Short- and longer-term all-cause mortality among SARS-CoV-2-infected individuals and the pull-forward phenomenon in Qatar: a national cohort study ☆

Hiam Chemaitelly [1,2,3], Jeremy Samuel Faust [4], Harlan M. Krumholz [5], Houssein H. Ayoub [6], Patrick Tang [7], Peter Coyle [8,9,10], Hadi M. Yassine [9,11], Asmaa A. Al Thani [9,11], Hebah A. Al-Khatib [9,11], Mohammad R. Hasan [7], Zaina Al-Kanaani [8], Einas Al-Kuwari [8], Andrew Jeremijenko [8], Anvar Hassan Kaleeckal [8], Ali Nizar Latif [8], Riyazuddin Mohammad Shaik [8], Hanan F. Abdul-Rahim [12], Gheyath K. Nasrallah [9,11], Mohamed Ghaith Al-Kuwari [13], Adeel A. Butt [4,8,14], Hamad Eid Al-Romaihi [15], Mohamed H. Al-Thani [15], Abdullatif Al-Khal [8], Roberto Bertollini [15], Laith J. Abu-Raddad [1,2,3,12,16],*

[1] Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar
[2] World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine–Qatar, Cornell University, Qatar Foundation – Education City, Doha, Qatar
[3] Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, New York, New York, USA
[4] Department of Emergency Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
[5] Center for Outcomes Research and Evaluation, Yale University School of Medicine, New Haven, Connecticut
[6] Mathematics Program, Department of Mathematics, Statistics, and Physics, College of Arts and Sciences, Qatar University, Doha, Qatar
[7] Department of Pathology, Sidra Medicine, Doha, Qatar
[8] Hamad Medical Corporation, Doha, Qatar
[9] Biomedical Research Center, QU Health, Qatar University, Doha, Qatar
[10] Wellcome-Wolfson Institute for Experimental Medicine, Queens University, Belfast, UK
[11] Department of Biomedical Science, College of Health Sciences, QU Health, Qatar University, Doha, Qatar
[12] Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar
[13] Primary Health Care Corporation, Doha, Qatar
[14] Department of Medicine, Weill Cornell Medicine, Cornell University, New York, New York, USA
[15] Ministry of Public Health, Doha, Qatar
[16] College of Health and Life Sciences, Hamad bin Khalifa University, Doha, Qatar

A R T I C L E   I N F O

A B S T R A C T

Objectives: We assessed short-, medium-, and long-term all-cause mortality risks after a primary SARS-CoV-2 infection.
Methods: A national, matched, retrospective cohort study was conducted in Qatar to assess risk of all-cause mortality in the national SARS-CoV-2 primary infection cohort compared with the national infection-naïve cohort. Associations were estimated using Cox proportional-hazards regression models. Analyses were stratified by vaccination status and clinical vulnerability status.
Results: Among unvaccinated persons, within 90 days after primary infection, the adjusted hazard ratio (aHR) comparing mortality incidence in the primary-infection cohort with the infection-naïve cohort was 1.19 (95% confidence interval 1.02-1.39). aHR was 1.34 (1.11-1.63) in persons more clinically vulnerable to severe COVID-19 and 0.94 (0.72-1.24) in those less clinically vulnerable. Beyond 90 days after primary infection, aHR was 0.50 (0.37-0.68); aHR was 0.41 (0.28-0.58) at 3-7 months and 0.76 (0.46-1.26) at ≥8 months. The aHR was 0.37 (0.25-0.54) in more clinically vulnerable persons and 0.77 (0.48-1.24) in

☆ Drs. Chemaitelly and Faust contributed equally.

* Corresponding author.
E-mail address: lja2002@qatar-med.cornell.edu (L.J. Abu-Raddad).

less clinically vulnerable persons. Among vaccinated persons, mortality incidence was comparable in the primary-infection versus infection-naïve cohorts, regardless of clinical vulnerability status.

Conclusions: COVID-19 mortality was primarily driven by an accelerated onset of death among individuals who were already vulnerable to all-cause mortality, but vaccination prevented these accelerated deaths.

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Introduction

SARS-CoV-2 infection causes mortality [1]. These deaths may occur because of factors related to the virus, the host, and available vaccinations and treatments. For example, death from COVID-19 may occur because of the infection's capacity to cause harm that results in death in otherwise healthy persons (viral virulence deaths). COVID-19-associated death may also occur because SARS-CoV-2 infection exacerbates the health condition of people who are more vulnerable to death in the short-term independent of the virus because of severe underlying coexisting conditions or advanced age ("forward displacement of mortality" [2,3]). COVID-19 death may also happen because of long-term consequences of the acute SARS-CoV-2 infection. While systemic damage at time of infection may not be sufficient to cause immediate death, it could introduce health conditions or Long COVID [4], causing death at a later stage.

The relative and absolute contribution from each of these pathways to COVID-19 mortality remains unknown, both in the overall population and within specific population groups categorized by vulnerability to severe COVID-19 or vaccination status. The distinct impact of these pathways on various population subgroups has not been characterized and could differ. Consequently, conducting a comprehensive analysis encompassing the entire population, alongside a focused investigation targeting specific key cohorts—such as those with older age or pre-existing conditions linked to heightened vulnerability to severe COVID-19, as well as those without, further differentiated by their vaccination status—provides an opportunity to gain clarity and enhance our understanding of the underlying factors driving mortality during the pandemic. The assessment of the relative and absolute influence of these pathways is imperative for informing effective public health strategies. This understanding is pivotal in guiding the optimal deployment of both pharmacological and non-pharmacological interventions for diverse population segments, ultimately leading to favorable modifications in COVID-19 mortality rates.

To address this knowledge gap, we investigated incidence of all-cause mortality, including COVID-19 mortality, after a primary SARS-CoV-2 infection in the Qatar national cohort of SARS-CoV-2 infected persons compared with a reference control cohort of infection-naïve persons from pandemic onset up to the present. We also sought to elucidate the contribution of these pathways to the overall COVID-19 mortality in specific population subgroups.

Methods

Study population and data sources

This study was conducted on the population of Qatar using data between February 5, 2020, when the first SARS-CoV-2 infection was documented in this country, and November 14, 2022. We analyzed the national, federated, mortality database managed by the Hamad Medical Corporation, the national public healthcare provider in Qatar [5]. The database includes all death records, including both deaths occurring at healthcare facilities and elsewhere (Section S1 of the Supplementary Appendix).

The study further analyzed the national, federated databases for COVID-19 laboratory testing, vaccination, and death, retrieved from the integrated, nationwide, digital-health information platform (Section S1). Databases include all SARS-CoV-2-related data with no missing information since the onset of the pandemic, including all polymerase chain reaction (PCR) tests and medically supervised rapid antigen tests (Section S2). SARS-CoV-2 testing in Qatar is done at large scale, and up to October 31, 2022, was mostly done for routine reasons such as for screening or travel-related purposes, with infections primarily diagnosed not because of appearance of symptoms, but because of routine testing [6,7]. Qatar launched its COVID-19 vaccination program in December 2020 using the BNT162b2 and mRNA-1273 vaccines [8]. Detailed descriptions of Qatar's population and the national databases have been reported previously [6,7,9,10].

Study design and cohorts

A matched, retrospective, cohort study was conducted to compare incidence of all-cause mortality in the national cohort of persons who had a documented primary SARS-CoV-2 infection (designated the primary-infection cohort) to that in a national reference control cohort of infection-naïve persons (designated the infection-naïve cohort).

Primary infection was defined as the first record of a SARS-CoV-2-positive test regardless of symptoms. All-cause mortality was defined as any death, regardless of cause (including COVID-19), that occurred during follow-up.

Cohorts' matching and eligibility

Cohorts were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions (0, 1, 2, 3, 4, 5, or ≥6 coexisting conditions; Section S1), vaccination status (unvaccinated, 1, 2, 3, or 4 doses), and vaccine type (BNT162b2, mRNA-1273, or pediatric BNT162b2), using the Stata 17.0 *ccmatch* command, to balance observed confounders between exposure groups that are potentially related to risks of mortality or infection [9,11–14]. Exact matching refers here to the pairing of individuals in these cohorts based on identical values for the matching factors [15].

Matching was also done by calendar week of the test diagnosing the primary infection for persons in the primary-infection cohort and of a SARS-CoV-2-negative test for the infection-naïve cohort. That is, persons who had the primary infection diagnosed in a specific calendar week were matched to unique infection-naïve persons who had a record of a SARS-CoV-2-negative test in that same calendar week. This was done to ensure that those in the infection-naïve cohort were not infected at the time of recruitment, to control for time-variable differences in mortality risk, and to ensure that matched pairs were present in Qatar in the same period. Cohorts were also matched exactly by SARS-CoV-2 testing method (PCR versus rapid antigen testing) and by reason for testing (Section S1) to control for potential differences in presence of testing modalities between cohorts.

Persons were eligible for inclusion in the primary-infection cohort if they had a record of a SARS-CoV-2-positive test, but no record of vaccine doses mixing different vaccines by the start of follow-up. Persons were eligible for inclusion in the infection-naïve cohort if they had a record for at least one SARS-CoV-2-negative test. Persons with a record of vaccination with a non-mRNA vaccine or an unspecified vaccine type were excluded.

Matching was performed iteratively such that persons in the infection-naïve control cohort were alive and had no record, by the start of follow-up, of a SARS-CoV-2-positive test, or vaccine doses mixing different vaccines, or a new vaccine dose between the time of the SARS-CoV-2-negative test and the start date of follow-up.

Cohorts' follow-up

Follow-up was from 1 day before the primary infection to account for situations where testing was done immediately post-mortem (to determine cause of death), through the end of the study (November 14, 2022). Some persons contributed follow-up time first in the infection-naïve cohort, while matched to persons with primary infections, and subsequently contributed data to the primary-infection cohort after infection (at which point they were matched to persons who were still infection-naïve). Matching was iterated with as many replications as needed until exhaustion (i.e., no more matched pairs could be identified).

For exchangeability [10,16], both members of each matched pair were censored as soon as the person in the primary-infection cohort was reinfected, or the person in the infection-naïve cohort was infected, or one of them received a new vaccine dose (change in vaccination status). Reinfection was defined as a documented infection ≥90 days after an earlier infection, to avoid misclassification of prolonged SARS-CoV-2-positivity as reinfection [6]. Accordingly, individuals were followed up until the first of any of the following events: a documented reinfection (with matched pair censoring), a documented infection (with matched pair censoring), a change in vaccination status (with matched-pair censoring), death from any cause, or administrative end of follow-up (November 14, 2022).

Classification of COVID-19 death

Classification of COVID-19 deaths followed World Health Organization (WHO) guidelines [17] (Section S1). 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 deceased patient since pandemic onset.

Clinical vulnerability status

Persons less clinically vulnerable to severe COVID-19 were defined as those <50 years of age and with one or no coexisting conditions [18]. Persons more clinically vulnerable to severe COVID-19 were defined as those ≥50 years of age, or <50 years of age but with ≥2 coexisting conditions [18].

Oversight

The institutional review boards at Hamad Medical Corporation and Weill Cornell Medicine–Qatar approved this retrospective study with a waiver of informed consent. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table S1). The authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. Data used in this study are the property of the Ministry of Public Health of Qatar and were provided to the researchers through a restricted-access agreement for preservation of confidentiality of patient data.

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 of ≤0.1 indicated adequate matching.

For both unvaccinated and vaccinated persons, two analyses were conducted to compare incidence of all-cause mortality in the primary-infection and infection-naïve cohorts during the first 90 days after the primary infection (Acute SARS-CoV-2 Infection Mortality Analysis) and from 91 days and thereafter (Post-acute SARS-CoV-2 Mortality Analysis).

Cumulative incidence of death (defined as proportion of persons at risk, whose primary endpoint during follow-up was death) was estimated using the Kaplan-Meier estimator method. Incidence rate of death in each of unvaccinated and vaccinated persons of each cohort, defined as number of deaths divided by number of person-years contributed by all individuals in the cohort, was estimated, with the corresponding 95% confidence interval (CI), using a Poisson log-likelihood regression model with the Stata 17.0 *stptime* command.

Overall hazard ratios, comparing incidence of death in the cohorts and corresponding 95% CIs, were calculated using Cox regression adjusted for the matching factors with the Stata 17.0 *stcox* command. The overall hazard ratios provided a weighted average of the time-varying hazard ratios [19]. Adjusted hazard ratios were also estimated for different time intervals after start of follow-up using separate Cox regressions with "failures" restricted to specific time intervals. These time intervals were informed by the observed cumulative incidence of death, estimated using the Kaplan-Meier method.

Schoenfeld residuals and log-log plots for survival curves were used to examine the proportional hazards assumption. CIs were not adjusted for multiplicity; thus, they should not be used to infer definitive differences between groups. Interactions were not considered except in sensitivity analysis. Adjusted hazard ratios were estimated for subgroups of the study cohorts including persons who are less or more clinically vulnerable to severe COVID-19.

The conceptual approach in this study was to construct the matched cohorts in a manner that allows disaggregation of the full cohorts into separate sub-studies for each unvaccinated and vaccinated person and assess study outcomes for these subgroups. A disadvantage is that this may entail different population compositions other than the ones of interest. In a sensitivity analysis to investigate whether this may have affected study results, study outcomes for these subgroups were calculated instead using interaction terms between study cohorts and vaccination or clinical vulnerability statuses. Cox interaction models were applied to the full cohorts.

Another sensitivity analysis was conducted by restricting the study to only Qataris, that is excluding all expatriates, to assess whether travel or leaving the country for expatriates may have affected study results. Statistical analyses were performed using Stata/SE version 17.0 (Stata Corporation, College Station, TX, USA).

Role of the funding source

The funders had no role in the study design; the collection, analysis, or interpretation of the data; or the writing of the manuscript.

Results

Figure S1 shows the study population selection process. Table S2 describes baseline characteristics of the full and matched cohorts. Matched cohorts each included 685,871 persons.

Table 1

Adjusted hazard ratio for all-cause death in the matched primary-infection and infection-naïve cohorts for each of unvaccinated and vaccinated persons.

Epidemiological measures	Unvaccinated		Vaccinated	
	Primary-infection cohort*	Control cohort*	Primary-infection cohort*	Control cohort*
Acute SARS-CoV-2 Infection Mortality Analysis				
Sample size	460,620	460,620	225,251	225,251
Total follow-up time (person-years)	94,267	94,271	40,426	40,424
Number of deaths during follow-up	342	288	59	74
Incidence rate of death (per 1,000 person-years; 95% CI)	3.63 (3.26 to 4.03)	3.06 (2.72 to 3.43)	1.46 (1.13 to 1.88)	1.83 (1.46 to 2.30)
Unadjusted hazard ratio for death (95% CI)	1.17 (1.00 to 1.36)		0.80 (0.57 to 1.12)	
Adjusted hazard ratio for death (95% CI)†	1.19 (1.02 to 1.39)		0.74 (0.50 to 1.09)	
Post-acute SARS-CoV-2 Infection Mortality Analysis				
Sample size	315,489	315,506	131,960	131,942
Total follow-up time (person-years)	187,359	187,319	56,521	56,509
Number of deaths during follow-up	72	142	45	44
Incidence rate of death (per 1,000 person-years; 95% CI)	0.38 (0.31 to 0.48)	0.76 (0.64 to 0.89)	0.80 (0.59 to 1.07)	0.78 (0.58 to 1.05)
Unadjusted hazard ratio for death (95% CI)	0.51 (0.38 to 0.68)		1.02 (0.67 to 1.55)	
Adjusted hazard ratio for death (95% CI)†	0.50 (0.37 to 0.66)		1.10 (0.68 to 1.78)	

CI denotes confidence interval.

* Each person in the primary-infection cohort was matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, vaccination status, vaccine type, SARS-CoV-2 testing method, reason for testing, and calendar week of testing to a person with a SARS-CoV-2-negative test who, by the start of the follow-up, was alive, infection free, and did not receive vaccine doses with different vaccines, or a new vaccine dose between the SARS-CoV-2-negative test and the start date of follow-up.

† Cox regression analysis adjusted for sex, 10-year age group, 10 nationality groups, number of coexisting conditions, vaccination status, vaccine type, SARS-CoV-2 testing method, reason for testing, and calendar week of testing.

Unvaccinated population

Acute SARS-CoV-2 Infection Mortality Analysis

In this analysis, the median follow-up was 91 days (interquartile range (IQR), 65-91 days) (Figure 1A). During follow-up, 342 deaths were recorded in the primary-infection cohort compared to 288 deaths in the infection-naïve cohort (Figure S1 and Table 1). Of the 342 deaths in the primary-infection cohort, 223 were COVID-19 deaths. Cumulative incidence of death was 0.085% (95% CI: 0.076-0.095%) in the primary-infection cohort and 0.072% (95% CI: 0.064-0.081%) in the infection-naïve cohort, 91 days after the start of follow-up (Figure 1A).

Adjusted hazard ratio (aHR) comparing incidence of death in the unvaccinated primary-infection cohort to the unvaccinated infection-naïve cohort during the acute phase was 1.19 (95% CI: 1.02-1.39; Table 1 and Figure 2A). Subgroup analyses estimated the aHR at 1.34 (95% CI: 1.11-1.63) in persons more clinically vulnerable to severe COVID-19 and 0.94 (95% CI: 0.72-1.24) in those less clinically vulnerable to severe COVID-19 (Figure 3A and Table S3A).

Post-acute SARS-CoV-2 infection mortality analysis

In this analysis, the median follow-up was 296 days (IQR, 202-336 days) for each of the cohorts (Figure 1B). During follow-up, 72 deaths were recorded in the primary-infection cohort compared to 142 in the infection-naïve cohort (Figure S1 and Table 1). Of the 72 deaths in the primary infection cohort, 5 were COVID-19 deaths related to the original primary infection. Cumulative incidence of death was 0.036% (95% CI: 0.027-0.048%) in the primary-infection cohort and 0.060% (95% CI: 0.050-0.074%) in the infection-naïve cohort, 450 days after the start of follow-up (Figure 1B).

The aHR comparing incidence of death in the unvaccinated primary-infection cohort to the unvaccinated infection-naïve cohort during the post-acute phase was 0.50 (95% CI: 0.37-0.68; Table 1). The aHR was 0.41 (95% CI: 0.28-0.58) in months 3-7 after the primary infection and increased to 0.76 (95% CI: 0.46-1.26) in ≥8 months (Figure 2A). The aHR during the post-acute phase was 0.37 (95% CI: 0.25-0.54) in persons more clinically vulnerable to severe COVID-19 and 0.77 (95% CI: 0.48-1.24) in those less clinically vulnerable to severe COVID-19 (Figure 3A and Table S3A).

Combined acute and post-acute SARS-CoV-2 infection mortality analysis

Figure 1C shows cumulative incidence of death in the unvaccinated population covering the entire time of follow-up, including both acute and post-acute phases. The aHR comparing incidence of death in the unvaccinated primary-infection cohort to the unvaccinated infection-naïve cohort was 0.97 (95% CI: 0.84-1.11). The aHR was 1.00 (95% CI: 0.85-1.19) in persons more clinically vulnerable to severe COVID-19 and 0.90 (95% CI: 0.71-1.14) in persons less clinically vulnerable to severe COVID-19 (Table S3A).

Vaccinated population

In the Acute SARS-CoV-2 Infection Mortality Analysis (Figure 4A), the aHR comparing incidence of death in the vaccinated primary-infection cohort to the vaccinated infection-naïve cohort was 0.74 (95% CI: 0.50-1.09; Table 1 and Figure 2B). Subgroup analyses estimated the aHR at 0.64 (95% CI: 0.41-1.02) in persons more clinically vulnerable to severe COVID-19 and 1.08 (95% CI: 0.51-2.29) in those less clinically vulnerable to severe COVID-19 (Figure 3B and Table S3B).

In the Post-acute SARS-CoV-2 Infection Mortality Analysis (Figure 4B), the aHR comparing incidence of death in the vaccinated primary-infection cohort to the vaccinated infection-naïve cohort was 1.10 (95% CI: 0.68-1.78; Table 1 and Figure 2B). Subgroup analyses estimated the aHR at 0.96 (95% CI: 0.56-1.66) in persons more clinically vulnerable to severe COVID-19 and 2.00 (95% CI: 0.68-5.84) in those less clinically vulnerable to severe COVID-19 (Figure 3B and Table S3B).

Figure 4C shows cumulative incidence of death in the vaccinated population in the Combined Acute and Post-acute SARS-CoV-2 Infection Mortality Analysis, covering the entire period of follow-up. aHR was 0.87 (95% CI: 0.64-1.18). The aHR was 0.76 (95% CI: 0.53-1.07) and 1.33 (95% CI: 0.72-2.46) in persons more and less clinically vulnerable to severe COVID-19, respectively (Table S3B).

Additional and sensitivity analyses

In the analysis combining acute and post-acute phases and unvaccinated and vaccinated persons, the aHR comparing incidence of death in the primary-infection cohort to the infection-naïve cohort was 0.95 (95% CI: 0.84-1.07; Table S4).
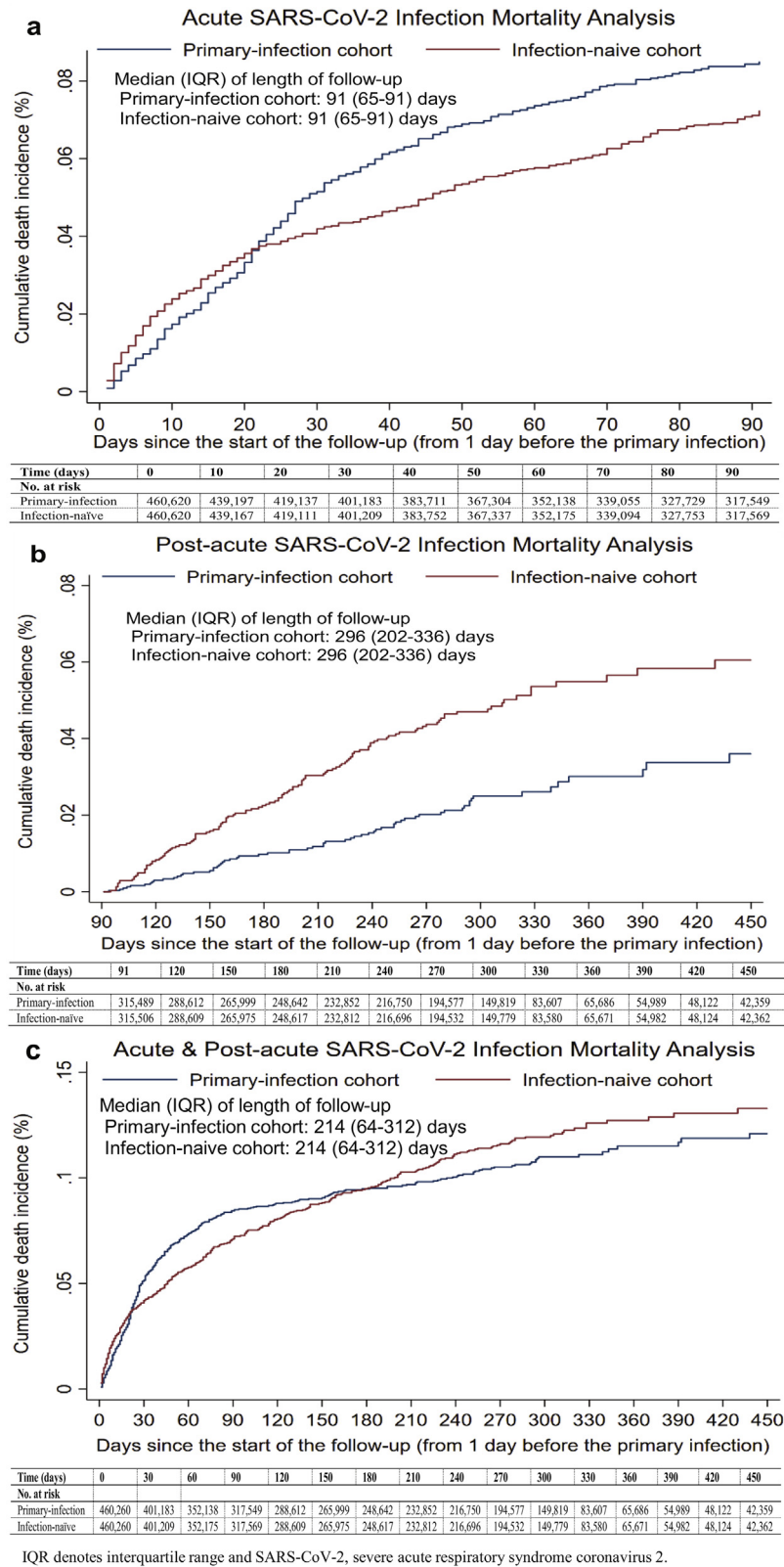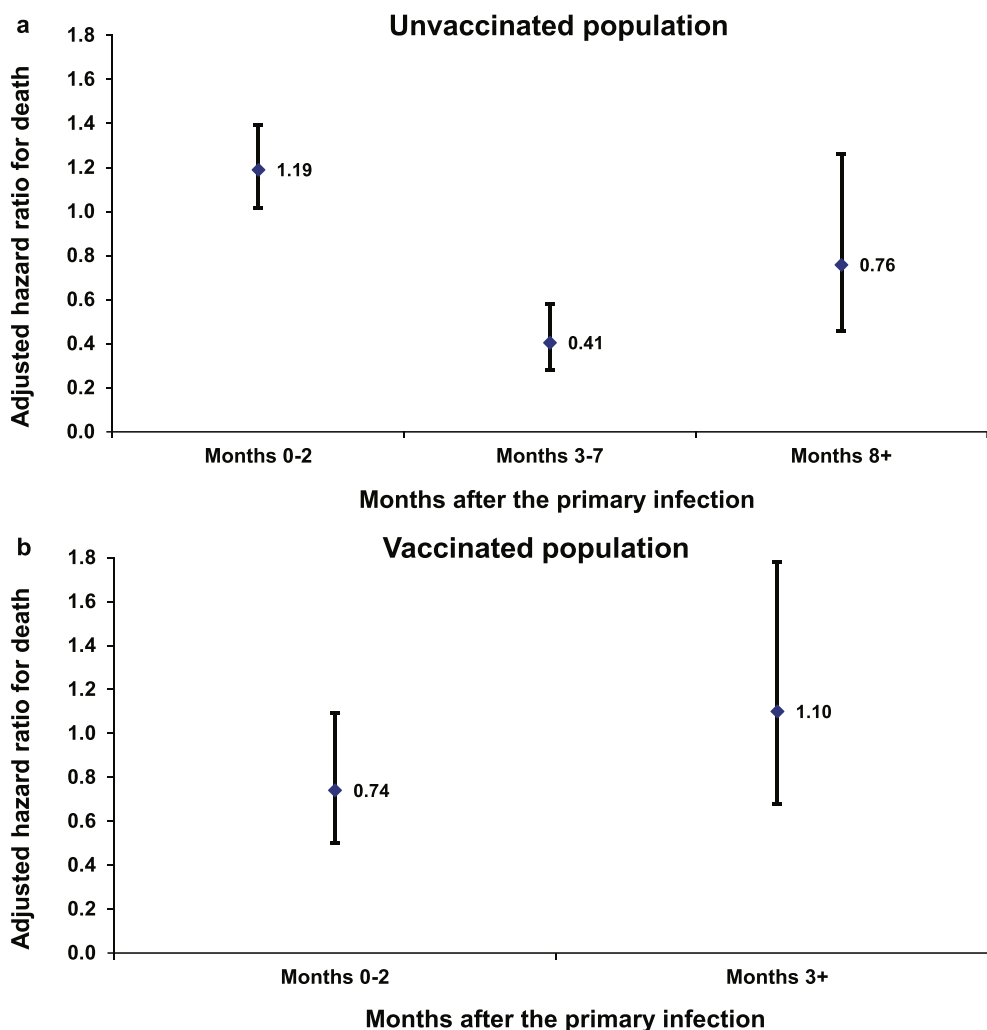
Figure 1. Cumulative incidence of all-cause death among unvaccinated persons of the matched primary-infection and infection-naïve cohorts in the A) Acute SARS-CoV-2 Infection Mortality Analysis, B) Post-acute SARS-CoV-2 Infection Mortality Analysis, and C) Combined Acute & Post-acute SARS-CoV-2 Infection Mortality Analysis.

With the small number of deaths among those vaccinated, it was not possible to estimate the adjusted hazard ratio separately for months 3-7 and month 8+.

Figure 2. Adjusted hazard ratios for all-cause death by time since the start of follow-up in the matched primary-infection cohort relative to the infection-naïve cohort for each of A) unvaccinated and B) vaccinated persons.

The sensitivity analysis calculating study outcomes through interaction terms with the interaction model applied to the full cohorts produced similar results to main analysis (Table S5A). The sensitivity analysis calculating study outcomes only for Qataris also generated similar results to main analysis (Table S5B).

Discussion

In this study, we find that COVID-19 mortality in Qatar is predominantly influenced by "forward displacement of death" among individuals with older age and preexisting conditions who are already highly vulnerable to all-cause mortality. The findings are consistent with the thesis that those who survived the infection were in better overall health, resulting in an enhanced survival rate shortly after their recovery from the infection, in contrast to individuals who had not been previously infected. Over time, as the effects of the forward displacement of death phenomenon diminished, mortality rates eventually leveled out for both groups.

Consequently, the occurrence of death among those who were infected, as opposed to those who were infection-naïve, exhibited a V-shaped trend based on time since infection. In the short term, there was a higher incidence of all-cause mortality among the in-

fected (excess mortality), followed by a lower incidence among the infected in the medium term (deficit mortality). No differences in the incidence of death were observed more than a year after the primary infection. This pattern mirrors the phenomenon of forward mortality displacement observed in the impact of heat waves and cold spells on mortality [2]. This finding is further supported by an ecological observation that noted the temporary presence of deficit mortality following significant COVID-19 waves [20].

The pull-forward effect of expedited onset of death in the primary-infection cohort was observed in the overall cohort but markedly pronounced among those more clinically vulnerable to severe COVID-19. Meanwhile, no such effect was observed among those less clinically vulnerable. In that subgroup, the hazard ratio for death comparing the infected to uninfected was approximately 1, during both the acute and post-acute phases of follow-up, further supporting mortality displacement among the clinically vulnerable as the main driver of COVID-19 mortality.

These findings do not diminish the importance of COVID-19 deaths in otherwise healthy persons or due to Long COVID. Such deaths have been documented globally. However, there was no discernable effect for these deaths in Qatar's population, perhaps because of insufficient statistical power to measure small effects
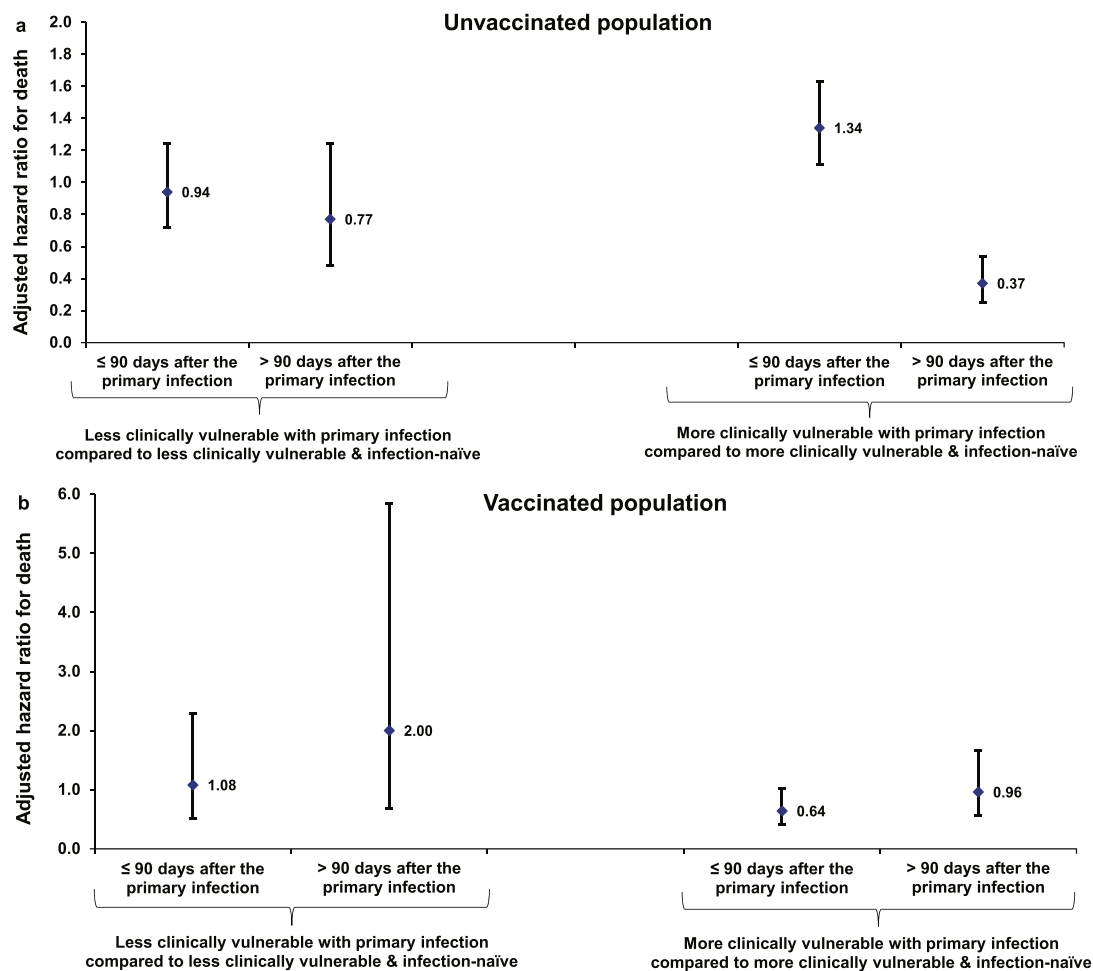
Figure 3. Adjusted hazard ratio for all-cause death in the A) unvaccinated and B) vaccinated populations by clinical vulnerability to severe COVID-19 in the Acute SARS-CoV-2 Infection Mortality Analysis (≤90 days after the primary infection) and in the Post-acute SARS-CoV-2 Infection Mortality Analysis (>90 days after the primary infection).

compared to the large effect of forward displacement of death, even in such a large cohort study.

Vaccination negated the infection's pull-forward (mortality displacement) effect by preventing early deaths. The hazard ratio for death was approximately 1 among vaccinated persons during both the acute and post-acute phases of follow-up, regardless of the clinical vulnerability to severe COVID-19. This revealed the occurrence of a theoretically expected (though potentially counterintuitive) finding; the incidence of all-cause death would be expected to be higher among vaccinated compared to unvaccinated persons at this later stage of the pandemic. This finding is likely because clinically vulnerable vaccinated persons had higher survival probabilities through repeated waves of infection and thus, unlike unvaccinated persons with similarly elevated baseline mortality risks, were able to survive long enough to contribute follow-up time to the analysis.

These findings may explain the low rate of COVID-19 mortality in Qatar, one of the lowest worldwide [5]. As of January 29, 2023, 686 COVID-19 deaths have been recorded in this country of three million people [9]; <0.1% of documented infections ended in COVID-19 death. About 60% of Qatar's population are craft and manual workers (CMW) [11,14] who are typically single men, 20-49 years of age [9]. CMW are healthy by recruitment (healthy worker effect [5,21]) and have lower levels of comorbidities such as diabetes and obesity [22]; that is a population not likely to be affected by the pull forward effect.

This study has limitations. Documented COVID-19 deaths may not include all deaths that occurred because of COVID-19 [3,23].

Some COVID-19 deaths may not have been confirmed due to insufficient information to confirm COVID-19 as the cause of death [3,23]. The differences in incidence rate of non-COVID-19 death between the primary-infection and infection-naïve cohorts in the acute phase of follow-up, which coincided with calendar times of high infection incidence during waves, suggest existence of COVID-19-associated deaths among those in the "infection-naïve" cohort that were never detected or confirmed.

All-cause mortality appeared qualitatively elevated among uninfected persons during the first 0-3 weeks after their matched pairs were infected. This observation may have risen because of differences in the risk of non-COVID-19 death between those recently diagnosed with the infection and uninfected persons. Isolation of infected persons in Qatar was enforced through mandatory requirements and isolation facilities. The reduced mobility of infected persons following diagnosis of infection should have reduced their risk of incidental causes of death, such as motor-vehicle road injuries, a leading cause of death that contributes ~10% of all deaths in Qatar [24,25]. An additional explanation is the selection of controls among those with a negative test. A recent negative test is perhaps a proxy of recent activity and mobility, and thus of higher likelihood of incidental death. Persons who are less active and staying at home are less likely to do a routine or screening test or to experience an incidental death.

Primary infections were determined based on records of documented infections, but other infections may have occurred and gone undocumented, for example due to tests being administered prematurely (i.e., during the viral incubation period). This may also
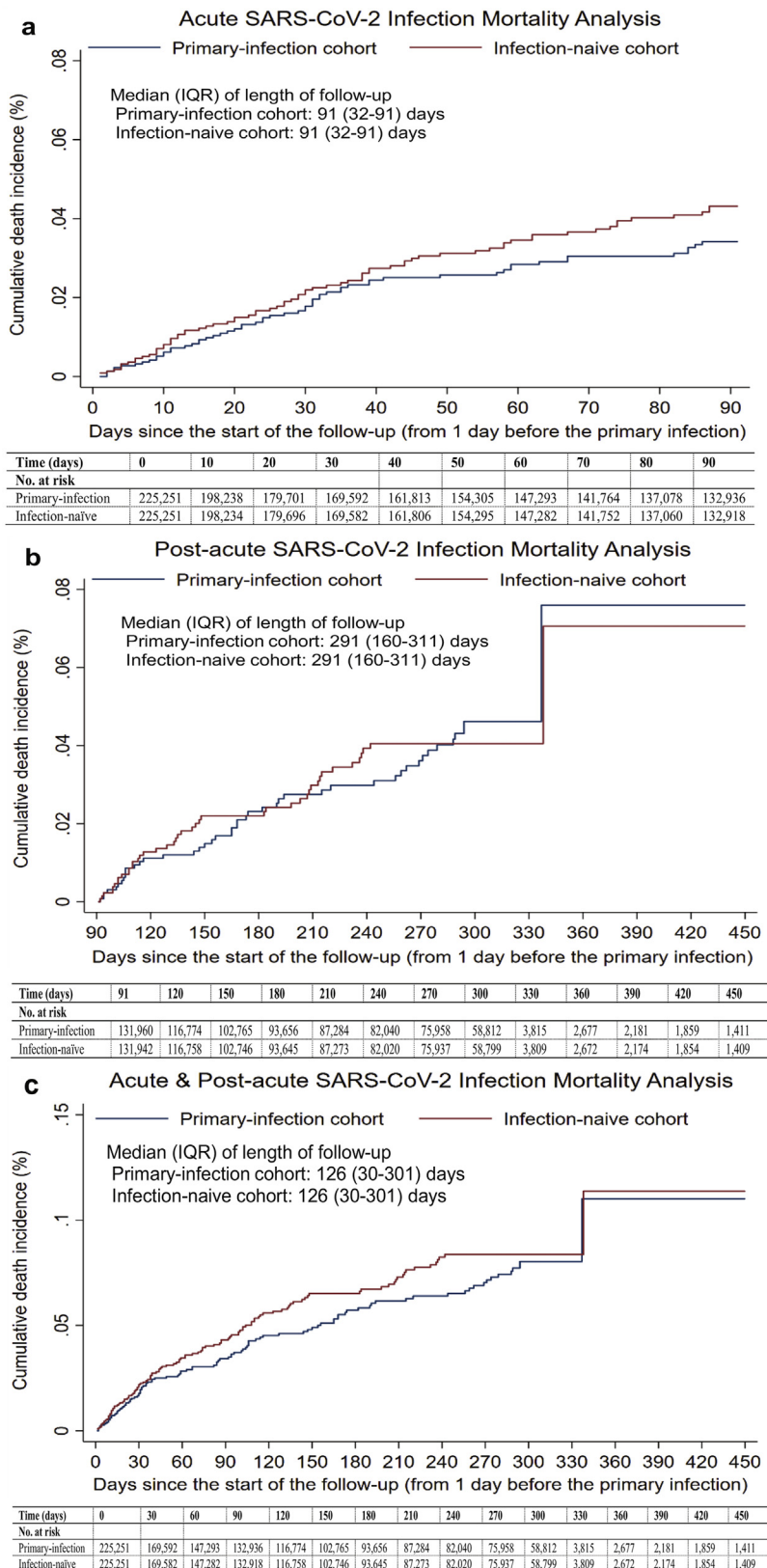
Figure 4. Cumulative incidence of all-cause death among vaccinated persons of the matched primary-infection and infection-naïve cohorts in the A) Acute SARS-CoV-2 Infection Mortality Analysis, B) Post-acute SARS-CoV-2 Infection Mortality Analysis, and C) Combined Acute & Post-acute Infection Mortality Analysis.

explain the qualitatively elevated risk of death among uninfected persons during the first 0-3 weeks of follow-up (Figure 1). Tests performed on persons with known exposure may have in some instances been administered too early, before viral loads were sufficient to mount positive tests.

The frequency of testing could have been influenced by various factors, including vaccination status, age, sex, nationality, and clinical vulnerability. Nevertheless, any disparities in testing frequency might not have appreciably impacted the outcomes and conclusions. This is because potential effects arising from these testing variations are likely mitigated by the matching process employed to control for these factors.

Improvements in case management, use of antivirals, and introduction of omicron with its lower infection severity [26,27] reduced COVID-19 mortality over time. This may have affected the observed trends; most of COVID-19 mortality effects were driven by incidence during the pre-omicron waves. The study analyzed all deaths that occurred in Qatar, but some deaths may have occurred outside Qatar, while expatriates were traveling abroad or if they left the country because of end of employment after initiation of follow-up. Travel data were not available to be incorporated into our analysis. These out-of-Qatar deaths may introduce differential ascertainment bias. However, the sensitivity analysis restricting the study to only Qataris showed similar results.

Classification of COVID-19 death was determined per WHO guidelines [17], as part of a national protocol applied to every deceased patient since pandemic onset. For a rigorous understanding of causes of death in Qatar, a national project has recently been initiated to methodologically review and analyze all deaths that occurred in Qatar, whether at healthcare facilities or elsewhere, since 2018 [5]. The project is ongoing and the specific causes of death are not yet available [5]. Therefore, our focus in the present study was to assess overall mortality, COVID-19 mortality, and other causes without specifying the specific cause of the other causes.

Since the magnitude of the Cox HR in presence of time-varying HR depends on the scale and distribution of losses to follow-up (censoring) even if the losses occur at random [19], the overall HRs in the post-acute analyses are skewed toward the earlier of times of follow-up rather than later times of follow-up. However, HRs were additionally provided for both early follow-up and late follow-up (Figure 2) to provide representative estimates for each of these durations.

The study was conducted in a specific national population consisting mainly of healthy working-age adults, and thus generalizability of the findings to other national populations is unknown. As an observational study, investigated cohorts were neither blinded nor randomized, so unmeasured or uncontrolled confounding cannot be excluded. Although matching covered key factors affecting risks of death or infection [9,11–14], it was not possible for other factors such as geography or occupation, for which 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, who come for employment [9]. Nationality, age, and sex provide a powerful proxy for socioeconomic status in this country [9,11–14]. Nationality is strongly associated with occupation [9,11,13,14].

The matching procedure used in this study was investigated in previous studies of different epidemiologic designs and using control groups to test for null effects [7,8,28–30]. These previous studies demonstrated at different times during the pandemic that this procedure balances differences in infection exposure to estimate vaccine effectiveness [7,8,28–30], suggesting that the matching strategy may also have overcome differences in mortality risk. Analyses were implemented on Qatar's total population and large samples, perhaps minimizing the likelihood of bias.

In conclusion, COVID-19 mortality in Qatar was primarily influenced by an accelerated onset of death among individuals who were already highly vulnerable to all-cause mortality and clinically vulnerable to severe COVID-19. Vaccination effectively averted these expedited deaths, including among those clinically vulnerable to severe COVID-19. The findings do not undermine the significance of COVID-19 deaths in individuals without underlying health issues or those attributed to Long COVID; however, there was no discernible effect of these deaths on Qatar's population.

Author contributions

JSF conceived the idea of this study. HC, JSF, and LJA conceived and designed the study analyses. HMK contributed to analysis plan. HC performed the statistical analyses and co-wrote the first draft of the article. LJA led the statistical analyses and co-wrote the first draft of the article. PT and MRH designed and conducted multiplex, RT-qPCR variant screening, and viral genome sequencing. PVC designed mass PCR testing to allow routine capture of SGTF variants and conducted viral genome sequencing. HY, AAA, and HAK conducted viral genome sequencing. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and the writing of the article. All authors have read and approved the final manuscript. Decision to publish the paper was by consensus among all authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.09.005.

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