Turning point in COVID-19 severity and fatality during the pandemic: a national cohort study in Qatar


ABSTRACT

Objective To assess the evolution of COVID-19 severity and fatality in a unique setting that consistently applied, throughout the pandemic, rigorous and standardised criteria for defining severe COVID-19 outcomes.

Methods and analysis We conducted a national cohort study on 312,109 Qatar citizens to investigate incidence of severe, critical or fatal COVID-19 classified according to the WHO criteria between 28 February 2020 and 21 April 2023. Incidence rates for severe, critical or fatal COVID-19 were estimated during the pre-omicron phase, first omicron wave, combined phases and throughout the pandemic.

Results Cumulative incidence of severe, critical or fatal COVID-19 after 3.14 years of follow-up was 0.45% (95% CI 0.43% to 0.47%). Incidence rate for severe, critical or fatal COVID-19 throughout the pandemic was 1.43% (95% CI 1.35 to 1.50) per 1000 person years. In the pre-omicron phase, first omicron wave, and combined phases, it was 2.01 (95% CI 1.90 to 2.13), 3.70 (95% CI 3.25 to 4.22) and 2.18 (95% CI 2.07 to 2.30) per 1000 person years, respectively. The post-first omicron phase saw a drastic drop to 0.10 (95% CI 0.08 to 0.14) per 1000 person years, a 95.4% reduction. Among all severe, critical and fatal cases, 99.5% occurred during the primary infection. Cumulative incidence of fatal COVID-19 was 0.042% (95% CI 0.036% to 0.050%), with an incidence rate of 0.13 (95% CI 0.11 to 0.16) per 1000 person years. In the post-first omicron phase, incidence rate of fatal COVID-19 decreased by 90.0% compared with earlier stages. Both severity and fatality exhibited an exponential increase with age and a linear increase with the number of coexisting conditions.

Conclusion The conclusion of the first omicron wave was a turning point in the severity of the pandemic. While vaccination and enhanced case management reduced severity gradually, the rapid accumulation of natural immunity during the first omicron wave appears to have played a critical role in driving this shift in severity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- COVID-19 severity varied during the pandemic in response to subsequent waves of infection, increasing population immunity, and emergence of new viral variants. However, no study investigated evolution of COVID-19 severity from the start of the pandemic to the present time in a national population cohort and using rigorous and standardised criteria applied throughout the pandemic.
- Qatar appears to be the only country to consistently implement the standardised WHO classification to assess the severity of COVID-19 cases throughout the pandemic.

WHAT THIS STUDY ADDS

- Based on a national population-based cohort study in Qatar, we found that the end of the first omicron wave marked a turning point in the pandemic, with a 95% drop in incidence rate of severe, critical or fatal COVID-19 compared with earlier stages.
- Vaccinations and advancements in case management reduced severity gradually over time, but the end of the first omicron wave served as the central turning point. By the end of this wave, severity rates reached very low levels not seen since the onset of the pandemic, and these levels have been sustained since then, despite the occurrence of several immune-evasive omicron subvariant waves.
- The rapid build-up of natural immunity during the first omicron wave appears to have played a pivotal role in driving this shift in severity levels.

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2, has resulted in significant morbidity and mortality globally. The pandemic has also caused extensive economic losses and societal disruptions due to the necessary implementation of social and physical distancing measures.

aimed at reducing virus transmission. The need for future public health interventions and restrictions will depend on the ongoing evolution of the virus, its disease severity and the effectiveness of current and future interventions. The WHO has established a specific classification system for COVID-19 case severity, criticality and fatality. Qatar appears to be the only country to have consistently implemented this standardised WHO classification at a national level to assess the severity of COVID-19 cases from the pandemic onset to the present. Trained medical personnel evaluate the severity of COVID-19 cases using a national protocol that applies to every hospitalised patient with COVID-19. Importantly, COVID-19-associated hospitalisations are not used as a proxy for COVID-19 severity, as these have limitations in accurately capturing the true severity of COVID-19. This presents a special opportunity to investigate the evolution of COVID-19 severity from the start of the pandemic to the present time, using rigorous and standardised criteria in a national population cohort.

The objective of this study was to examine how COVID-19 severity changed over the course of the pandemic in response to subsequent waves of infection, increasing population immunity, and the emergence of new viral variants. The study analysed the incidence of COVID-19 acute-care hospitalisations, COVID-19 intensive care unit (ICU) hospitalisations, as well as the incidence of severe, critical and fatal COVID-19 cases, according to the WHO classification, in the national cohort of Qatari citizens.

Qatar’s population includes Qatari and a large expatriate workforce. A considerable proportion of the expatriate population consists of healthy men who are craft and manual workers aged 20–49, who may undergo strenuous physical labour. As a result, they may not represent a natural national population. In contrast, Qatari citizens represent a typical national population, including both healthy and unhealthy individuals, making them relevant for assessing the severity of SARS-CoV-2 infections in this study.

METHODS

Study population and data sources

This study assessed the severity of COVID-19 in the national cohort of Qatari citizens from 28 February 2020, which marks the earliest record of a SARS-CoV-2-positive test in Qatar, to 21 April 2023. The study used the national, federated databases for COVID-19 laboratory testing, vaccination, hospitalisation and death, obtained from the integrated, nationwide, digital-health information platform (online supplemental section S1). The databases contain SARS-CoV-2-related data with no missing information since the pandemic’s onset, including all PCR tests and, from 5 January 2022, all medically supervised rapid antigen tests (online supplemental section S2).

SARS-CoV-2 testing in Qatar was conducted on a large scale, primarily for non-clinical reasons. The national mortality database was used to obtain data on all-cause mortality, including deaths occurring at healthcare facilities and elsewhere. Qatar launched its COVID-19 vaccination programme in December 2020 using the BNT162b2 and mRNA-1273 vaccines. Detailed descriptions of Qatar’s population and national databases have been previously reported.

COVID-19 acute-care and ICU hospitalisations

This study tracked COVID-19 hospitalisations based on a national protocol for COVID-19 case management administered at Hamad Medical Corporation, the national public healthcare provider, and the only authorised entity to provide COVID-19 healthcare in Qatar. A COVID-19 acute-care admission was defined as a record of an acute-care bed admission for an individual who had an active SARS-CoV-2 infection, irrespective of the clinical condition of the admitted individual. Initially, the duration of an active SARS-CoV-2 infection was defined to be 21 days following a SARS-CoV-2-positive test. However, this duration definition was subsequently reduced to 14 days on 1 July 2020 and then to 5 days on 17 October 2022, reflecting changes in policy guidelines in the country.

COVID-19 ICU admission was defined as an ICU bed admission for an individual with an active SARS-CoV-2 infection, and for which the ICU admission clinical team determined that the clinical condition could be related to COVID-19. If an ICU admission for an individual with an active SARS-CoV-2 infection was determined to be unrelated to COVID-19, it was classified as a COVID-19 acute-care admission according to the national protocol.

Severe, critical and fatal COVID-19

To ensure stringent and standardised assessment of COVID-19 infection severity, the national protocol for COVID-19 case management required that each hospitalised patient with COVID-19, in an acute-care or ICU bed, undergoes an infection severity assessment every 3 days using WHO guidelines until discharge or death. Trained medical personnel, independent of study investigators, performed the classification of cases into severe, critical or fatal COVID-19 categories using individual chart reviews (online supplemental section S3). This team of medical personnel operated independently from the clinical teams responsible directly for care of patient with
COVID-19, whether in acute care or ICU beds. Severe cases were typically hospitalised in acute-care beds, and sometimes in ICU beds out of precaution, while critical cases were always hospitalised in ICU beds.

The incidence of severe COVID-19 cases was defined as the first assessment indicating severe COVID-19 for a given individual during their hospitalisation. Similarly, the incidence of critical and fatal COVID-19 cases were defined based on the first assessment indicating critical or fatal COVID-19 during hospitalisation. Additionally, if a severe or critical assessment for a newly admitted patient with COVID-19 occurred ≥30 days after discharge from the hospital, it was considered a new diagnosis that is independent of the first one.

Cohort study of incidence of severe, critical or fatal COVID-19

In addition to examining the link between hospitalisation and severity, a national retrospective cohort study was conducted to investigate the incidence of severe, critical or fatal COVID-19 cases among Qataris between 28 February 2020 and 21 April 2023. The study cohort included all Qataris alive on 28 February 2020, who had at least one record of a SARS-CoV-2 test during the pandemic, which served as a proxy for their presence in Qatar during the study period.

Considering the various testing mandates implemented throughout the pandemic and large-scale routine testing (online supplemental section S1), it is unlikely that any Qatari residing in Qatar did not undergo at least one SARS-CoV-2 test. In total, 2,915,088 SARS-CoV-2 tests were conducted among this cohort of 312,109 Qataris from the onset of the pandemic until 21 April 2023, with an average rate of 9.3 tests per person. With this volume of testing, this cohort is expected to represent virtually the entire Qatari population, a stable affluent population. The size of the cohort is also consistent with the figures reported in the Qatar Census 2020.

We retrieved COVID-19 severity, criticality and fatality records for every documented SARS-CoV-2 infection or reinfection since the pandemic onset. SARS-CoV-2 reinfection was defined as a documented infection that occurred ≥90 days after an earlier infection, to avoid misclassifying prolonged SARS-CoV-2 positivity as reinfection. Patients who progressed to severe, critical or fatal COVID-19 after a documented infection (or reinfection) were classified based on the worst assessment outcome related to that infection (or reinfection), starting with death, followed by critical disease, and then severe disease (online supplemental section S3). The date of incidence of the outcome in this analysis was set as the day of the positive SARS-CoV-2 test that documented the infection that progressed into the severe forms of COVID-19.

All individuals were followed from the study start date (28 February 2020) until any of the following events: documented infection/reinfection associated with fatal COVID-19, or non-COVID-19-related death, or administrative end of follow-up (21 April 2023). The pandemic was categorised into distinct phases based on the level of SARS-CoV-2 incidence and the predominant variant (online supplemental section S4).

Statistical analysis

The national cohort was characterised by calculating frequency distributions and measures of central tendency. The cumulative incidence of severe, critical or fatal COVID-19 was defined as the proportion of individuals at risk (that is members of this national cohort) who had at least one episode of severe, critical or fatal COVID-19 and was estimated using the Kaplan-Meier estimator method. Likewise, the cumulative incidence of fatal COVID-19 was estimated.

The incidence rate of any severe, critical or fatal COVID-19 outcome was determined by dividing the number of episodes by the total person years contributed by all individuals in the cohort. To estimate the incidence rate, we employed a Poisson log-likelihood regression model with the Stata 17.0 stptime command, which provided both the incidence rate and its corresponding 95% CI.

The hazard rate for any severe, critical or fatal COVID-19 outcome was also calculated and its estimates were smoothed by applying kernel-density weighting. The hazard rate quantifies the instantaneous probability at a specific point in time of an individual in the observed cohort experiencing an event (in this case, severe, critical or fatal COVID-19) per unit interval of time, assuming that this individual has survived up to that moment.

Using the same approach, we also estimated the incidence rate of a fatal COVID-19 outcome and the hazard rate for a fatal COVID-19 outcome. The incidence rates were assessed for the entire follow-up period as well as for different phases of the pandemic to investigate temporal trends.

Adjusted HRs (AHRs) were estimated to compare the incidence of severe, critical or fatal COVID-19 by sex, 10-year age group, number of coexisting medical conditions (0, 1, 2, 3, 4, 5, 6+; online supplemental section S5), and vaccination dose status (unvaccinated, 1 dose, 2 doses, 3+ doses). This analysis estimated associations using a multivariable Cox regression model to adjust simultaneously for the different factors. To account for changes in vaccination status over time, vaccination was included as a time-varying covariate. Standard errors were adjusted for clustering effects. Interactions were not investigated. Analogously, the same analysis was done for only fatal COVID-19. All statistical analyses were conducted using Stata/SE V.17.0 (StataCorp LLC).

Oversight

The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (online supplemental table S1).
RESULTS
Acute-care hospitalisations and severe cases

Figure 1A presents the occurrence of COVID-19 acute-care hospitalisations and of severe COVID-19 cases among Qataris throughout the pandemic. (A) Comparison of the number of new COVID-19 admissions into acute-care hospital beds and the number of new severe COVID-19 cases according to the WHO definition for COVID-19 severity. (B) Comparison of the number of new COVID-19 admissions into ICU hospital beds and the number of new critical COVID-19 cases according to the WHO definition for COVID-19 criticality.

Out of the total acute-care admissions, 1362 cases met the criteria set by the WHO for severe COVID-19 (figure 1A). Among these severe cases, 1103 were reported during the pre-omicron phase, 228 during the first omicron wave, and 31 in the post-first omicron phase. The higher number of acute-care admissions compared with severe cases is attributed to admissions that did not meet the exact definition of severe COVID-19 and hospitalisations with COVID-19 rather than strictly because...
of COVID-19—incidental hospitalisations or hospitalisations for conditions that COVID-19 may have directly or indirectly worsened. In the very early stage of the pandemic, hospitalisation was also used for isolation purposes.

**ICU hospitalisations and critical cases**

Figure 1B presents the occurrence of COVID-19 ICU hospitalisations and of critical COVID-19 cases among Qatars. The data include a total of 641 ICU admissions, with 485 occurring during the pre-omicron phase, 121 during the first omicron wave and 35 in the post-first omicron phase.

Out of the total ICU admissions, 281 cases met the criteria set by the WHO for critical COVID-19 (figure 1B). Among these critical cases, 215 were reported during the pre-omicron phase, 54 during the first omicron wave, and 12 in the post-first omicron phase.
Table 1 Baseline characteristics of study participants

<table>
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<tr>
<th>Characteristics</th>
<th>National Qatari cohort n=312109</th>
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<tbody>
<tr>
<td>Median age (IQR)—years</td>
<td>23 (11–39)</td>
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<tr>
<td>Age group</td>
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<tr>
<td>0–9 years</td>
<td>74519 (23.9)</td>
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<tr>
<td>10–19 years</td>
<td>68051 (21.8)</td>
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<tr>
<td>20–29 years</td>
<td>53644 (17.2)</td>
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<td>30–39 years</td>
<td>43099 (13.8)</td>
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<tr>
<td>40–49 years</td>
<td>30243 (9.7)</td>
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<tr>
<td>50–59 years</td>
<td>22401 (7.2)</td>
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<tr>
<td>60–69 years</td>
<td>13200 (4.2)</td>
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<td>70+ years</td>
<td>6952 (2.2)</td>
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<tr>
<td>Sex</td>
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<tr>
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<tr>
<td>Female</td>
<td>158503 (50.8)</td>
</tr>
<tr>
<td>Number of coexisting medical conditions</td>
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<td>None</td>
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<td>1</td>
<td>71225 (22.8)</td>
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<tr>
<td>2</td>
<td>28129 (9.0)</td>
</tr>
<tr>
<td>3</td>
<td>12547 (4.0)</td>
</tr>
<tr>
<td>4</td>
<td>8439 (2.7)</td>
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<tr>
<td>5</td>
<td>5659 (1.8)</td>
</tr>
<tr>
<td>6+</td>
<td>7245 (2.3)</td>
</tr>
<tr>
<td>Vaccination status at end of follow-up</td>
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</tr>
<tr>
<td>1 dose</td>
<td>1706 (0.6)</td>
</tr>
<tr>
<td>2 doses</td>
<td>155495 (49.8)</td>
</tr>
<tr>
<td>3+ doses</td>
<td>41490 (13.3)</td>
</tr>
</tbody>
</table>

The number of ICU admissions surpassed the count of critical cases, although the difference was not as large as the gap observed between acute-care admissions and severe cases. The gap appears to be attributed to precautionary admissions not meeting the precise criteria for critical COVID-19, and some admissions being with COVID-19 rather than strictly because of COVID-19.

All-cause and COVID-19 deaths

Figure 2 depicts the occurrence of all-cause deaths and fatal COVID-19 cases among Qataris. The data comprise a total of 2002 all-cause deaths, with 1045 occurring during the pre-omicron phase, 192 during the first omicron wave and 765 in the post-first omicron phase (Figure 2A).

Among all-cause deaths, 131 cases met the WHO criteria for fatal COVID-19 (Figure 2A). Out of these deaths, 86 were reported during the pre-omicron phase, 33 during the first omicron wave, and 12 in the post-first omicron phase. COVID-19 deaths comprised 6.5% of all-cause deaths. This proportion was highest during the first omicron wave at 17.2% and lowest during the post-first omicron phase at only 1.6% (Figure 2B).

Incidence rate of severe, critical or fatal COVID-19

Table 1 provides the baseline characteristics of the participants in the cohort study. Figure 3A visually represents the incidence of SARS-CoV-2 infection, including periods of dominance of various variants throughout the pandemic (dates are found in online supplemental section S4).

There were 1396 episodes of severe, critical or fatal COVID-19 during a total follow-up of 978041 person years. The median follow-up time was 3.14 years (IQR: 3.14–3.14 years). The majority of infected individuals (99.5%) progressed to severe, critical or fatal COVID-19 subsequent to the primary infection (as opposed to subsequent to reinfection). The cumulative incidence of severe, critical or fatal COVID-19 after 3.14 years of follow-up was 0.45% (95% CI 0.43 to 0.47%), with two major jumps in incidence during the beta and omicron waves (Figure 4A).

The incidence rate of severe, critical or fatal COVID-19 was 1.43 (95% CI 1.35 to 1.50) per 1000 person years throughout the pandemic (Figure 5A). During the pre-omicron phase, the first omicron wave, and these two phases combined, it was 2.01 (95% CI 1.90 to 2.13), 3.70 (95% CI 3.25 to 4.22) and 2.18 (95% CI 2.07 to 2.30) per 1000 person years, respectively. In the post-first omicron phase, the incidence rate dropped drastically to 0.10 (95% CI 0.08 to 0.14) per 1000 person years, a 95.4% reduction compared with earlier phases.

The highest incidence rates were observed during the beta and first omicron waves, while the post-first omicron waves consistently had very low incidence rates (Figure 3B).

The hazard rate for severe, critical or fatal COVID-19 exhibited fluctuations over time with the occurrence of waves (online supplemental figure S1A). Its peak was observed during the beta wave, but a rapid decline in the hazard rate followed, coinciding with the rapid scale-up of primary-series vaccination (refer to vaccination scale-up data in online supplemental figure S2). During the first omicron wave, the hazard rate swiftly declined, reaching a very low level by the end of this wave that was sustained for the remainder of the study despite several subsequent omicron subvariant waves.

Incidence rate of fatal COVID-19

A total of 131 individuals developed fatal COVID-19 during follow-up, all of which occurred after the primary infection and none during reinfection. The cumulative incidence of fatal COVID-19 after 3.14 years of follow-up was 0.042% (95% CI 0.036% to 0.050%), with two major jumps in incidence during the beta and omicron waves (Figure 4B).

The incidence rate of fatal COVID-19 was 0.13 (95% CI 0.11 to 0.16) per 1000 person years throughout the pandemic (Figure 5B). During the pre-omicron phase,
Figure 3  Temporal patterns of infections and severe and fatal COVID-19 during the waves and phases of the pandemic. (A) Daily count of newly diagnosed SARS-CoV-2 infections. (B) Incidence rate of severe, critical or fatal COVID-19. (C) Incidence rate of fatal COVID-19.
the first omicron wave, and these two phases combined, it was 0.16 (95% CI 0.13 to 0.19), 0.60 (95% CI 0.44 to 0.83) and 0.20 (95% CI 0.17 to 0.24) per 1000 person years, respectively. In the post-first omicron phase, the incidence rate dropped drastically to 0.02 (95% CI 0.01 to 0.04) per 1000 person years, a 90.0% reduction compared with earlier phases.

The highest incidence rates were observed during the beta and first omicron waves, while the post-first omicron waves consistently had very low incidence rates (figure 3C).

The hazard rate for fatal COVID-19 exhibited fluctuations over time with the occurrence of waves, peaked during the beta wave, and very rapidly declined during
the first omicron wave (online supplemental figure S1B). It reached a very low level by the end of the first omicron wave that was sustained for the remainder of the study despite several subsequent omicron subvariant waves.

**Associations with severe and fatal COVID-19**

The AHR for severe, critical or fatal COVID-19 was lower in females compared with males, increased exponentially with age and linearly with the number of coexisting conditions, and decreased extensively, in a dose—response relationship, with the number of vaccine doses (figure 6A–D). Similar associations were observed for fatal COVID-19 (figure 6E–H).

**DISCUSSION**

The end of the first omicron wave marked a turning point in the pandemic, with a 95% drop in the incidence rate of severe, critical or fatal cases of COVID-19 compared with earlier stages. Vaccinations and advancements in case management contributed to reducing severity and fatality gradually over time, and there was a rapid decline in severity during the mass scale-up of primary-series vaccination. However, the end of the first omicron wave served as the central turning point in severity. By the end of this wave, severity rates reached very low levels not seen since the onset of the pandemic, and these levels
Figure 6  Adjusted HRs for severe, critical or fatal COVID-19 and for only fatal COVID-19 across sex (A and E), age (B and F), number of coexisting conditions (C and G), and vaccination dose status (D and H), respectively.

*Upper bound of confidence interval truncated for better visibility due to wide interval.
have been sustained since then, despite the occurrence of several immune-evasive omicron subvariant waves. There has been no appreciable rebound in severity at any time since this first omicron wave, with nearly total decoupling between the incidence of infection and incidence of severe COVID-19.

This turning point is likely attributed to the rapid buildup of natural immunity during the first omicron wave, which had the highest infection incidence throughout the pandemic. This aligns with earlier studies in Qatar, demonstrating strong protection against severe reinfection among individuals with prior infection and limited waning in protection. Other factors, such as lower severity in omicron subvariants, the overall decreased infection incidence in the post-first omicron phase, and the forward displacement of deaths of individuals with relatively short life expectancy, have all also likely contributed to this shift in severity.

A defining aspect of this transition is the near-complete decoupling between infection and severity after the first omicron wave (figure 3), and between acute-care admissions and severe cases (figure 1A), as reported elsewhere. Meanwhile, there was some decoupling between ICU admissions and critical cases, although to a lesser extent (figure 1B), suggesting ICU admissions as an early warning indicator for changes in COVID-19 severity.

COVID-19 severity varied throughout the pandemic based on the circulating variant and infection incidence, as well as population immunity due to vaccination and previous infections. The beta wave exhibited the highest severity due to the severity of that variant and concentrated incidence (figure 3). The first omicron wave followed with high severity, despite the lower severity of the omicron variant compared with earlier variants. This was primarily due to a high concentration of infections within a short duration, and perhaps a stretched healthcare system dealing with a large number of severe cases.

The introduction of the delta variant, occurring in Qatar, demonstrating strong protection against severe reinfection among individuals with prior infection, and limited waning in protection. Other factors, such as lower severity in omicron subvariants, the overall decreased infection incidence in the post-first omicron phase, and the forward displacement of deaths of individuals with relatively short life expectancy, have all also likely contributed to this shift in severity.

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In summary, while vaccinations and advancements in case management have contributed to a gradual reduction in severity and fatality over time in Qatar, the end of the first omicron wave marked a significant turning point in the trajectory of severity during this pandemic. The post-first omicron phase exhibited a remarkable 95% reduction in the incidence rate of severe, critical, or fatal cases compared with earlier stages, accompanied by a 90% decrease in the incidence rate of fatal COVID-19. Severity reached sustained very low levels with no rebound despite subsequent occurrence of several immune-evasive omicron subvariant waves. This shift in severity is believed to be driven by the rapid accumulation of natural immunity during the initial omicron wave. Given the limited observed waning in the protection provided by natural immunity against severe reinfection, it is plausible that the phase of low severity could be sustained as long as the virus does not undergo extensive evolution beyond what has been observed since the introduction of omicron, and the population does not have high rates of comorbidity, which could dangerously exacerbate a repeat infection.

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