	664 936 (8.0)		17 788 (5.9)	17 788 (5.9)	
60–69 years	9104 (2.1)	216 037 (2.6)		3863 (1.3)	3863 (1.3)	
70+ years	2688 (0.6)	58 911 (0.7)		794 (0.3)	794 (0.3)	
Sex						
Male	309 604 (72.0)	5 846 746 (70.6)	0.03	215 812 (71.7)	215 812 (71.7)	0.00
Female	120 592 (28.0)	2 439 590 (29.4)		85 059 (28.3)	85 059 (28.3)	
Nationality§						
Bangladeshi	36 752 (8.5)	468 018 (5.6)	0.29	23 170 (7.7)	23 170 (7.7)	0.00
Egyptian	23 583 (5.5)	425 667 (5.1)		16 150 (5.4)	16 150 (5.4)	
Filipino	38 642 (9.0)	500 249 (6.0)		29 362 (9.8)	29 362 (9.8)	
Indian	114 011 (26.5)	2 228 037 (26.9)		85 785 (28.5)	85 785 (28.5)	
Nepalese	46 690 (10.9)	584 670 (7.1)		31 212 (10.4)	31 212 (10.4)	
Pakistani	22 249 (5.2)	399 394 (4.8)		15 486 (5.1)	15 486 (5.1)	
Qatari	51 232 (11.9)	1 370 472 (16.5)		38 730 (12.9)	38 730 (12.9)	
Sri Lankan	13 850 (3.2)	186 190 (2.2)		9251 (3.1)	9251 (3.1)	
Sudanese	11 292 (2.6)	191 916 (2.3)		7735 (2.6)	7735 (2.6)	
Other nationalities¶	71 895 (16.7)	1 931 723 (23.3)		43 990 (14.6)	43 990 (14.6)	
Coexisting conditions						
0	341 326 (79.3)	6 728 125 (81.2)	0.05	251 878 (83.7)	251 878 (83.7)	0.00
1	49 504 (11.5)	841 617 (10.2)		30 545 (10.2)	30 545 (10.2)	
2	20 906 (4.9)	353 107 (4.3)		11 018 (3.7)	11 018 (3.7)	
3	8445 (2.0)	160 336 (1.9)		3650 (1.2)	3650 (1.2)	
4	4609 (1.1)	91 729 (1.1)		1738 (0.6)	1738 (0.6)	
5	2661 (0.6)	54 008 (0.7)		918 (0.3)	918 (0.3)	
6+	2745 (0.6)	57 414 (0.7)		1124 (0.4)	1124 (0.4)	
Vaccine doses**						
0	393 213 (91.4)	5 579 037 (67.3)	0.70	274 460 (91.2)	274 460 (91.2)	0.00
1	14 750 (3.4)	183 299 (2.2)		8743 (2.9)	8743 (2.9)	
2	21 974 (5.1)	2 462 022 (29.7)		17 526 (5.8)	17 526 (5.8)	
3	259 (0.1)	61 872 (0.7)		142 (0.0)	142 (0.0)	
4+	0 (0.0)	106 (0.0)		--	--	
Method of testing						
PCR	430 196 (100.0)	8 286 336 (100.0)	--	300 871 (100.0)	300 871 (100.0)	--
RA	--	--		--	--	
Reason for testing						

Continued

Table 1 Continued

Characteristics	Unmatched sample			Matched sample		
	Cases	Controls		Cases†	Controls†	
	N=430 196	N=8 286 336	SMD*	N=300 871	N=300 871	SMD*
Clinical suspicion	169 301 (39.4)	776 472 (9.4)	1.17	58 145 (19.3)	58 145 (19.3)	0.00
Contact tracing	80 509 (18.7)	470 961 (5.7)		73 143 (24.3)	73 143 (24.3)	
Port of entry	55 203 (12.8)	2 812 485 (33.9)		54 118 (18.0)	54 118 (18.0)	
Individual request	19 829 (4.6)	438 567 (5.3)		18 342 (6.1)	18 342 (6.1)	
Survey	62 689 (14.6)	1 570 226 (18.9)		58 145 (19.3)	58 145 (19.3)	
Healthcare routine testing	23 492 (5.5)	304 119 (3.7)		21 937 (7.3)	21 937 (7.3)	
Pretravel	10 664 (2.5)	1 791 856 (21.6)		10 048 (3.3)	10 048 (3.3)	
Postantibody	9 (0.0)	755 (0.0)		1 (0.0)	1 (0.0)	
Other	8500 (2.0)	120 895 (1.5)		6992 (2.3)	6992 (2.3)	

*SMD is the difference in the mean of a covariate between groups divided by the pooled SD. An SMD of ≤0.1 indicates adequate matching.
†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, the number of coexisting conditions, the 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 for the mean difference between groups divided by the pooled SD.
§Nationalities were chosen to represent the most populous groups in Qatar.
¶These comprise up to 184 and 127 other nationalities in Qatar in the unmatched and matched samples, respectively.
**Ascertained at the time of the SARS-CoV-2 test.
RA, rapid antigen; SMD, standardised mean difference.

Based on the test-negative study design, effectiveness and corresponding 95% CIs were calculated as 1–OR of previous infection among cases versus controls if the OR was ≤1[37] and as (1/OR)−1 if the OR was >1.[35 53] This method ensures a symmetric scale for both negative and positive effectiveness, ranging from −100% to 100%.[35 53] In instances where conditional logistic regression failed to converge due to zero events among exposed cases, the 95% CIs were obtained using McNemar's test. This approach provides only an approximate estimate of the CIs in these specific situations, following a method used in earlier studies.[23 54]

The effectiveness by time since previous infection was also assessed in 3-month intervals by restricting the study samples to cases and controls with a previous infection falling within the specified 3-month time-interval categories. Subgroup analyses were also performed, restricting the study sample to vaccinated and unvaccinated individuals separately. Statistical analyses were conducted using STATA/SE software V.18.0 (StataCorp).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Study populations

Online supplemental figures S2 and S3 illustrate the study population selection process for estimating the protection of a preomicron infection in preventing reinfection with a preomicron virus and of an omicron infection in preventing reinfection with an omicron virus, respectively.

Table 1 describes the characteristics of the unmatched and matched study samples for the preomicron period, while online supplemental table S1 presents the same information for the omicron period. The study was conducted on the entire population of Qatar, reflecting the country's internationally diverse but predominantly young and male population.

Protection of preomicron infection against preomicron reinfection

The effectiveness of a preomicron infection in preventing asymptomatic and symptomatic reinfections with a preomicron virus was 80.9% (95% CI: 79.1% to 82.6%) and 87.5% (95% CI: 86.1% to 88.9%), respectively (table 2 and figure 1A). The median time between the previous infection and the study test was 236.5 days (IQR: 164–301.5 days) for asymptomatic reinfection and 249 days (IQR: 179–302 days) for symptomatic reinfection.

Table 2 Effectiveness of (A) a preomicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with a preomicron virus and (B) an omicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with an omicron virus

Effectiveness of	Cases (SARS-CoV-2-positive tests)		Controls (SARS-CoV-2-negative tests)		
	Previous infection (n)	No previous infection (n)	Previous infection (n)	No previous infection (n)	Effectiveness* in % (95% CI)†
(A) A preomicron infection against reinfection with a preomicron virus					
Asymptomatic infection‡§	658	57 487	3086	55 059	80.9 (79.1 to 82.6)
Symptomatic infection‡¶	381	57 764	2835	55 310	87.5 (86.1 to 88.9)
Severe COVID-19 infection**	9	7917	1356	31 829	97.8 (95.7 to 98.9)
Critical COVID-19 infection**	0	1055	149	4049	100.0 (97.5 to 100.0)††
Fatal COVID-19 infection**	2	397	50	1365	88.1 (50.3 to 97.2)
(B) An omicron infection against reinfection with an omicron virus					
Asymptomatic infection‡§	398	23 927	591	23 734	46.4 (36.9 to 54.4)
Symptomatic infection‡¶	330	23 995	564	23 761	52.8 (44.4 to 60.0)
Severe COVID-19 infection**	0	155	10	465	100.0 (55.4 to 100.0)††
Critical COVID-19 infection**	0	44	6	133	100.0 (15.1 to 100.0)††
Fatal COVID-19 infection**	1	23	6	58	75.2 (–58.8 to 97.5)

*Effectiveness of infection in preventing reinfection was estimated using the test-negative, case–control study design.
†CIs were not adjusted for multiplicity and thus should not be used to infer definitive differences between different groups.
‡Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, the number of coexisting conditions, the 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.
§Asymptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test result obtained when the reason for testing was a survey, with no symptoms compatible with a respiratory tract infection reported.
¶Symptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test prompted by 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, the number of coexisting conditions, the 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. Severity, criticality and fatality were defined according to the WHO guidelines.
††The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases.
RA, rapid antigen.

The effectiveness of a preomicron infection in preventing each of severe, critical and fatal COVID-19 reinfections with a preomicron virus showed all very high effectiveness at nearly 100% (table 2 and figure 1A). However, estimates for fatal COVID-19 reinfection lacked sufficient statistical precision due to the small number of cases.

The effectiveness by time since previous infection showed no discernible decline in protection over time against all forms of reinfection (table 3). Similar patterns of effectiveness were observed among vaccinated and unvaccinated individuals (online supplemental figure S4).

Protection of omicron infection against omicron reinfection

The effectiveness of an omicron infection in preventing asymptomatic and symptomatic reinfections with an omicron virus was 46.4% (95% CI: 36.9% to 54.4%) and 52.8% (95% CI: 44.4% to 60.0%), respectively (table 2 and figure 1B). The median time between the previous infection and the study test was 255 days (IQR: 197–299 days) for asymptomatic reinfection and 272 days (IQR: 194–305 days) for symptomatic reinfection.

The effectiveness of an omicron infection in preventing each of severe and critical COVID-19 reinfections with an omicron virus was 100%, as no cases of severe or critical COVID-19 were observed among those with a previous infection (table 2 and figure 1B). However, these effectiveness measures, along with the one against fatal COVID-19, lacked statistical precision due to the small number of cases.

The effectiveness by time since previous infection showed a rapid decline in protection over time against asymptomatic and symptomatic reinfections (table 4). Effectiveness was highest within three to less than 6 months after infection (>80%) but dropped to negligible levels by 1 year or more after the previous infection. While the effectiveness against each of severe, critical and fatal COVID-19 reinfections appeared to remain very high across time intervals, the small number of cases in

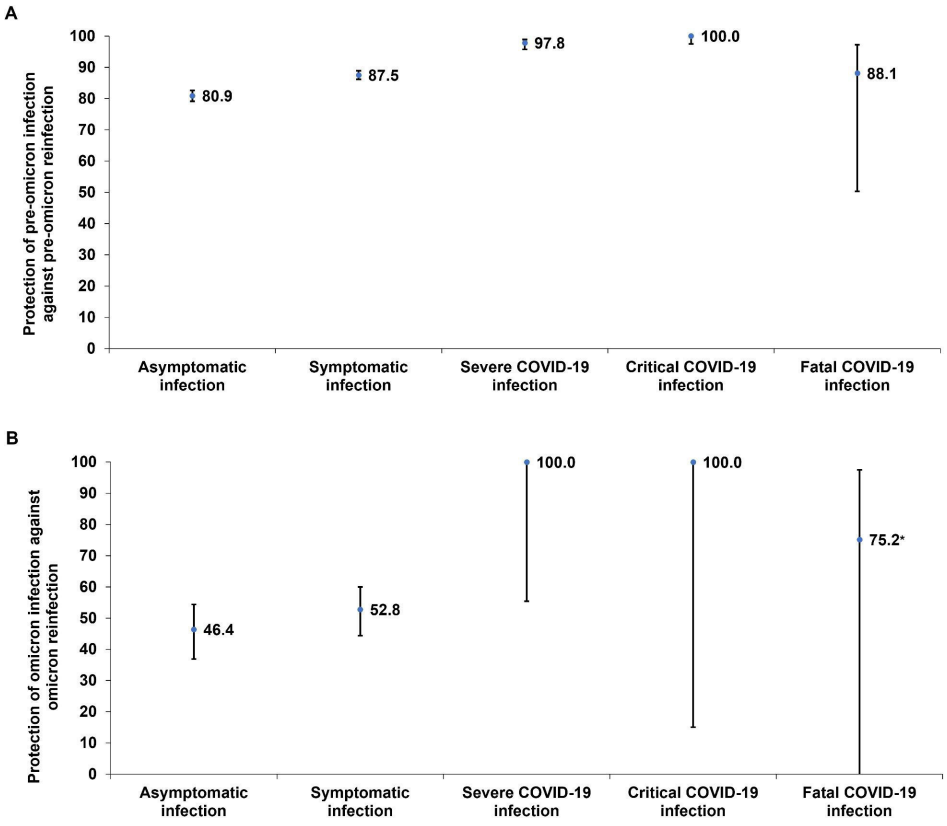

Figure 1 Effectiveness of (A) a preomicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with a preomicron virus and (B) an omicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with an omicron virus. Data are presented as effectiveness point estimates. Error bars indicate the corresponding 95% CIs. *The negative lower bound for the CI was truncated because the CI was too wide. COVID-19, coronavirus disease 2019.

these categories limited the statistical precision of these estimates. Similar patterns of effectiveness were observed among vaccinated and unvaccinated individuals (online supplemental figure S4).

DISCUSSION

The study's results suggest distinct patterns for SARS-CoV-2 natural immunity. First, a gradient in effectiveness against reinfection is observed based on the severity and presence of symptoms, with higher protection corresponding to more symptomatic and severe reinfections. The lowest protection was against asymptomatic reinfection, while the highest protection was against severe forms of COVID-19 at reinfection. Second, this gradient in immune protection becomes more pronounced over time after the previous infection. While protection against asymptomatic or symptomatic reinfections can wane over time, particularly for omicron immunity against omicron reinfection,[3] protection against severe forms of reinfection appears to remain robust. Third, the results indicate modest differences in protection levels against each of severe, critical and fatal COVID-19 reinfections.

Remarkably, the observed patterns for natural immunity mirror those documented for vaccine-induced immunity,[23] suggesting that these are generic features of SARS-CoV-2 immunity, regardless of whether it is acquired through infection or vaccination. These patterns may reflect the distinct roles played by different components of the immune system. Protection against asymptomatic or symptomatic infections appears to be primarily driven by humoral immunity, specifically the presence of neutralising antibodies that prevent the virus from entering cells.[55–58] However, these antibodies decline over time,[55 59 60] potentially leading to waning protection against asymptomatic and symptomatic reinfections. Meanwhile, cellular immunity,[61] particularly the generation of memory T cells, provides more enduring protection against severe outcomes.[62 63] Although these cells may not prevent the initial establishment of infection, they can rapidly respond to it, substantially mitigating the likelihood of severe infection in individuals with prior immunity, whether acquired through infection or vaccination.[62 63]

This study has limitations. While the study relied on documented SARS-CoV-2 infections, it is certain that some infections were never documented. However, this is not likely to materially impact the estimates, as our previous analyses and their recent updates have demonstrated that even substantial misclassification of prior infection status has minimal influence on the estimated

Table 3 Effectiveness at 3-month intervals since the time of previous infection for a preomicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with a preomicron virus

	Cases		Controls		
Effectiveness of	Previous infection (n)	No previous infection (n)	Previous infection (n)	No previous infection (n)	Effectiveness* in % (95% CI)†
3 months to <6 months since previous infection					
Asymptomatic infection‡§	232	57 351	940	56 643	76.0 (72.3 to 79.3)
Symptomatic infection‡¶	106	57 477	693	56 890	84.9 (81.5 to 87.8)
Severe COVID-19 infection**	3	7857	322	32 518	95.5 (89.1 to 98.9)
Critical COVID-19 infection**	0	1049	39	4120	100.0 (90.1 to 100.0)††
Fatal COVID-19 infection**	1	395	10	1385	71.4 (–57.6 to 96.5)
6 months to <9 months since previous infection					
Asymptomatic infection‡§	143	57 395	1170	56 368	87.9 (85.6 to 89.9)
Symptomatic infection‡¶	108	57 430	1003	56 535	89.7 (87.4 to 91.6)
Severe COVID-19 infection**	3	7864	459	32 424	97.5 (92.3 to 99.2)
Critical COVID-19 infection**	0	1049	50	4111	100.0 (92.3 to 100.0)††
Fatal COVID-19 infection**	0	396	15	1383	100.0 (72.1 to 100.0)††
9 months to <1 year since previous infection					
Asymptomatic infection‡§	209	57 382	889	56 702	78.1 (74.4 to 81.2)
Symptomatic infection‡¶	135	57 456	816	56 775	83.8 (80.5 to 86.5)
Severe COVID-19 infection**	3	7873	520	32 382	97.8 (93.2 to 99.3)
Critical COVID-19 infection**	0	1048	61	4098	100.0 (93.8 to 100.0)††
Fatal COVID-19 infection**	1	396	28	1369	88.9 (17.0 to 98.5)
≥1 year since previous infection					
Asymptomatic infection‡§	71	57 360	269	57 162	74.7 (66.9 to 80.7)
Symptomatic infection‡¶	30	57 401	310	57 121	90.3 (85.9 to 93.3)
Severe COVID-19 infection**	0	7841	49	32 692	100.0 (92.2 to 100.0)††
Critical COVID-19 infection**	0	8	1047	4138	100.0 (99.6 to 100.0)††
Fatal COVID-19 infection**	0	395	0	1389	Omitted‡‡

*Effectiveness of infection in preventing reinfection was estimated using the test-negative, case–control study design.
†CIs were not adjusted for multiplicity and thus should not be used to infer definitive differences between different groups.
‡Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, the 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.
§Asymptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test result obtained when the reason for testing was a survey, with no symptoms compatible with a respiratory tract infection reported.
¶Symptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test prompted by the presence of symptoms consistent with a respiratory tract infection.
**Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-five by sex, 10-year age group, nationality, the number of coexisting conditions, the 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. Severity, criticality and fatality were defined according to the WHO guidelines.
††The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases.
‡‡Effectiveness could not be estimated as there were no previous infections among both cases and controls.
RA, rapid antigen.

effectiveness of infection against reinfection.[3 37] This robustness is an advantage of the test-negative study design.[3 37] Furthermore, a recently completed analysis assessed the effectiveness of infection against reinfection using two distinct study designs—a test-negative design and a cohort study design—applied to the same datasets.[3] The findings from the cohort study design corroborated and validated those obtained through the test-negative design.[3]

In the preomicron era, the effectiveness against asymptomatic and symptomatic reinfections appeared slightly higher 6 to less than 9 months after the previous infection compared with 3 to less than 6 months. This seemingly counterintuitive result can be explained by the rare

Table 4 Effectiveness at 3-month intervals since the time of previous infection for an omicron infection in preventing asymptomatic, symptomatic, severe COVID-19, critical COVID-19 and fatal COVID-19 reinfections with an omicron virus

	Cases		Controls		
Effectiveness of	Previous infection (n)	No previous infection (n)	Previous infection (n)	No previous infection (n)	Effectiveness* in % (95% CI)†
3 months to <6 months since previous infection					
Asymptomatic infection‡§	34	23 849	145	23 738	81.0 (71.1 to 87.5)
Symptomatic infection‡¶	28	23 855	128	23 755	84.7 (75.0 to 90.7)
Severe COVID-19 infection**	0	152	3	467	100.0 (–58.7 to 100.0)††
Critical COVID-19 infection**	0	42	1	133	100.0 (–97.4 to 100.0)††
Fatal COVID-19 infection**	0	22	3	56	100.0 (–97.4 to 100.0)††
6 months to <9 months since previous infection					
Asymptomatic infection‡§	161	23 856	263	23 754	48.8 (35.3 to 59.4)
Symptomatic infection‡¶	90	23 927	193	23 824	62.8 (50.1 to 72.3)
Severe COVID-19 infection**	0	153	3	468	100.0 (–58.7 to 100.0)††
Critical COVID-19 infection**	0	41	0	133	Omitted‡‡
Fatal COVID-19 infection**	0	20	0	56	Omitted‡‡
9 months to <1 year since previous infection					
Asymptomatic infection‡§	171	23 857	170	23 858	–0.8 (–23.0 to 21.7)
Symptomatic infection‡¶	175	23 853	247	23 781	38.9 (22.8 to 51.7)
Severe COVID-19 infection**	0	153	2	468	100.0 (–81.2 to 100.0)††
Critical COVID-19 infection**	0	42	1	133	100.0 (–97.4 to 100.0)††
Fatal COVID-19 infection**	0	20	0	56	Omitted‡‡
≥1 year since previous infection					
Asymptomatic infection‡§	23	23 796	22	23 797	–12.5 (–68.3 to 58.6)
Symptomatic infection‡¶	9	23 810	11	23 808	28.6 (–55.6 to 77.3)
Severe COVID-19 infection**	0	153	2	469	100.0 (–81.2 to 100.0)††
Critical COVID-19 infection**	0	43	3	133	100.0 (–58.7 to 100.0)††
Fatal COVID-19 infection**	1	21	3	58	18.4 (–92.4 to 95.0)

*Effectiveness of infection in preventing reinfection was estimated using the test-negative, case–control study design.
†CIs were not adjusted for multiplicity and thus should not be used to infer definitive differences between different groups.
‡Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-one by sex, 10-year age group, nationality, the number of coexisting conditions, the 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.
§Asymptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test result obtained when the reason for testing was a survey, with no symptoms compatible with a respiratory tract infection reported.
¶Symptomatic infection was defined as a positive SARS-CoV-2 PCR or RA test prompted by the presence of symptoms consistent with a respiratory tract infection.
**Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-five by sex, 10-year age group, nationality, the number of coexisting conditions, the 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. Severity, criticality and fatality were defined according to the WHO guidelines.
††The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases.
‡‡Effectiveness could not be estimated as there were no previous infections among both cases and controls.
RA, rapid antigen.

occurrence of prolonged PCR positivity in a few cases,[64] where individuals still tested positive for over 90 days after their infection. This misclassification of prolonged positivity as reinfection underestimates effectiveness 3 to less than 6 months after the previous infection.

Given Qatar's relatively young population,[26] our results may not be generalisable to regions with a high proportion of elderly individuals. While a robust matching method was employed, limitations in data availability prevented matching based on factors such as geography or occupation. However, as a city-state, Qatar exhibited relatively consistent infection rates across neighbourhoods. Additionally, considering nationality, age and sex as strong socioeconomic indicators in Qatar,[26 47–50] matching based on these factors may have partially controlled for unmeasured variables like occupation.

This matching strategy, validated in previous studies with diverse epidemiological designs and using control groups to test for null effects,[29 32 44–46] has been shown to effectively mitigate differences in infection exposure between study groups.[29 32 44–46]

However, real-world data can harbour biases from unforeseen or unexpected sources. These biases may stem from variations in test-seeking behaviour, changes in testing patterns due to evolving policies, differences in test accessibility and disparities in the likelihood of being tested between individuals who have previously recovered from an infection and those who have never been infected or lack documentation of a past infection.

Despite the large study population and the use of national-level data, the relatively low number of critical and fatal COVID-19 infections limited the statistical precision of certain estimates, particularly in the omicron era. The study focused on characterising the protection conferred by natural immunity against a spectrum of SARS-CoV-2 infection symptoms and severities, independent of other aspects of immune history. It did not investigate the interactions between vaccine-induced and natural immunity, a complex phenomenon influenced by factors such as vaccine type, number of doses, infection variant, the order and timing of sequential immunological exposures and the variant of infection challenge, among other variables.[30 35 65–67]

This study has strengths. First, it was conducted at a national level, involving a diverse population with nearly 89% of the residents being expatriates from over 150 countries.[26] Second, the study used comprehensive and validated databases established through numerous SARS-CoV-2 infection studies. Third, the control group was drawn from the entire national population, with a robust matching method implemented to ensure accurate pairing of cases and controls. Finally, the study design leveraged the advantages of the test-negative design and controlled for vaccination status, enabling a clear distinction between the effects of previous infection and vaccination.

In conclusion, this study observed distinct patterns in SARS-CoV-2 natural immunity. A gradient of protection against reinfection was observed, with the highest effectiveness against severe forms of COVID-19. This gradient becomes more pronounced over time, with protection against asymptomatic and symptomatic reinfections waning, while protection against severe outcomes remains robust. These findings mirror observations for vaccine-induced immunity, suggesting these patterns may be fundamental to SARS-CoV-2 immunity regardless of the source of immune response. The differential roles of humoral and cellular immunity may underpin these patterns, with neutralising antibodies primarily driving protection against asymptomatic and symptomatic infections, and memory T cells providing enduring defence against severe outcomes. Continuous monitoring and updating of public health strategies are warranted to adapt to the evolving landscape of protection against SARS-CoV-2 reinfections.

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