

Rapid Communication

Protection of natural infection against reinfection with SARS-CoV-2 JN.1 variant

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Evidence at the level of neutralizing antibodies suggests that the SARS-CoV-2 JN.1 variant demonstrates increased immune evasion compared to its parent lineage BA.2.86 and to recently circulating variants, such as XBB.1.5 and EG.5.1.¹ JN.1 has also exhibited a growth advantage over other variants and triggered large SARS-CoV-2 waves in various countries,² prompting the World Health Organization to classify it as a variant of interest on 19 December 2023.² We estimated the effectiveness of natural infection in preventing reinfection with JN.1 during a large JN.1 wave in Qatar using the test-negative case-control study design.^{3,4}

Qatar's national COVID-19 databases were analysed between 4 December 2023, when JN.1 dominated incidence (Fig. S1 of the Supplementary Appendix), and 12 February 2024. These databases encompass all laboratory and medically supervised SARS-CoV-2 testing, infection clinical outcomes, COVID-19 vaccination and demographic details within the country (Sections S1-S2).

Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-two by factors

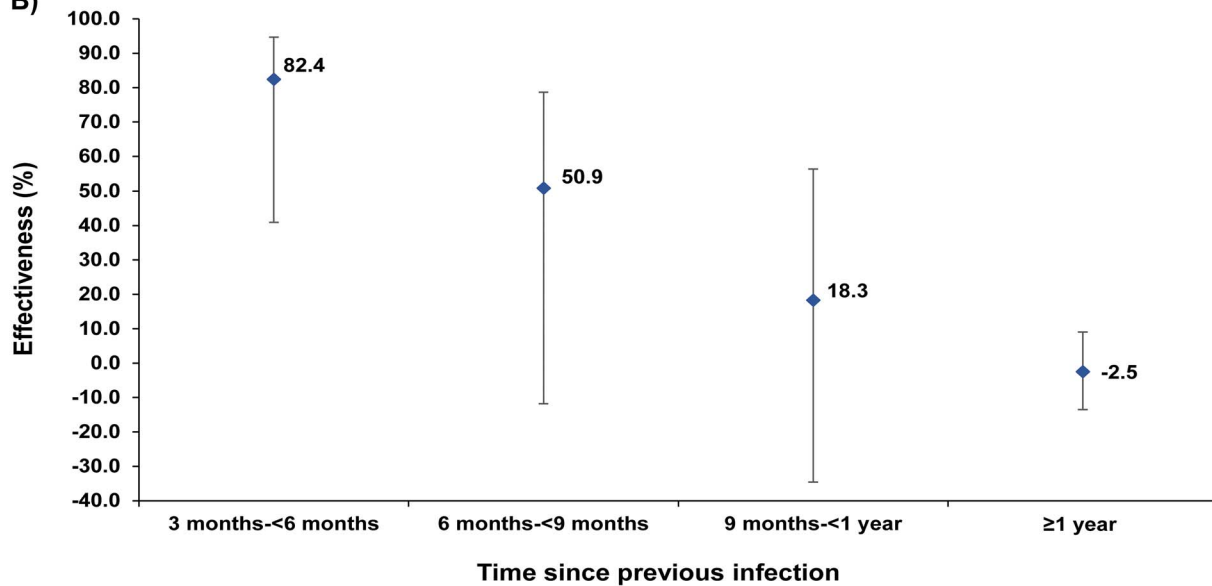
that could influence the risk of infection, including sex, 10-year age group, nationality, number of coexisting conditions, number of vaccine doses, calendar week of the SARS-CoV-2 test, method of testing (polymerase chain reaction versus rapid antigen) and reason for testing (Section S3). Previous infection was defined as a SARS-CoV-2-positive test ≥ 90 days before the study test. Subgroup analyses estimating effectiveness against specifically symptomatic reinfection, and by vaccination status, were conducted.

Figure S2 and Table S1, respectively, show the study population selection process and characteristics. The overall effectiveness of previous infection in preventing reinfection with JN.1, regardless of symptoms, was estimated at 1.8% (95% CI: -9.3 to 12.6%) (Fig. 1). This effectiveness demonstrated a rapid decline over time since the previous infection, decreasing from 82.4% (95% CI: 40.9 to 94.7%) within 3 to less than 6 months after the previous infection to 50.9% (95% CI: -11.8 to 78.7%) in the subsequent 3 months, and further dropping to 18.3% (95% CI: -34.6 to 56.3) in the subsequent 3 months. Ultimately, it reached a negligible level after one year. The effectiveness was

A)

Effectiveness against reinfection	Cases*		Controls*		Effectiveness† in % (95% CI)‡
	Previous infection (n)	No previous infection (n)	Previous infection (n)	No previous infection (n)	
Any previous infection	1,158	1,571	1,634	2,368	1.8 (-9.3 to 12.6)
By time since previous infection					
Subgroup analysis 1					
3 months§-<6 months	3	1,195	24	1,925	82.4 (40.9 to 94.7)
6 months-<9 months	8	1,197	26	1,934	50.9 (-11.8 to 78.7)
9 months-<1 year	19	1,203	35	1,944	18.3 (-34.6 to 56.3)
≥1 year	1,066	1,545	1,468	2,352	-2.5 (-13.5 to 9.0)
Subgroup analysis 2					
<1 year	37	1,227	96	1,958	49.1 (20.4 to 67.5)
≥1 year	1,066	1,545	1,468	2,352	-2.5 (-13.5 to 9.0)

B)



CI denotes confidence interval, PCR polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

*Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were matched exactly one-to-two by sex, 10-year age group, nationality, number of coexisting conditions (ranging from 0 to ≥6), number of vaccine doses at time of the SARS-CoV-2 test (ranging from 0 to ≥4), calendar week of the SARS-CoV-2 test, method of testing (PCR or rapid antigen), and reason for testing.

†Effectiveness of previous infection in preventing reinfection was estimated using the test-negative, case-control study design.³

‡CIs were not adjusted for multiplicity and thus should not be used to infer definitive differences between different groups.

§Individuals with a record for a SARS-CoV-2 test within 90 days were excluded from the analysis.

Figure 1 Protection against reinfection with JN.1, irrespective of symptoms, overall (A) and by time since previous infection (A and B)

estimated at 49.1% (95% CI: 20.4 to 67.5%) during the first year and at -2.5% (95% CI: -13.5 to 9.0%) thereafter.

The effectiveness against symptomatic reinfection with JN.1 demonstrated a similar pattern to that observed for any reinfection (Table S2). The overall effectiveness against symptomatic reinfection was -2.3% (95% CI: -14.4 to 10.3%). Subgroup analyses for unvaccinated and vaccinated individuals yielded results similar to those of the main analysis (Table S2). Limitations are discussed in Section S3. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table S3).

The protection of natural infection against reinfection was strong among those who were infected within the last 6 months, with variants such as XBB*. However, this protection waned rapidly and was entirely lost one year after the previous infection. These findings support a considerable immune evasion by JN.1, and that this immune evasion led to the observed rapid waning of the protection against JN.1 (Fig. 1), a pattern for the effect of

immune evasion first characterized for SARS-CoV-2 following the omicron variant emergence at the end of 2021.^{4,5}

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Author contributions

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Data availability

The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. The data are available under restricted access for preservation of confidentiality of patient data. Access can be obtained through a direct application for data access to Her Excellency the Minister of Public Health (<https://www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-HealthCommunication-Center.aspx>). The raw data are protected and are not available due to data privacy laws. Aggregate data are available within the paper and its supplementary information.

References

1. Yang S, Yu Y, Xu Y *et al.* Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressure. *Lancet Infect Dis* 2024; **24**: e70–2.
2. World Health Organization. *Executive Summary Initial Risk Evaluation of JN.1*. 2023. https://www.who.int/docs/default-source/coronaviruse/18122023_jn.1_ire_clean.pdf?sfvrsn=6103754a_3 (31 January 2024, date last accessed).
3. Ayoub HH, Tomy M, Chemaitelly H *et al.* Estimating protection afforded by prior infection in preventing reinfection: applying the test-negative study design. *Am J Epidemiol* 2023;kwad239. <https://doi.org/10.1093/aje/kwad239>.
4. Chemaitelly H, Tang P, Coyle P *et al.* Protection against reinfection with the omicron BA.2.75 subvariant. *N Engl J Med* 2023; **388**: 665–7.
5. Chemaitelly H, Nagelkerke N, Ayoub HH *et al.* Duration of immune protection of SARS-CoV-2 natural infection against reinfection. *J Travel Med* 2022; **29**:taac109. <https://doi.org/10.1093/jtm/taac109>.