Epidemiological Assessment of Sars-Cov-2 Reinfection

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Abstract

Introduction. Vaccination against SARS-CoV-2 infection has been shown to reduce the severity of infection; however, the overall reinfection rate in those unvaccinated, partially vaccinated and fully vaccinated remains unclear. Therefore, this study was undertaken to elucidate the rates and associated factors for such occurrences.

Methods. This was a retrospective epidemiological report analysing 1362 COVID-19 reinfection cases in the Kingdom of Bahrain between April 2020 and July 2021. The differences in disease severity and characteristics of reinfection between various levels of vaccination statuses were determined among fully vaccinated, interrupted vaccination (positive test less than 14 days after receiving the second dose of vaccine), one dose of vaccination, post-reinfection vaccination and unvaccinated. Data were collected from the National COVID-19 Contact Tracing Team Database of individuals who tested positive for SARS-CoV-2.

Results. During the study, reinfection cases increased from zero cases per month in April – June 2020 to a sharp peak of 579 reinfection cases in May 2021 followed by a rapid decline. Males constituted a significantly larger proportion of reinfections (n=821, 60.3%) than females (39.7%) (p<0.0001). Reinfection episodes were highest amongst the 30-39 years of age (n=405, 29.7%). The rate of reinfection increased with time from the initial infection with the lowest reinfection rate occurring at 3-6 months after the first infection (n=281, 20.6%) and the highest episodes occurring ≥ 9 months after initial infection (n=632, 46.4%). Comparison of the symptomatology between initial infection and reinfection episode for each individual showed that most individuals were asymptomatic during both episodes (n=486, 35.7%), while 265 (19.5%) individuals were symptomatic during both episodes. Reinfection disease severity was mild and differed across the cohort (χ^2 test p=0.003) with vaccinated patients less likely to have symptomatic reinfection (OR 0.71, p=0.004). Only 89 (6.6%) reinfection cases required hospitalization and there were no deaths (Poisson exact, 97.5% CI 2.7 per 1000).

Conclusion. Vaccine induced immunity and prior infection with or without vaccination were effective in reducing disease severity of reinfection episodes.

Introduction

Coronavirus Disease 2019 (COVID-19) started as an outbreak in Wuhan, China, on December 2019, and was declared a pandemic by the World Health Organisation in March 2020¹. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that has affected more than 271,900,000 people worldwide and led to over 5,000,000 deaths as of 19 December 2021². There are currently five SARS-CoV-2 variants that are classified as variants of concern; Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and more recently, Omicron (B.1.1.529)³. COVID-19 disease manifests with significant variation; however, the classic symptoms include fever, cough, shortness of breath, fatigue, headache, sore throat, and changes to taste or smell that may appear 2-14 days after viral exposure⁴.

Global pandemic control and national policies have been constructed on herd immunity theory and the assumption that viral exposure would be sufficient to provide long-standing immunity. With the availability of vaccines, demonstrating the efficacy of viral exposure against infection was possible. Research showed that vaccine-induced immunity against the alpha^{5,6}, beta⁷, gamma⁸ and delta⁹ variants was achievable. Despite this, there have recently been an increasing number of reports of SARS-CoV-2 reinfections. The first case of reinfection was reported in the USA by Tillett et al., where a 25-year-old man tested positive on two occasions 48 days apart, separated by 2 negative PCR tests¹⁰. After genetic analysis, the authors concluded that the genetic variation between the two SARS-CoV-2 specimens was too significant to be explained by short-term in vivo evolution. Currently, there are over 900 studies published regarding reinfection in COVID-19¹¹, highlighting the genuine possibility of reinfection that needs to be taken into account by researchers and policymakers.

With the emergence of the Omicron variant another global infection wave with the risk of national restrictions and lockdowns is likely. If reinfection is indeed a feature of COVID-19 infections, it poses a significant obstacle in tackling the pandemic as this jeopardises the assumption of herd immunity that many control measures have adopted in the context of containing the spread COVID-19. In this paper, we studied the characteristics of cases with recorded reinfection in the Kingdom of Bahrain to understand reinfection and epidemiologically compared vaccine-induced and natural infection-induced immunity.

Methods

1. Study Design

This was a retrospective epidemiological report analyses SARS-CoV-2 reinfection cases in Bahrain between April 1 2020, and July 23 2021, obtained from the Bahrain National COVID-19 database of individuals who tested positive for SARS-CoV-2 on ≥ 2 episodes. Information collected in this study included reinfection status, vaccination status, age, symptoms, time to reinfection and hospitalization. Symptomatic and asymptomatic patients of any age, identified in several screening and contact-tracing programs, and those from travel testing and random screening, were included. A total of 1390 cases of reinfection were identified for the study period, of which 28 cases were excluded due to incomplete information. A total of 1362 reinfection cases were further analyzed.

We first examined the general characteristics of individuals with reinfection, including gender, age group, symptom, hospitalisation status, and available SARS-CoV-2 variant of interest from the national genome database. Characterisation of disease severity and hospitalisation status were based on the Bahrain COVID-19 National Protocol¹²; (a) isolation refers to home isolation without hospitalisation, (b) moderate disease status refers to a temperature of $\geq 38^\circ\text{C}$ with either one of shortness of breath, chest pain, change in mental status or respiratory rate >30 , (c) severe disease status refers to a patient requiring $\geq 15\text{L}$ oxygen in addition to moderate status criteria. Symptom status was defined as per the US Center for Disease Control (CDC)¹³. Symptomatic status describes an infection of SARS-CoV-2 where symptoms have developed, including fever, cough, shortness of breath, fatigue, headache, a new loss of taste or smell, sore throat and other symptoms. Asymptomatic status describes a SARS-CoV-2 infection where no symptoms developed throughout the episode.

Next, we analysed the differences in these characteristics in reinfection between differing vaccination statuses. We defined a vaccinated individual as having received 2 doses of a COVID-19 vaccine ≥ 14 days before reinfection episode. We defined reinfection as any individual with a positive RT-PCR test ($Ct < 35$) ≥ 90 days from the first episode of infection, regardless of symptoms, and supported by close-contact exposure or outbreak settings. Given this, we categorised reinfection by vaccination statuses as follows (Table 1):

Table 1. Description of the categories used to classify the data in the study. Individuals were sorted into 5 different categories according to their vaccination status. Reinfection was then compared between these categories.

Fully vaccinated	individuals who tested positive for reinfection episode at 14 days or longer after receiving the second dose of vaccine.
Interrupted vaccination	individuals who tested positive for reinfection episode less than 14 days after receiving the second dose of vaccine.
1-dose vaccination	individuals who tested positive for reinfection episodes after receiving only one dose of vaccine.
Post-reinfection vaccination	individuals who started vaccinating after their reinfection episode.
Unvaccinated	individuals who did not receive any vaccine dose during the study period.

In addition to general demographics, we also analysed time to reinfection and CT values by vaccination status.

2. Data collection

Beginning in February, 2020, the National COVID-19 Task Force of Bahrain began testing all travelers on arrival into the country, suspected cases, symptomatic individuals, asymptomatic contacts (including family members) of those who had tested positive for SARS-CoV-2, all hospitalized and critically ill patients suspected of being infected with SARS-Cov2, and through large-scale random testing of individuals. The following categories of persons undergo PCR testing as per the testing strategy: (1) Incoming travelers: all travelers, regardless of their vaccination status, required a PCR test upon arrival and a second PCR test 10 days later. (2) Symptomatic patients: patients exhibiting symptoms suggestive of COVID-19 underwent PCR testing at a medical facility or a designated drive-through testing site after reporting their symptoms through the “BeAware” mobile application or by calling the toll-free COVID-19 hotline. (3) Admitted and pre-operative patients: All patients admitted to the hospital were required to undergo a test regardless of the medical condition that prompted admission. (4) Close contacts: all close contacts identified in contact tracing were required to quarantine for 10 days from the date of last exposure and to undergo a PCR test at the beginning and following the quarantine period.

In addition, random tests were conducted daily. SMS messages were sent to citizens and residents randomly, inviting them to conduct a free test at their nearest testing site. Mobile units were also dispatched to supermarkets, malls, banks, construction sites, markets, and other areas where people from multiple socio-economic, cultural, and national backgrounds gathered.

We collected the data from the National COVID-19 Contact Tracing Team Database of individuals who tested positive for SARS-CoV-2. The diagnosis followed the national Validation Protocol of Novel Coronavirus Nucleic Acid detection method. The process was based on RT-PCR tests of nasopharyngeal samples using Thermo Fisher Scientific (Waltham, MA) TaqPath 1-Step RT-qPCR Master Mix, CG (catalogue number A15299) on the Applied Biosystems (Foster City, CA) 7500 Fast Dx Real-time PCR Instrument. The assay used followed the WHO protocol and targeted E gene. If positive, the sample was confirmed by RdRP and N genes. The E gene CT value was reported and used in this study. CT values < 35 were considered positive.

SARS-CoV-2 variant sequencing was undertaken at the National COVID-19 Molecular Public Health Laboratory. Whole genome sequencing was used to identify the standard variants of interest and concern using Congenica Illumina/ARTIC and COVID-Seq protocols. The data were analysed with the Abiomics platform. Spike gene target status on PCR was used as a second approach for identifying each variant. Data regarding sequencing of the variant was only available for 145 patients, of which none were excluded in the analysis.

3. Data Handling and Statistical Analysis

Epidemiological data is presented as (n, [%]), where (n) is the sample size corresponding to each category, and [%] is the category sample size as a proportion of the total cohort studied, unless otherwise stated. We report proportions calculated using Agresti Coull 95% CIs and use Pearson’s Chi-Squared tests to report statistical significance unless otherwise indicated. We used z-test of proportion to compare vaccine breakdown between reinfection cases and the general population and ANOVA test to statistically analyse the difference in time to reinfection by vaccination status. P-values were considered statistically significant at $p < 0.05$. SPSS version 26 was used for statistical analysis (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).(IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Figures were created using GraphPad Prism version 9.3.1 (350) for macOS GraphPad Software, La Jolla California USA, www.graphpad.com.

4. Ethical approval

The protocol and manuscript for this study were reviewed and approved by the National COVID-19 Research Committee in Bahrain (CRT-COVID2021-148).All methods and retrospective analysis of data were approved by the National COVID-19 Research and Ethics Committee, informed consent obtained from all participants and the study carried out following local guidelines and ethical guidelines of the Declaration of Helsinki 1975.

Results

1. Epidemiological patterns of reinfection

The first SARS-CoV-2 infection case in Bahrain was detected on February 23, 2020. During the study period, the number of reinfection cases steadily increased from zero cases per month in April – June 2020 to a peak of 579 reinfection cases in May 2021. The cases decreased to 36 cases by July 2021 (Figure 1).

1.1 Demographics

Within the study cohort of 1362 reinfection cases, males constituted a significantly greater proportion of reinfections (n=821, 60.3%) than females (39.7%) (p<0.0001). Reinfection episodes were highest amongst the 30-39 years of age (n=405, 29.7%) and lowest amongst the 0-9 years of age (86, 6.3%), as summarised in Table 2.

1.2 Time to reinfection

Upon studying the time interval from initial infection to reinfection, the number of cases of reinfection showed a linear decrease with decreasing the time interval between infections and reinfections. Most reinfection episodes occurred at 9 months or longer after initial infection (n=632, 46.4%) and the lowest total cases of reinfection occurred at a period of 3-6 months between episodes of infection (n=281, 20.6%) (Table 2).

1.3 Presentation and outcome

We compared each individual's symptom status between initial infection and reinfection episodes. Most individuals were asymptomatic during both episodes (n=486, 35.7%), while 265 (19.5%) individuals were symptomatic during both episodes. The differences in symptoms between both episodes were significant across the cohort (p=0.003). Only 89 (6.6%) reinfection cases required hospitalisation, of which 80 (5.9%) were of moderate disease status and 9 (0.7%) were of severe disease status (p<0.0001) (Table 2).

1.5 Variant sequencing

Data regarding sequencing of the SARS-CoV-2 variant was only available for 145 individuals (Table 3). Most cases of reinfection corresponded to the delta variant (B.1.617) (n= 67, 46.2%), followed by the alpha variant (B.1.17) (n= 60, 41.3%).

Table 2. Summary of data from 1362 cases of reinfection in Bahrain. Data is stratified by vaccination status, as indicated in the row headings, with the “Total” row summarizing all reinfection data, independent of vaccination status. Values are presented as “n [%]”, where (n) is the total number of individuals corresponding to each category, and [%] is the (n) as a proportion of the column total shown in the first row.

		Total n [%]	Fully vaccinated n [%]	Interrupted vaccination n [%]	1-dose vaccination n [%]	Post-reinfection vaccination n [%]	Unvaccinated n [%]
No. of reinfection cases		1,362	387	23	116	171	665
Gender							
	Male	821 [60.3]	287 [74.2]	17 [73.9]	74 [63.8]	113 [66.1]	330 [49.6]
	Female	541 [39.7]	100 [25.8]	6 [26.1]	42 [36.2]	58 [33.9]	335 [50.4]
Age group distribution							
	0-9	86 [6.3]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	86 [12.9]
	10-19	128 [9.4]	3 [0.8]	0 [0.0]	1 [0.9]	3 [1.8]	121 [18.2]
	20-29	363 [26.7]	106 [27.4]	7 [30.4]	35 [30.2]	52 [30.4]	163 [24.5]
	30-39	405 [29.7]	133 [34.4]	10 [43.5]	47 [40.5]	59 [34.5]	156 [23.5]
	40-49	226 [16.6]	85 [22.0]	3 [13.0]	21 [18.1]	31 [18.1]	86 [12.9]
	50+	154 [11.3]	60 [15.4]	3 [13.0]	12 [10.3]	26 [15.2]	53 [8.0]
Period between infections (months)							
	3-6	281 [20.6]	33 [8.5]	3 [13.0]	24 [20.7]	68 [39.8]	153 [23.0]
	6-9	449 [33.0]	98 [25.3]	9 [39.1]	31 [26.7]	63 [36.8]	248 [37.3]
	9+	632 [46.4]	256 [66.1]	11 [47.8]	61 [52.6]	40 [23.4]	264 [39.7]
Symptoms status							
	Symptomatic first infection episode only	224 [16.4]	70 [18.1]	4 [17.4]	17 [14.7]	30 [17.5]	103 [15.5]
	Symptomatic second infection episode only	387 [28.4]	90 [23.3]	7 [30.4]	39 [33.6]	53 [31.0]	198 [29.8]
	Symptomatic at both episodes	265 [19.5]	64 [16.5]	2 [8.7]	25 [21.6]	28 [16.4]	146 [22.0]
	Asymptomatic at both episodes	486 [35.7]	163 [42.1]	10 [43.5]	35 [30.2]	60 [35.1]	218 [32.8]
Hospitalization status							
	Isolation	1273 [93.5]	378 [97.7]	23 [100.0]	110 [94.8]	156 [91.2]	606 [91.1]
	Moderate	80 [5.9]	9 [2.3]	0 [0.0]	4 [3.4]	15 [8.8]	52 [7.8]
	Severe	9 [0.7]	0 [0.0]	0 [0.0]	2 [1.7]	0 [0.0]	7 [1.1]

Table 3. Breakdown of variant causing reinfection in 145 individuals. Figures are represented as n [%], where (n) is the total number of individuals corresponding to each category, and [%] is the n as a proportion of the total (N=145).

Variant	n [%]
B.1.617	67 [46.2]
B.1.17	60 [41.3]
B.1.351	4 [2.8]
B.1.281	1 [0.7]
B.1	4 [2.8]
Other	9 [6.2]

2. Analysis by vaccination status

Of the 1362 individuals studied, 388 (28.5%) were vaccinated, and 974 (71.5%) were unvaccinated before reinfection. We further stratified this data into 5 levels of vaccination (see Methods: 1.0 Study Design) and summarised in Table 1.

2.1 Demographics

In addition to males representing the majority of reinfection cases overall, the male gender was higher in proportion across all vaccination statuses ($p < 0.0001$) in accord with Bahrain's demographics. Reinfection was highest amongst the 30-39 age group across most vaccination statuses, except the unvaccinated group, where the 20-29 age group predominated. Similarly, reinfection was least amongst the 0-9 age group in most vaccination statuses, except the unvaccinated age group, where the 50+ age group showed the least reinfection.

2.2 Time to reinfection

We observed an increase in the number of reinfection cases with increasing time periods from initial infection episode. The lowest number of cases correspond to 3-6 months between the two infection episodes, and the highest cases occurred at 9 months or longer after initial infection. This was observed across the majority of vaccination statuses, except the post-reinfection vaccination status, where this trend was reversed ($p < 0.0001$): most reinfection cases in this group occurred 3-6 months from initial infection ($n=68$, 39.8%) and the least occurred at 9 months or longer after initial infection ($n=40$, 23.4%). To further dissect time to reinfection, we compared average number of days to reinfection between the various vaccination statuses. The highest number of days to reinfection was observed in the fully vaccinated group (mean=300.7, SD=78.0, 95% CI 292.9 – 308.5), and the lowest was observed amongst the post-reinfection vaccination group (mean=208.3, SD=79.8, 95% CI 196.2 – 221.3). The data are summarised in Figure 2. ANOVA analysis showed that average number of days to reinfection was significantly different between the various vaccination statuses ($p < 0.0001$).

2.3 Presentation and outcome

Most reinfections were asymptomatic during both initial infection and reinfection. This was observed in all vaccination status groups ($p=0.001$), except individuals who received 1-dose of vaccination before reinfection. Here, the majority were symptomatic, but only during their reinfection episode ($n=39$, 33.6%) (Table 2). We used logistic regression analysis to examine the effect of symptom status at first infection, gender and age on the probability of being symptomatic on reinfection. The risk of symptomatic presentation of reinfection rose with age (OR for a 1-decade increase in age 1.13, $p=0.002$) and was higher in females (OR 1.3, $p=0.022$). Patients whose first infection was symptomatic were more likely to have a symptomatic second infection (OR 1.5, $p=0.001$). Adjusted for these, unvaccinated patients were more likely to have symptomatic reinfection (OR 1.62, $p=0.001$).

Investigation of the effect of vaccination status on hospitalization showed that most reinfection cases required self-isolation as observed in all vaccination status groups ($p < 0.0001$). Moderate and severe disease statuses, which required hospitalization, were predominantly individuals with 1-dose of vaccine, post-reinfection or unvaccinated. Absence of vaccination was a significant predictor of requiring hospital treatment, with rates of 4.3% in the vaccinated and 8.9% in the unvaccinated groups, giving a preventable fraction in the vaccinated group of 52% (95% CI 26% to 67%, $p < 0.001$). The risk of requiring hospital treatment rose with age (OR for a 1-decade increase in age 1.7, $p < 0.001$) but did not differ significantly between male and female. Although 9 (2.3%) vaccinated individuals required hospitalisation, no deaths were recorded in the vaccination group (Poisson exact, 97.5% CI 2.7 deaths per 1000), while 1 death was recorded among those unvaccinated ($p=0.009$).

2.4 Vaccine type

Of the 387 fully vaccinated individuals, 87.3% ($n=338$) reinfection cases corresponded to Sinopharm vaccine. After adjusting for population proportions of Sinopharm vaccine uptake, the proportion of reinfections following Sinopharm vaccination was statistically significant ($p < 0.0001$). All other vaccines showed a significantly lower proportion of reinfection compared to the general population uptake of each vaccine (Table 4).

Table 4. Vaccine breakdown amongst cases of reinfection compared to general population in the kingdom. Data is presented as n [%], where (n) is the total number of individuals corresponding to each category, and [%] is the n as a proportion of the column total shown in the first row. We report results from z-test of proportions to compare vaccine breakdown amongst reinfection cases to the proportion of the population receiving each vaccine.

Vaccine	Sample breakdown n, [%]	Population breakdown n, [%]	Z-statistic	P-value
Total	387	1,033,078		
Sinopharm	338 [87.3]	575,159 [55.7]	12.51	<0.0001
Covishield	20 [5.2]	192,357 [18.6]	6.78	<0.0001
Sputnik	20 [5.2]	186,275 [18.0]	6.55	<0.0001
Pfizer	9 [2.3]	79,287 [7.7]	3.99	0.0001

Discussion

The epidemiological data presented in this study indicates that reinfection can occur for both vaccinated and unvaccinated individuals. Through analysis of reinfection by vaccination status, we report that vaccine-induced immunity may be more effective at reducing reinfection episodes, indicated by the relatively lower proportion of vaccinated reinfections amongst the studied population. These results are in contrast to the notion that vaccine-induced and infection-induced immunity are comparable¹⁴. And although it is difficult to compare effectiveness without analyzing incidence, the relative benefit of vaccine-induced immunity has already been observed and reported extensively¹⁵. Additional studies showed that those who recovered from COVID-19 were twice as likely to become reinfected than those who were vaccinated¹⁶. Another study showed the relative risk to be five times in the recovered compared to those who were vaccinated¹⁷. It had been suggested that there is a difference in the immune response in these two groups with infection-induced immunity producing a lower antibody level, but longer memory cells and vice versa for vaccination-induced immunity^{18,19}. We observed no deaths amongst vaccinated reinfections, however this observed rate showed an upper 97.% CI of 2.7 deaths per 1000. Nonetheless, the number recorded for unvaccinated reinfections is very small, and hence caution must be taken on the interpretation of mortality from the data presented in this study.

The rate of reinfections has been persistently low throughout the literature. A systemic review on reinfection involving 113,715 patients highlighted that most reports quote a low reinfection rate of 1% amongst populations²⁰. These findings suggest that the risk of reinfection to the public health is low. However, it also challenges the perception of herd immunity towards policies for tackling COVID-19. For instance, Pinto et al. suggested that immunity passports are based on the assumption that reinfection is unlikely, which may need to be re-evaluated. Pinto et al. also argued that the perspective of vaccine failure and booster requirements should include iatrogenic immune response decay similar to the natural immune response²¹.

Interestingly, we observed a steady increase in reinfection cases with an increased time period from the last infection. This was true for both vaccinated and unvaccinated reinfections. This may be due to natural waning of immunity, specifically due to Sinopharm as it corresponded to the highest vaccinated reinfections, even after comparing to population uptake in the country. However, the peak of reinfection in May 2021 may also be influenced by behavioral factors due to its concurrence with the Ramadan period with increased communal gatherings. We also observed reinfections at periods more than 6 months from primary infection, mostly amongst unvaccinated individuals, in accord with CDC reports stating that “vaccine-induced immunity was more protective than infection-induced immunity”¹⁷. However, some reports show persistent immunological memory more than 6 months after primary infection^{22,23}. The dominant theory in the current literature is that of immune decay. Protective immunity is assessed as a correlate of neutralising antibody responses, which exclusively recognise the viral spike protein²⁴. A recent study showed that the risk of reinfection among vaccinated and recovered individuals remained low at least within the first six months of infection or vaccination¹⁵. Several studies show a decline in these antibodies within 2-3 months after SARS-CoV-2 infection²⁵⁻²⁷. A study by Cromer et al. suggested that the rapid initial decay of immunity was due to the short half-life of serum antibodies and antibody-secreting cells¹⁴. This may explain the increased risk of reinfection with longer periods from the primary infection.

Nonetheless, immune decay is an expected phenomenon following both vaccine-induced and infection-induced immunity and characteristic of many viral infections²⁸. However, in the context of SARS-CoV-2, acquired immunity may only be protective for months rather than years, though this is likely to be a reflection of the interplay between immune decay and improved variant immune evasion with novel SARS-CoV-2 variants.

We reported that 46% of reinfection was due to the delta (B.1.617) variant, closely followed at 41% by the alpha (B.1.1.7) variant. Both these variants have evolved immune evasion, seen for both vaccine induced and natural immunity²⁹. However, due to data limitations, the variant breakdown results reported in our study correspond to a small sample size of 145.

Through analysis of reinfection by age, we report the highest reinfection episode amongst the 20-39 age group. This finding is consistent with reports of increased susceptibility to the infection among individuals aged >20 years^{30,31}. More specifically, the highest proportion corresponded to the 30-39 age group. This result is also directly comparable to results from our previous report on SARS-CoV-2 cases in Bahrain³². We argued that specific to the Bahraini population, this increased susceptibility was attributable to this being the working-age group in Bahrain, and hence are increasingly exposed to social interactions. Moreover, the spike and subsequent fall coincided with Ramadan (the month of fasting) when traditional large communal gatherings occur enhancing the social interaction seen coinciding with the lifting of restrictions on gatherings in restaurants, coffee-shops and cinemas may influence the rate of interaction and hence transmission of COVID-19 amongst these age groups. Interestingly, this trend was observed across both vaccinated and unvaccinated reinfections, further suggesting that the reinfection risk was driven by environmental factors rather than vaccination status.

However, these findings contradict those from a large study by Hansen et al., studying reinfection amongst 4 million individuals in Denmark³³. The study reports higher protection against reinfection in individuals aged <65 years, and lower protection in those >65 years. Although our results do not assess protection, we report higher proportions of reinfections amongst 20-39 than those aged 50+ years. We believe our findings are influenced by the proactive vaccination policy with priority to those over 65 years in Bahrain and possible increased precautionary measures amongst this age group. Additionally, we believe these differences may be due to factors such as environmental effects, demographics, way of life and the differences in the phase of the pandemic between Denmark and Bahrain. In addition, this research was conducted between September and December 31, 2020, while the first cases of alpha (B.1.1.7) and delta (B.1.617) variants only appeared in Denmark on November 9 and December 5, 2020, respectively³⁴. Due to the difference in cohort sampling times, it is possible that the results also report characteristics of different variants. Alternatively, the first cases of alpha (B.1.1.7) and delta (B.1.617) variants in Bahrain were reported on February 14 and April 5, 2021, respectively³⁵. This may explain the sharp rise in cases of reinfection in both February and May (Figure 1).

We analysed reinfection amongst vaccinated individuals with regards to the vaccine administered that showed the highest proportion (87.4%) of reinfections corresponded to the Sinopharm vaccine, despite accounting for only 55.7% of the vaccinated population. However, the Sinopharm vaccine was the first to be approved for use in Bahrain³⁶ and combining this with immune decay, it is possible that these individuals who had taken early vaccination with Sinopharm during the pandemic were the most likely to be reinfected due to the longer period of immune decay. However, the number of subjects analysed were relatively low and further data is needed to confirm these findings.

It is interesting to note that this cohort of cases had mild symptoms or were asymptomatic (93.5%). This is comparable to results from a systemic review of reinfection cases, stating that 75% of cases were categorized as "mildly symptomatic"¹¹. However, asymptomatic infection was 42.1% among fully vaccinated vs. 32.8% among those who were not vaccinated. Notably, the interrupted vaccination (re-infected less than 14 days from 2nd dose) did not show the same result. The vaccine had been developed and tested to decrease severe disease and mortality. In a systematic analysis, the vaccine efficacy/effectiveness was 80-90% in fully vaccinated individuals against symptomatic and asymptomatic infections³⁷. In addition, one study among healthcare workers showed a decline in symptomatic and asymptomatic SARS-CoV-2 infections following the vaccination despite high rates of COVID-19 disease nationally³⁸.

It is expected that vaccination protects against moderate and severe diseases. In this cohort, moderate and severe disease rates were 2.3% among those fully vaccinated vs 8.9% among those not vaccinated showing that vaccinated individuals have less hospitalization than unvaccinated. One study of a mRNA vaccine showed lower hospitalization among vaccine breakthrough infections vs those without vaccination³⁹. In addition, another study of inactivated COVID-19 vaccine showed a significant reduction in symptomatic disease following vaccination⁴⁰.

As noted above, COVID-19 testing in Bahrain has been extensive and includes a large proportion of random testing conducted daily. We believe this ensures that the number and nature of confirmed cases accurately reflect actual incidence rates. Finally, it is essential to note that reinfection with SARS-CoV-2 is not unexpected, as this is an established characteristic of viruses causing mucosal infections²⁸, and hence an important factor moving forward to establish better COVID-19 policies to address the pandemic effectively.

LIMITATIONS AND FURTHER WORK

The main limitation of this study is that vaccination status was determined by time since the first infection. This introduces the possibility of immortal time bias, where the longer the period is before reinfection, the higher the chance the person will have attained a full vaccination status. Hence, time to reinfection may be influencing vaccination status simultaneously as vaccination status is influencing time to reinfection. Secondly, our primary cohort analysis constituted only 1362 reinfection cases, which is further minimised when divided into different analysis categories. Additionally, the majority of vaccinations in the cohort were Sinopharm, meaning analysis of vaccination is mainly a reflection of Sinopharm. It would be important to replicate this study with a larger cohort and different ethnic populations to expand our understanding of SARS-CoV-2 reinfection patterns. Epidemiological confirmation of reinfection and viral genotype assays of the first and second specimens are needed; however, it was not possible in this study; therefore, we were unable draw reliable conclusions. Vaccine analysis suggested that Sinopharm vaccine was associated with more reinfection but again this needs to be confirmed in a larger population or by meta-analysis. Studying variant breakdown and vaccine breakdown simultaneously could improve our understanding of vaccine efficacy with variant evolution. Finally, we believe replicating this study with added focus on differentiating reinfection and reactivation would be instrumental to understanding and controlling COVID-19 spread.

In conclusion, vaccine induced immunity and prior infection with or without vaccination were effective in reducing disease severity of reinfection episodes.

Declarations

Funding

None.

Competing interests

The authors declare no competing interests.

Ethics approval

Approval granted after review from National COVID-19 Research and Ethics Committee (Approval Code: CRT-COVID2021-148).

Consent to participate

Not applicable.

Consent for publication

All authors approved the publishing of this data.

Data availability

The datasets used and analysed in this study are available from the corresponding author on reasonable request. Requests may need prior approval from the ethical committee, and data may need to be de-identified.

Authors' contributions

AAA provided the data from the National COVID-19 Database. MAM and MAQ analyzed and interpreted the data and wrote the manuscript. ASA and RC conducted the statistical analysis and contributed to the writing of the manuscript. SA and JAAT contributed to the interpretation and writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Figures

Figure 1

Graphical representation of number of reinfection cases reported per month over the study period. The number of cases reported is represented by the number above the bar corresponding to the month.

Figure 2

Summary of number of days to reinfection across different vaccination statuses for 1362 individuals. Boxplot charts plotting minimum, IQR, median and maximum for each status on the y-axis, with corresponding descriptive statistics tabulated.

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