



Research Article

COVID-19 Vaccine Breakthrough Infections and Compliance to Non-Pharmaceutical Public Health Interventions: A Nested Case-Control Study

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Abstract

Vaccination against SARS-CoV-2 was a leading strategy to change the course of the COVID-19 pandemic worldwide. Nonetheless, some people still contracted the infection. Causes for breakthrough infections post vaccination with at least 1 dose, can be many such as age, time since vaccination, level of immunity at the moment of exposure, variant to which the individual was exposed, and compliance to non-pharmaceutical interventions. Out of the 2549 SARS CoV-2 infections, majority (42.6%) got infected between 31-90 days after receiving the second dose, 22% were infected within 14 days of receiving the second dose, and 12.3% were infected before receiving the second dose while only 5% of the cases were infected after 3 months post-second dose. This retrospective nested case-control study was conducted to examine whether non-compliance to non-pharmaceutical public health interventions can explain the SARS-CoV-2 breakthrough infection among the vaccinated population. Irrespective of the vaccination status, majority of the 4456, adhered to avoiding social-gatherings (76.9%), avoided physical-contacts (59.5%), wearing facemasks (59.4%), regular hand-hygiene (53.9%) and social-distancing (49.5%). People who adhered to getting vaccinated against the infection, adhered to the precautionary measures mandated to prevent spread of infection, though may not always. Our study found significant association between vaccination status and compliance to the non-pharmaceutical public health interventions as well as between compliance to the non-pharmaceutical public health interventions and breakthrough SARS-CoV-2 infections. A short-term public health response to an increase in severe breakthrough infections, would be to reimpose non-pharmaceutical preventive measures to slow the transmission while a medium-term solution would be to develop newer vaccine formulations or identify newer non-pharmaceutical interventions.

Keywords: Breakthrough infections; Non-pharmaceutical public health interventions; SARS-CoV-2 breakthrough cases

Background

A stable public health control measure for early containment of an emerging outbreak of directly transmitted infections involves the early detection of infected persons, their isolation as well as the tracing, testing and quarantine of their contacts. [1] Non-pharmaceutical interventions (NPIs) are actions, apart from getting vaccinated and taking medicine, that aim to prevent and/or control the transmission of infectious diseases like pandemic flu and COVID-19 or when a new flu virus appears among people. NPIs include personal preventive measures e.g. isolation, hand washing, using hand sanitizers, use of face masks in public, avoiding physical contacts (like hand shaking); community interventions like social/physical distancing (Keeping a distance of at least two metres from people who have symptoms of illness), stay-at-home orders, school and venue closures, workplace restrictions and restrictions on movement and travel; and environmental measures, such as environmental cleaning, maintaining good ventilation indoors, etc. NPIs are the most effective public health interventions against COVID-19, after vaccination. [2] Vaccination against SARS-CoV-2 was a leading strategy to change the course of the COVID-19 pandemic worldwide including Qatar. Qatar was one of the first few countries to procure and start Covid-19 vaccination campaigns. In Qatar, COVID vaccination commenced on 23rd December 2020, primarily with the Pfizer BNT162b2 mRNA vaccine and Moderna mRNA-1273 being introduced later. Four COVID vaccines namely Pfizer, Moderna, AstraZeneca, Jansen & Jansen were approved in Qatar and few others like Sinopharm, Sputnik and Sinovac were conditionally approved. Qatar's vaccination campaign was swift, effective, and had a significant impact on the local COVID-19 dynamics. Factors that played a huge role here were small geographical area and population size, abundant resources as well as effective inter-sectoral cooperation. As of 31st of May 2021, 55.3% of the resident population, 16 years old and above had received at least 1 dose and 41% had received both doses of the primary series. Within one year of commencement of the vaccination campaign, majority (81.5% and 80.2%) of the eligible population residing in Qatar had received at least 1 dose and both doses, respectively. Nonetheless, some people still contracted COVID-19 infection after vaccination.

A breakthrough case is the first SARS-CoV-2 infection or COVID-19 illness diagnosed after the date an individual was fully vaccinated. [3] COVID-19 breakthrough infections were observed in clinical trials in a small percentage of vaccinated individuals in the United States. [4-8] Breakthrough infections were first reported in individuals immunized with the Pfizer-BioNTech vaccine in Israel in January 2021. Subsequently, similar cases occurred in individuals vaccinated with the inactivated vaccine (Covaxin by

Bharat Biotech) in India. Immediately afterwards, breakthrough infections of vaccinated groups occurred in Italy, the United States, the United Kingdom and other countries [9-14]. According to the CDC, as of April 26th 2021, 0.01% of more than 95 million fully vaccinated people in the United States, had been infected with the coronavirus. Just over a quarter of the breakthrough infections, never had symptoms and 1% died. [8] During June 2021, in India, in a cohort of health care workers, among whom 58.5% received at least one dose of the ChAdOx1 nCoV-19 vaccine (AZD1222), an incidence of 2.57% breakthrough infections was reported. [10] In Israel 0.4% of health-care workers who received two doses of the BNT162b2 vaccine, were infected post-vaccination, mostly mild or asymptomatic. [15] As of September 2021, in Qatar, a total of 8203 breakthrough infections had been recorded among those who had received one dose of BNT162b2 and 10543 among those who had received two doses. [16] Studies analyzing vaccinated people in the real-world show that not only are breakthrough COVID-19 cases rare (at least based on analyses of the mRNA vaccines), it also lessens the chances of severe disease, COVID-19-related hospitalizations, and death. Rising numbers of breakthrough infections have a significant negative impact, and increases panic and speculation on the possibility of vaccine failure, leading to vaccine hesitancy in the society. [17,18] When people hear about breakthrough infections, they automatically think 'oh, these vaccines are not working' or 'they're not effective,' says Richard Teran, an epidemiologist with the U.S. Centers for Disease Control and Prevention's Epidemic Intelligence Service. "That is just not true, majority of individuals who do get the vaccine are protected against COVID infection and also from severe disease."

Researchers are now scrutinizing the cases popping up in those who are fully vaccinated. COVID vaccines are not 100% effective nor is any vaccine. In clinical trials, the BNT162b2 mRNA vaccine was shown to be 95% efficacious in preventing symptomatic disease; a similarly high protective effectiveness has also been found in real-world settings. [4,19] Estimated BNT162b2 effectiveness against any SARS-CoV-2 infection was negligible for the first 2 weeks after the first dose, increased to 36.8% (95% CI, 33.2 to 40.2) in the third week after the first dose, and reached its peak at 77.5% (95% CI, 76.4 to 78.6) in the first month after the second dose. However, effectiveness declined gradually, starting from the first month after the second dose. The decline accelerated after the fourth month, and effectiveness reached a low level of approximately 20% in months 5 through 7 after the second dose [16].

The genetic variant of SARS-CoV-2 to which one is exposed can also affect the degree of protection offered by vaccine-induced immune responses. The BNT162b2 mRNA vaccines demonstrated high protection levels yet apprehension exists if the emerging new SARS CoV-2 variants can overpower the immune response generated by the vaccine. Therefore, a few cases following vaccination are expected. There is evidence from case-control studies in Qatar

[20] and Israel [21] of reduced vaccine effectiveness against the Beta variant compared with the Alpha variant, although another contact tracing-based study in Israel [22] found vaccine effectiveness against the Beta variant in exposed individuals to be similar to that previously found against the Alpha variant [21]. The probability of breakthrough infections caused by Delta, Alpha and Kappa variants was 64.8%, 4.7% and 3.7%, respectively in India. [17] Although breakthrough infections are common for the Delta variant, vaccination can still help prevent severe infections and reduce associated hospitalizations [23-25] (Figure 1).

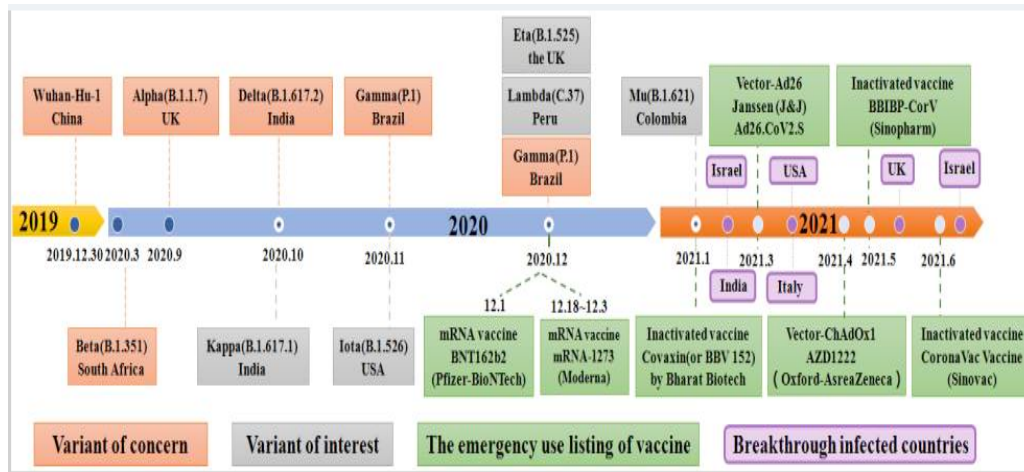


Figure 1: A timeline depicting the origin of SARS-CoV-2 VOC (Variant of Concern) and SARS-CoV-2 VOI (Variant of Interest), as well as the SARS-CoV-2 vaccine breakthrough infection.

Taking strong precautionary measures to limit the spread of COVID, on the 9th of March, Qatar announced closure of all schools and universities and switched to online education until further notice.[26] From 12th March,2020, the metro train services, metrolink services and public transit bus services were suspended on the weekends to start with, and later suspended completely. [27] Even the road transport except for those carrying essential items was hit during the partial lockdown from mid-March,2020. [28] To safeguard the health and wellbeing of the public, new set of precautionary measures were announced on the 13th of March,2020. Because of the potential presence of asymptomatic carriers of SARS CoV-2 in the community, the need to impose physical-distancing, wearing of face-masks and cancellation of public events, including sports and religious gatherings, was important. On 20th March,2020, Ministry of Municipality and Environment closed all parks and public beaches to curb the spread of COVID-19.[29] Three days later, the Ministry of Commerce and Industry decided to temporarily close all restaurants, cafes and food outlets in selected locations. The measures also extended to closure of mosques, cinemas, theatres, children’s play areas, gyms and wedding venues, including those in hotels.[30] The MOPH urged all agencies and individuals to follow personal preventive measures such as frequent hand washing, wearing face-masks in public, physical distancing and restrictive social gathering. The public was urged to adhere to the requirements of home isolation to ensure their safety and that of their community, and not to go

out unless absolutely necessary. Starting in mid-May, face-masks became mandatory in public places [31].

Public health restrictions have been easing gradually in Qatar with Phase 1 of the Gradual Lifting of COVID-19 restrictions began on the 28th of May,2021; but differently for vaccinated and unvaccinated persons.[32] Many social, work, and travel activities required evidence of vaccination (a “health pass”) displayed on one’s mobile using a mandatory app, “Ehteraz”. However, with increasing time since receipt of the second dose, there could be a progressive normalization of behavior.[33] Vaccinated persons presumably have a higher rate of social contact than unvaccinated persons and may also have lower adherence to safety measures. This behavior could reduce real world effectiveness of the vaccine as compared with its theoretical effectiveness [34,35]. Many countries dropped non-pharmaceutical interventions after high vaccine coverage but had to reinstate them due to the COVID-19 resurgence. They used third-dose booster vaccination campaigns to avoid restrictions. Others gradually relaxed interventions and did age-dependent third-dose vaccination. It is essential to protect those at risk of post-vaccination infection. Identifying risk factors for SARS-CoV2 infection post-vaccination is becoming increasingly salient because when a population reaches a high level of vaccine coverage, most infections will occur in vaccinated people, simply because most people are vaccinated. To identify the risk-factors for breakthrough infection, it is important to compare the

incidence of breakthrough infections (among the vaccinated) to the non-breakthrough infections among the unvaccinated, who apart from their vaccination status, are similar to the vaccinated.

The objective of this study is to examine whether non-compliance to non-pharmaceutical public health interventions like maintaining physical distance, washing hands regularly, avoiding social gatherings and physical contact and wearing masks can explain the SARS-CoV2 breakthrough infections among the vaccinated population. Evidence on breakthrough risk can inform the policy makers or feed the public health policies, like enforcement of these public health measures even after vaccination.

Methodology

As the COVID vaccination campaign rolled out successfully, the country faced two waves of SARS CoV-2 between January and June 2021, which were predominantly caused by B.1.1.7 (alpha) and B.1.351 (beta) variants. Appreciable community transmission of B.1.617.2 (delta) variant was first detected towards the end of March 2021, which had become the dominant strain by the summer.[36-39] With the proven high effectiveness of the mRNA vaccines, initial studies showed very low number of breakthrough infections. The Case Investigators under the Surveillance section of HP-CDC, MOPH, investigated every laboratory-confirmed SARS-CoV-2 infection case within 48 hours of confirmation. Information on demographics (eg, age, sex, nationality, occupation), travel history, geographical location, and information on reason for testing, exposure setting, date of positive RT-PCR result, symptomatic status, hospitalization status, and reported adherence to mask-wearing, maintaining physical distance, washing hands regularly, avoiding social gatherings and physical contact (post-vaccination for the vaccinated), were collected during the investigation and documented. The compliance to the precautionary measures was marked on a scale of three- 3-always/ 2-sometimes/ 1-never. Details of vaccination like manufacturer of COVID vaccine, date of receiving 1st dose and 2nd dose of COVID vaccine, were extracted from the National Vaccine Registry. The study participants were divided into 3 categories based on vaccination status- fully vaccinated and immune (those who had received both doses of the primary series and completed 14 days from the second dose), partially immune or partially vaccinated (those who had not completed 14 days after receiving the second dose of vaccine/ those who had received only one dose), and unvaccinated (those who had not received any dose of the vaccine). Hence, to capture all breakthrough cases, we planned to extract all incident cases of laboratory-confirmed SARS-CoV-2 infections from the 1st of January,2021 to 31st of May,2021, irrespective of their vaccination

status from the national surveillance database. Any individual who was tested for SARS-CoV-2 and the PCR result was inconclusive/negative were excluded. A retrospective nested case-control study was conducted.

Cases- People aged 18 years and above, with laboratory-confirmed SARS-CoV-2 infections using RT-PCR test and had received atleast one dose of the COVID vaccine.

Controls- People aged 18 years and above, with laboratory-confirmed SARS-CoV-2 infections using RT-PCR test who had not received any dose of the COVID vaccine.

Each case was matched with an unvaccinated infected individual (control) who tested positive on a similar date (± 3 days) to reduce bias associated with differential exposure. De-identified details of 6044 individuals with laboratory-confirmed SARS-CoV-2 infection, positive on RT-PCR test between the January 1st,2021 and May 31st,2021, were extracted. After excluding those cases with missing details or had not answered the calls from MOPH team, we were left with a dataset of 4456 individuals for further analysis. To assess if vaccination status has any association with hospitalization, and symptomatic status; and whether compliance with non-pharmaceutical public health interventions might have any association with vaccination status and with breakthrough infections, a chi square test or Fisher's exact test was used.

Results & Discussion

Majority of the study participants were males (72.1%), and more than half were non-Qataris (59.9%) (Figure 2). The median age of the study population was 39 (IQR 33.47), ranging between 18-90 years. Nearly equal proportions were tested either as part of contact tracing when they were exposed to a positive case (42.4%) or as they were symptomatic and seeking healthcare (44.9%). The remaining 12.6% were picked up during routine screening done for people returning from travel, in workplace like beauty salons, schools, etc (Figure 3). It is quite possible that those with contact history were more likely to be tested for SARS-CoV-2 infection, especially if symptomatic. A history of contact with a confirmed case and presence of symptoms were independently associated with higher risk [40] We tried to mitigate this limitation in our study by including any laboratory confirmed case irrespective of the reason for testing; hence the study participants tested as part of routine screening (though only a minor proportion) were also included. This also helps mitigate the difference in health care seeking behavior of the vaccinated and unvaccinated.

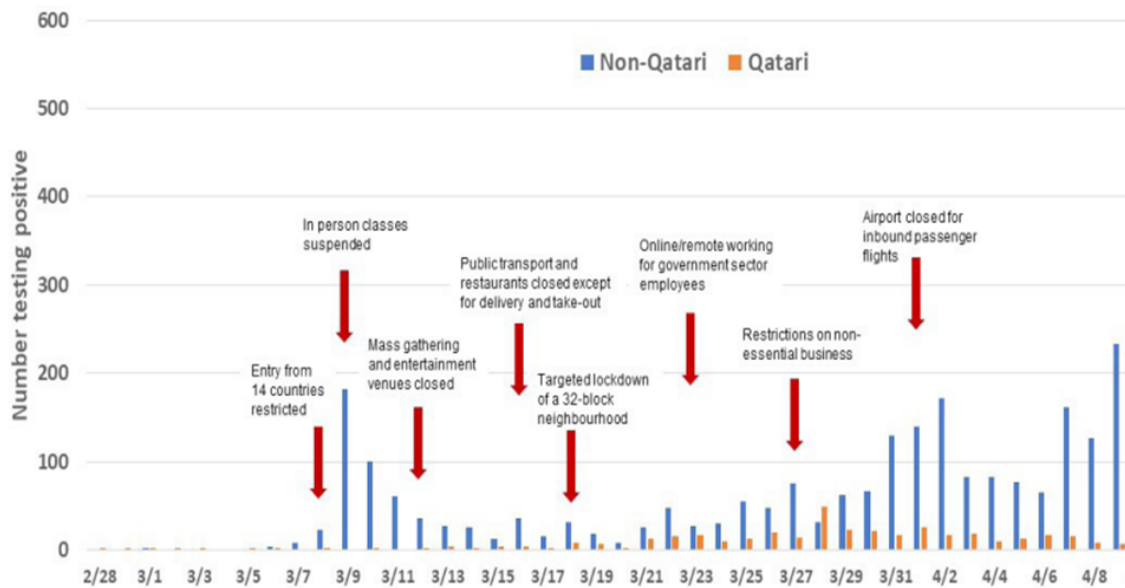


Figure 2: A timeline depicting the institution of various non-pharmaceutical measures in the beginning of the COVID pandemic in Qatar.

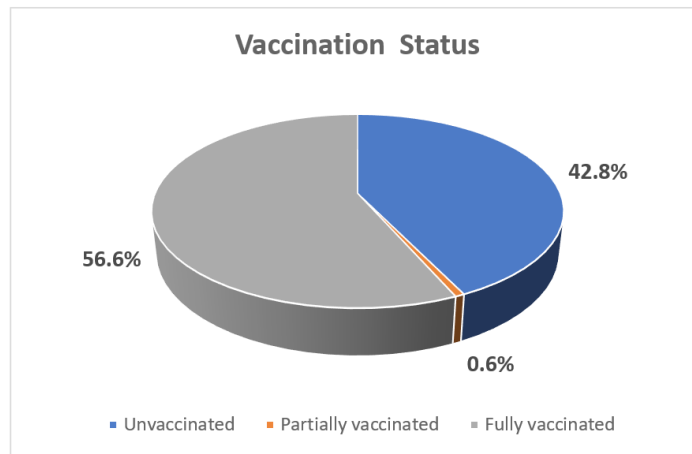


Figure 3: Distribution by Vaccination Status (N=4456).

More than half (57.2%) had received at least one dose of COVID vaccine and 56.6% of the 2549 who had received at least one dose, were fully vaccinated while 0.6% had received only one dose. (Figure 4) This is similar to the national statistics reported at that time period, however the proportion of fully vaccinated in our study was higher than the national statistics. In the UK, between December 8th,2020, and July 4th,2021, 0.5% of the COVID Symptom Study app users who reported a first vaccine dose, subsequently tested positive for SARS-CoV-2, and 0.2% of those who reported receiving a second dose, subsequently tested positive for SARS-CoV-2. [41] In another study done in UK, breakthrough infections in people who received only one or no doses of vaccination was nearly four times as likely as fully vaccinated individuals [18].

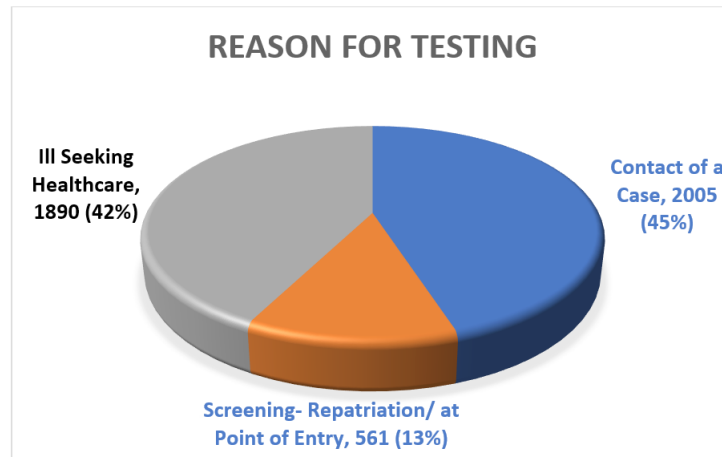


Figure 4: Distribution by Reason for testing (N=4456).

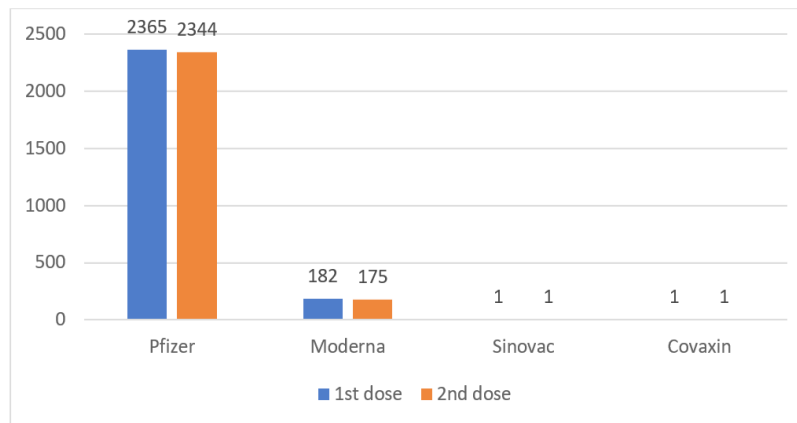


Figure 5: Distribution by Manufacturer of COVID vaccine.

In our study, while more than half (57.2%) the infections were among those vaccinated with one or two doses, only one-third (37.6%) were breakthrough infections ie, following 14 days post both doses of vaccine, as per the definition of breakthrough case. Table 1 depicts that out of the 2549 infections among those partially or fully vaccinated, majority (42.6%) got infected between 31-90 days after receiving the second dose. Only 5% of the cases were infected after 3 months post-second dose. More than one-fifth (22%) were infected within 14 days of receiving the second dose, while 12.3% were infected before receiving the second dose. The potential waning of vaccine immune response after a few months of second dose was documented in similar studies from Israel [46], Qatar [47] and United States [48]. Maccabi Healthcare Services members, over the age of 16, who were vaccinated with the second dose in January 2021 had a 2.26-fold increased risk (95% CI 1.80-3.01) for breakthrough infection compared to individuals who completed their vaccination in April 2021.[49] In the early months after vaccination, mRNA vaccines had efficacy [4] (as measured

in randomized trials) and effectiveness [19,50] (as measured in population-wide observational studies) above 90% for a range of disease outcomes (from symptomatic infection to death). An increased proportion of B.1.351 was found in individuals fully vaccinated with Pfizer BNT162b2, 7-14 days after the second dose, as compared to the matched unvaccinated controls. Furthermore, an increased proportion of B.1.1.7 was found in partially vaccinated individuals, 14 days after the first dose until 6 days after the second dose, as compared to the matched unvaccinated control, yet we find no evidence for increased breakthrough rates of B.1.1.7 a week or more after the second dose [3]. Most of the vaccinated individuals (>90%) had received Pfizer in our study (Figure 5), hence analyzing the breakthrough depending on the manufacturer did not seem relevant. Current evidence suggests that, although mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) vaccines show more than 90% efficacy in preventing COVID-19 after the second dose, Moderna's vaccine is shown to generate more than double the antibodies than Pfizer's vaccine. [42-44] Another

study shows that breakthrough infections are less likely to occur among those vaccinated with Moderna compared with Pfizer, and the rate of hospitalization was lower among the Moderna-vaccinated cohort versus the Pfizer cohort [45].

While 56.1% of the males with confirmed SARS CoV-2 infection were fully/ partially vaccinated; 60.1% females were fully/partially vaccinated (Table 2). Table 2 also shows among both nationals and non-nationals majority were fully vaccinated.

Most (66.3%) of our study participants were symptomatic at the time of testing irrespective of vaccination status. Most of the symptomatic were having only mild symptoms (82.2%) and only 4% had severe symptoms. Of the 122 with severe symptoms, more than three-fourths were unvaccinated; there was significant association between vaccination status (compared to unvaccinated) and symptomatic status or severity of symptoms (Table 3). In the study by Antonelli M et al vaccination (compared with no vaccination) was associated with having more than five symptoms in the first week of illness following the first or second dose, and long-duration (≥ 28 days) symptoms following the second dose. Almost all symptoms were reported less frequently in infected vaccinated individuals than in infected unvaccinated individuals, and vaccinated participants were more likely to be completely asymptomatic, especially if they were 60 years or older.[41] In another study done in UK, 88.4% of the fully vaccinated had only mild symptoms and 1.9% had severe symptoms and 64% of those breakthrough infections were asymptomatic.[18] These vaccines were also shown to be highly effective irrespective of age and other factors, although effectiveness against any infection (irrespective of symptoms) was somewhat lower, the initial immune response is lower in older adults and declines in all individuals from a peak in the early weeks after vaccination [21].

Table 1: COVID-19 tested positive after the vaccine (N = 2549).

COVID-19 tested positive after getting the vaccine	Covid-19 positive (Frequency)	Percentage
≤ 14 days after dose 1	12	0.5
15- 30 days after dose 1	12	0.5
>30 days after dose 1 and before getting dose 2	287	11.3
≤ 14 days of after getting 2 nd dose	562	22.0
15-30 days after getting 2 nd dose	463	18.2
31-60 days after getting 2 nd dose	748	29.3
61-90 days after getting 2 nd dose	338	13.3
>90 days after getting 2 nd dose	127	5.0
Total	2549	100.0

Table 2: Distribution of study participants by Vaccination status, Gender and Nationalities.

Vaccination status	Distribution by Gender		
	Male	Female	Total
Unvaccinated	1411	496	1907
Partially vaccinated	18	10	28
Fully vaccinated	1784	737	2521
Total	3213	1243	4456
Vaccination status	Distribution by Nationalities		
	Qataris	Non-Qataris	Total
Unvaccinated	621	1286	1907
Partially vaccinated	9	19	28
Fully vaccinated	1155	1366	2521
Total	1785	2671	4456

Table 3: Distribution of study participants by Vaccination status and symptom profile and hospitalization.

Vaccination status					p value
Symptomatic status (N= 4456)	Unvaccinated	Partially vaccinated	Fully vaccinated	Total	<0.0000001
Yes	1518	25	1410	2953	
No	389	3	1111	1503	
Total	1907	28	2521	4456	
Severity of symptoms (N= 2953)					<0.0000001
Mild	1161	20	1246	2427	
Moderate	263	4	137	404	
Severe	94	1	27	122	
Total	1518	25	1410	2953	
Hospitalization (N= 4456)					0.000000507
Yes	200	6	164	370	
No	1707	22	2357	4086	
Total	1907	28	2521	4456	

In our study only 8.3% were hospitalized and there were no deaths. Of the 370 participants hospitalized, 54% were unvaccinated while 41.8% of those non-hospitalized did not receive any dose (Table 3). Though, only a minority were hospitalized irrespective of the vaccination status (10.5% among the unvaccinated, 21.4% among the partially vaccinated and 6.5% among the fully vaccinated), there was significant relation between vaccination status and hospitalization. The Antonelli M et al study showed that vaccination (compared with no vaccination) was associated with reduced odds of hospitalization. [41] A multicentric cohort study across 17 hospitals that included individuals with positive RT-PCR for SARS-CoV-2, and received both doses of Pfizer BioNTech Vaccine, only a small minority were hospitalized in the COVID 19 unit. National surveillance data from the first four months of Israel’s vaccination campaign showed that two doses of BNT162b2 reduced both symptomatic and asymptomatic infections, COVID-19 related hospitalizations, severe disease and death. [50] A small minority of the fully vaccinated presented with severe SARS CoV-2 infection and needed inpatient care despite the high vaccine effectiveness of the vaccine. [51] In India, where breakthrough infections occurred extensively, only 9.8% of breakthrough cases required hospitalization and the mortality rate was only 0.4%. [52] Data from the International Severe Acute Respiratory and Emerging Infection Consortium in the UK suggest that although COVID-19 is usually milder if contracted

after vaccination compared to the unvaccinated, mortality remains high in hospitalized individuals (27%) more than 21 days after vaccination, similar to mortality rates observed during the first wave (March–April, 2020) [51,53].

Whether a breakthrough infection occurs when a vaccinated host is exposed to an infectious person depends on whether the immune response present in that person at the moment of exposure is sufficient to abort or rapidly control the infection. Given the kinetics of immune responses, it is not surprising that the amount of protection offered by a vaccine against infection might decline over time, allowing more breakthrough infections as the immune response wanes over months (as with the influenza vaccines) [54-57] and/or as immune memory wanes over years. [58] For a virus like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), sterilizing immunity is difficult to achieve, even with vaccines, and protection is expected to decline with time since vaccination. [59] Not every individual responds to the vaccine in a similar manner, there may be partial responders and non-responders. Contribution of other factors such as age, the level of immunity of the individual at the moment of exposure, the variant to which the individual is exposed, and the severity of disease should be considered. It is also unsurprising that older individuals, whose neutralizing antibody responses to COVID-19 vaccines are typically lower appear to be at greater risk of breakthrough infections at any given time following vaccination [15,45,53].

It has been shown that cases with low viral load may be a lesser concern from a public health perspective, as they are associated with less symptoms and decreased transmission.[7] Modelling and experiences with other vaccines suggest that exposure to a higher viral inoculum can reduce vaccine effectiveness and increase the probability of breakthrough infection [36,59]. However, if this effect were important for SARS-CoV-2, it could imply that populations employing better non-pharmaceutical interventions (such as masking) that reduce typical viral inoculums would see higher vaccine effectiveness, although any synergy between masking and vaccination is speculative at present. Hence, compliance to non-pharmaceutical public health interventions like wearing face masks, hand hygiene and social distancing remain essential to limiting transmission. In this study, irrespective of the vaccination status, most of the participants were adherent to the precautionary measures, even if not always. As seen in Table 4 more than half adhered always to wearing facemasks always (59.4%), regular hand-hygiene (53.9%) and nearly half (49.5%) always adhered to social distancing. Majority adhered to avoiding physical contacts (59.5%) and avoiding social gatherings (76.9%). Table 4 also depicts the significant association between vaccination status and compliance to various precautionary measures (always / sometimes / never) among those with laboratory-confirmed SARS-CoV-2 infection. The possible explanation for this may be that people who tend to get vaccinated against the infection generally tends to adhere to the precautionary measures. However, when compliance was considered as a binary variable (yes/no) adherence to wearing facemasks and avoiding social gatherings were found to be non-significant (p0.526 and p 0.0837 respectively). It's seen that majority of the unvaccinated (91.1%) and partially vaccinated (92.9%) were wearing facemasks always, whereas most of the fully vaccinated were not adhering to wearing the facemasks always. This can be explained by the possibility that a person on being fully vaccinated, have a sense of protection / immunity and may refrain from wearing face masks. Similarly, with regards to avoiding social gatherings, during this period though these precautionary measures were prevalent in the country, laxity on restrictions existed for those fully vaccinated. However, significant association was still noted between vaccination status and compliance to other precautionary measures like keeping social distance, hand hygiene and avoiding physical contact (Yes/No).

Table 4: Association between vaccination status and compliance to precautionary public health measures.

Vaccination Status	Precautionary measures				p-value
	Wearing Mask				
	Always	Sometimes	Never	Total	
Unvaccinated	1738	87	82	1907	<0.0000001
Partially vaccinated	26	2	0.0	28	
Fully vaccinated	882	1534	105	2521	
Total	2646	1623	187	4456	
Keeping social distance					
Unvaccinated	1417	402	88	1907	<0.0000001
Partially vaccinated	23	5	0	28	
Fully vaccinated	764	1691	66	2521	
Total	2204	2098	154	4456	
Avoiding Physical contact					
Unvaccinated	225	961	721	1907	<0.0000001
Partially vaccinated	6	19	3	28	
Fully vaccinated	55	1388	1078	2521	
Total	286	2368	1802	4456	
Washing Hands					

Unvaccinated	706	863	338	1907	<0.0000001
Partially vaccinated	9	18	1	28	
Fully vaccinated	1687	809	25	2521	
Total	2402	1690	364	4456	
Avoiding Social Gathering					
Unvaccinated	341	1096	470	1907	<0.0000001
Partially vaccinated	0	21	7	28	
Fully vaccinated	30	1941	550	2521	
Total	371	3058	1027	4456	

Table 5: Association between breakthrough infection and compliance to precautionary public health measures.

Break through infection [SARS-CoV-2 infection diagnosed after the date an individual was fully vaccinated]	Precautionary measures				P - value
	Wearing Mask				
	Always	Sometimes	Never	Total	
Yes	664	1473	101	2238	<0.0000001
No	1959	169	90	2218	
Total	2623	1642	191	4456	
Keeping social distance					
Yes	590	1588	60	2238	<0.0000001
No	1589	535	94	2218	
Total	2179	2123	154	4456	
Physical contact					
Yes	27	1244	967	2238	<0.0000001
No	252	1122	844	2218	
Total	279	2366	1811	4456	
Washing hands					
Yes	1531	702	5	2238	<0.0000001
No	890	972	356	2218	
Total	2421	1674	361	4456	
Social gathering					
Yes	8	1763	467	2238	<0.0000001
No	361	1297	560	2218	
Total	369	3060	1027	4456	

When a population reaches a high level of vaccine coverage, most infections will occur in vaccinated people, simply because most people are vaccinated. It is essential to protect those at risk of post-vaccination infection. Though most of the participants were adherent to the precautionary measures, even if not always, Table 5 above shows that a lesser proportion of those who always complied to the measures had breakthrough infections and this was found to be significant.

Conclusion:

Some countries that attempted to drop all non-pharmaceutical interventions after reaching high levels of vaccine coverage were forced to reinstate most (for example, vaccination passes, indoor face masks) in face of massive resurgence [52] while applying a

population-wide third dose mass-vaccination campaign to avert the need of further restrictions. [60-64] Other countries have more gradually relaxed some non-pharmaceutical interventions and performed more gradual and age-dependent third dose vaccination campaigns or did not even experience a strong wave of Delta variant infections. Identifying and protecting individuals at increased risk of post-vaccination infection is becoming increasingly salient as more people are vaccinated.

Around one-third of our participants had breakthrough infections ie, after 14 days of receiving both doses. Our study found significant association between compliance to the non-pharmaceutical public health interventions and vaccination status as well as breakthrough infections. Our findings showed that people who adhered to getting vaccinated against the infection, adhered to the precautionary measures mandated by the ministry though not always. And that lesser proportion of those who always complied to the measures had breakthrough infections. In this case, a short-term public health response to an increase in severe breakthrough infections, would be to reimpose social measures to slow transmission while a medium-term solution would be to develop and rapidly and deploy vaccines that more closely match the circulating variant.

Recommendations:

A combination of mass vaccination with two doses coupled with non-pharmaceutical interventions can control and contain COVID-19. If breakthrough infections are common, severe or highly transmissible, then there may be a need for additional vaccine doses, or changes in vaccine formulations. It is imaginable that variants of SARS-CoV-2 may arise in future which escape from immunity, so boosting with the original spike protein is ineffectual. The key questions for scientists studying breakthrough infections surround their timing, frequency, causes, severity and levels of infectiousness.

Ethical considerations

Ethical Clearance was obtained from the Health Research Governance Department, MOPH, Qatar vide ERC-821-3-2022 dated August 21,2022. There was no issue of subject withdrawal/ withdrawal of consent as we are using secondary data. Moreover, there was no foreseen risk/ harm/ discomfort to the study subjects associated with this study as we were using secondary data. There was no collection of bio-specimens involved in this study. The personal information of any participant was not extracted hence there is no disclosure of personal identifiable data. All data was kept in encrypted password protected laptops and stored in locked cabinets at the Principal Investigator's office at HP-CDC, MOPH. Only the Principal Investigator and Co-Investigators had access to the study data.

Strength

SARS-CoV-2 testing was free-of-charge and widely available in Qatar and mostly RT-PCR. Testing was required for people returning from travel abroad, in close contact with an infected person, or with suggestive symptoms such as fever or acute respiratory illness. A specimen is collected via nasal or nasopharyngeal swab. Specimens are tested, using national testing standards, at the National Virology laboratories with use of real-time PCR tests.

Limitations

- Exposure to the different variants were not analyzed. no sequencing so don't know the variants. However, it is still possible that other confounding effects were present and were not controlled for.
- The compliance to preventive measures is subjective and as reported by them. We do not have any method to cross check the accuracy of this information
- Vaccinees were exempt from testing following exposure to a positive case and quarantine. This may affect when and how they chose to be tested. Most vaccinees were likely to be tested only when they were symptomatic which created a bias in their symptomatic status. For eg; vaccinees in Israel were exempt from quarantine and testing following exposure to a positive patient, and this may affect when and how they chose to be tested.
- Some individuals in this cohort may have been infected before the immunity from the boost was fully established.
- Measurement of breakthrough infections is challenging outside of randomized, placebo-controlled, double-blind field trials. Some individuals who are unvaccinated will nonetheless have some immunity as a result of prior infection, complicating comparisons of immunity between these groups. The individuals with breakthrough infection or had a previous infection with prolonged shedding could not be differentiated.
- Confounders like comorbidities were not available and hence could not be factored into our analysis.
- When a population reaches a high level of vaccine coverage, most infections will occur in vaccinated people, simply because most people are vaccinated
- Our focus is only on infected individuals; we ignore non-infected individuals, and do not measure absolute infection rates in the vaccinated or control population.

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