Original Article

Association of Prior COVID-19 Infection with Risk of Breakthrough Infection Following Vaccination: A Cohort Study in Isfahan, Iran

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Abstract

Background: Many people worldwide have developed a combination of natural and vaccine-induced immunity to COVID-19. This study investigated whether exposure to SARS-CoV-2 before full vaccination promotes protection against a breakthrough infection. **Methods:** We studied a total of 2,902,545 people in the Isfahan COVID-19 Registry. All the participants had received two doses of either Sinopharm BIBP, ChAdOx1-nCoV-19, Gam-COVID-Vac, or BIV1-CovIran vaccines. A cohort study examined the association between prior COVID-19 infection and the risk of a breakthrough infection for each vaccine. Cohorts in each pair were matched by gender, age group, calendar week of the first dose, the interval between the first and second doses, and the proportion of healthcare workers. The probable virus variant for the previous infections was also considered. Each individual's follow-up started 14 days after their second vaccine dose until either the end of the study censoring date, occurrence of a COVID-19 infection, or death. The breakthrough infection risk was compared between each cohort pair by using the hazard ratio (HR) and incidence rate ratio (IRR). **Results:** Total breakthrough HRs (95% confidence interval) (previously infected over infection-naïve matched cohort) were 0.36 (0.23–0.55), 0.35 (0.32–0.40), 0.37 (0.30–0.46), and 0.43 (0.32–0.56) for the BIV1-CovIran, Sinopharm BIBP, Gam-COVID-Vac, and ChAdOx1-nCoV-19 vaccine groups, respectively. The breakthrough infection IRRs were approximately similar to the total HRs mentioned above. **Conclusion:** Prior SARS-CoV-2 infection conferred additive immunity against breakthrough after vaccination, no matter which vaccine brand was injected. Such a result could guide health authorities to codify low-cost high-benefit vaccination protocols and protect the community's well-being.

Keywords: *COVID-19, COVID-19 breakthrough, COVID-19 RT-PCR testing, COVID19 vaccine*

Introduction

Since the emergence of the novel Coronavirus Disease in 2019 (COVID-19), flaring mortalities and morbidities worldwide have led governments and societies to impose strict regulations to prevent the spread of the disease.[1-3] The serious health effects, as well as the economic and psychosocial troubles that these cumbersome regulations caused to affected individuals and their families,[4,5] prompted a call for immediate action to combat the underlying cause of the epidemic, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As history taught us, most societies agreed that generating vaccines to induce immunity against the virus was the most appropriate option to prevent such a massive disease burden.[6] Thereafter, many companies worldwide started inexhaustible investigations and efforts whose results are now available as COVID-19 vaccines, effectively controlling the burden of the disease.[7,8]

It has been rigorously examined to see whether COVID-19 confers post-infectious immunity following recovery, as is seen after most infections, and found that some degree of immunity occurs;[9,10] however, this may not be wholly protective because of the fast and continuous mutations within the viral genome, along with the waning of infection-induced immunity over time.[11-14] The same concern regarding vaccine-induced immunity has raised questions such as how effective vaccines are, how many booster doses are needed to develop sufficient immunity, and whether vaccination creates more robust protection than a previous infection against breakthrough or *vice versa*.[15,16] In addition, some studies suggest that the combination of a prior infection

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with a single-dose vaccine is as effective as a two-dose vaccination.[12,17]

COVID-19 and its vaccines are two novel entities introduced to the medical literature, subject to demanding needs for widespread assessments and investigations. Many vaccine types with different mechanisms for production and inducing the immune response have been generated and distributed worldwide, raising the need to investigate them separately.

As booster dose vaccination has been recommended to tackle the waning immunity against infection,[18] the purpose of this study was to answer the question among fully vaccinated people in a middle-income country: "Are people who experienced PCR-confirmed COVID-19 infection before vaccination less prone to a breakthrough than infection-naïve ones?" The answer to this question may help healthcare authorities prioritize candidates for booster doses in the setting of a vaccine shortage. Similar studies have answered this question about available vaccines in their countries;[19,20] however, to our knowledge, no other research has investigated such a question for vaccine brands, including Gam-COVID-Vac, BIV1-CovIran, and Sinopharm BIBP. That is why this study aimed to extend the answer to other available vaccine brands.

Methods

This study was a retrospective cohort conducted in Isfahan, Iran, approved by the Research Ethics Committee of the Isfahan University of Medical Sciences (Study Project number: 2400115, Ethics Code: IR.MUI.MED.REC.1400.483). In view of the retrospective nature, the need for individual patient consent was waived by this committee as a data protection safeguard was in place.

Data acquisition

The data for this study were acquired from two sources:

1. The Isfahan COVID-19 Registry (I-CORE): Documented all the polymerase chain reaction (PCR) test results and related demographics since the start of this epidemic.[21] Data on vaccination, including the brand of vaccine and the first and second dose dates, have also been recorded by this registry.
2. The Medical University of Isfahan Vice-Chancellor of Health: Gathered the mortality data of Isfahan province, with the cause of death provided by a medical physician.

Individuals' National IDs were used to merge the data from these databases.

Participants

The study included all residents of Isfahan province who were vaccinated with Sinopharm BIBP, ChAdOx1-nCoV-19, Gam-COVID-Vac, or BIV1-CovIran vaccine between February 9, 2021 (the issuance of vaccination in Isfahan) and October 22, 2021.

The association of prior COVID-19 infection with the risk of breakthrough was investigated using a separate cohort study for each vaccine. After full vaccination (14 days after the second dose), the incidence of a defined outcome (Section 2.4) was compared between a cohort of people with a positive test result before the first dose and a cohort of individuals without it.

Individuals who had not received two vaccine doses, 14 days had not passed since their second dose, had a positive PCR test after the first dose and before the start of follow-up, died before the start of follow-up, or had their previous infection less than 90 days before the breakthrough one were excluded from this study.

Each cohort was matched to its pair in a 1:3 ratio (previously infected: not previously infected) by gender, 10-year age group, calendar week of the first dose, the interval between the first and second doses in weeks, and the proportion of healthcare workers.

Each participant was followed up from their full vaccination until the occurrence of a positive PCR test, all-cause death, or end of the study censoring (February 5, 2021).

Exposure

A positive PCR test, regardless of the reason for testing, before the first dose of vaccination was considered an exposure. The probable variant of concern was taken into account for previous infections, based on the calendar date on which the PCR test was acquired. Positive test results before June 10, 2021 were considered alpha (B.1.1.7) variant infections; results on this date or later were deemed delta (B.1.617.2) variant infections.[22]

In addition, we sought to retrogradely examine if a reinfected individual had a greater chance of exposure more than 6 months before the first dose of vaccination, or less than and equal to this interval.[19] Six months had not elapsed since the confirmed delta variant outbreak to the end of the study censoring date. Therefore, previously infected individuals with the delta variant were excluded from this analysis.

Outcomes

The outcome was having a positive PCR test result after full vaccination.

Statistical analysis

Preprocessing of data was done in Python by using the Pandas and NumPy libraries. Data were cleaned and entered into Stata software, Stata Corp LLC, Texas, USA, (version 16). Each vaccine brand was analyzed separately.

Data were restructured to effectively reflect the population size, sex, age, and healthcare worker composition of each cohort. The interval between the first and second vaccine doses was also calculated for each cohort in days.

Before analysis, systematic random sampling was performed on all exposed cases. For each participant in the exposed group, three matched people were allocated to the unexposed group as controls. Figure 1 illustrates the details of the sampling and matching processes. Based on a 1-week Caliper width, the weeks between the first and second vaccine doses were matched. The exact method was also used to match other variables. This technique matches each case to control with exactly the same values on the covariates.

To describe continuous variables, mean and standard deviation (SD) and/or median and interquartile range (IQR) were used; frequencies were reported by percentage and number. Standardized difference was utilized to quantify the differences between exposed and unexposed groups with regard to any single variable. A standardized difference of <0.1 between the matched cohorts could ensure adequate matching.

The Kaplan-Meier method was used to calculate the cumulative incidence of infection using the log-rank test to assess the equality of failure functions. On the contrary, the Cox and Poisson regression models were used to estimate the hazard ratios (HRs) and incidence rate ratios (IRRs), respectively. HRs were also reported based on the cumulative incidence of infection at the end of each follow-up month.

An independent sample *t*-test or Mann-Whitney U test was used to compare the mean distances, the latter for those with an abnormal distribution. In all estimations, a significance level of 5% was assumed, and a 95% confidence interval (CI) was calculated.

Among the reinfected participants, odds ratio (OR) was used to report the likelihood of the previous infection having occurred more than 6 months before the vaccination over the same chance in less than or equal to 6 months; the binominal logistic regression model was used to calculate 95%CI for each OR.

The effect of temporal variation in the virus variant was managed by stratified analysis (alpha and delta variants) to estimate the HR and IRR.

Results

Study population and matching

Data were collected from a total of 2,902,545 vaccinated people who were eligible to participate in the study.

Figure 1 illustrates how the study population was stratified into vaccine groups and participated in the matching process. Most of the participants had received the Sinopharm BIBP COVID-19 vaccine, followed by ChAdOx1-nCoV-19, BIV1-CovIran, and Gam-COVID-Vac. Other vaccine brands were administered to 6842 subjects, who were excluded from the study because of their small population size.

As illustrated in Table 1, the distribution of age, sex, and the proportion of healthcare workers differed

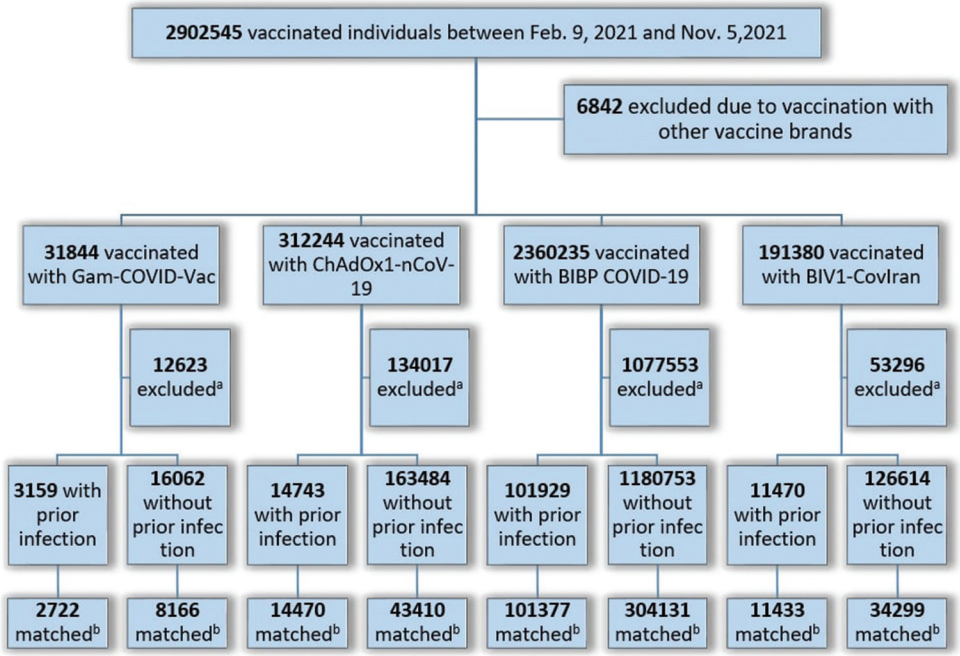

Figure 1: Participant Selection Algorithm. [a]excluded due to: had not received two vaccine doses, 14 days had not passed since their second dose, had a positive PCR test after the first dose and before the start of follow-up, died before the start of follow-up, or had their previous infection less than 90 days before the breakthrough one. [b]an exact exerted between the previously PCR-confirmed COVID-19-infected and non-infected cohorts for each vaccine brand. Distributions of age, sex, healthcare occupations, and the time interval between the two vaccine doses were matched, defined as standardized differences <0.1 between each cohort pair. Achieving a proportion of 1:3 was desired for the size of paired cohorts. PCR: polymerase chain reaction

Table 1: Demographic characteristics of full cohorts

Characteristics	Gam-COVID-Vac (19221)			ChAdOx1-nCoV-19 (178227)		
	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference
Population size	3159	16,062		14,743	163,484	
Female *n* (%)	1688 (53.4)	8234 (51.3)	0.043	6305 (42.77)	74,608 (45.64)	0.057
Age groups *n* (%)						
<20	1 (0.03)	15 (0.09)	0.370	11 (0.07)	165 (0.1)	0.140
20–29	386 (12.22)	1946 (12.12)		669 (4.54)	6839 (4.18)	
30–39	1004 (31.78)	3508 (21.84)		2019 (13.69)	14,677 (8.98)	
40–49	894 (28.3)	3447 (21.46)		1888 (12.81)	17,741 (10.85)	
50–59	566 (17.92)	3128 (19.47)		1847 (12.53)	23,070 (14.11)	
60–69	103 (3.26)	936 (5.83)		1145 (7.77)	12,757 (7.8)	
≥70	205 (6.49)	3082 (19.19)		7164 (48.59)	88,235 (53.97)	
Healthcare worker *n* (%)	2760 (87.37)	11,699 (72.84)	0.370	1810 (12.28)	12,759 (7.80)	0.149
Interval between the first and second dose of vaccination-days						
Mean (SD)	32.67 (14.57)	34.88 (14.46)	0.152	82.87 (14.21)	83.89 (15.45)	0.068
Median (Q1–Q3)	29 (28–31)	29 (28–40)	-	84 (72–90)	84 (72–91)	-
Characteristics	**Sinopharm BIBP (1282682)**			**BIV1-CovIran (138084)**		
	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference
Population size	101,929	1,180,753		11,470	126,614	
Female *n* (%)	54,082 (53.06)	618,727 (54.40)	0.109	4029 (35.13)	71,266 (56.29)	0.176
Age groups *n* (%)						
<20	1420 (1.39)	40,919 (3.47)	0.113	54 (0.47)	1358 (1.07)	0.041
20–29	10,651 (10.45)	150,230 (12.72)		825 (7.19)	10,467 (8.27)	
30–39	23,549 (23.1)	252,781 (21.41)		2610 (22.76)	20,962 (16.56)	
40–49	19,606 (19.23)	236,108 (20)		2898 (25.27)	31,820 (25.13)	
50–59	17,436 (17.11)	207533 (17.58)		3384 (29.5)	44,540 (35.18)	
60–69	21,000 (20.6)	213,431 (18.08)		1324 (11.54)	14,286 (11.28)	
≥70	8267 (8.11)	79,751 (6.75)		375 (3.27)	3181 (2.51)	
Healthcare worker *n* (%)	3371 (3.31)	18,907 (1.60)	0.110	115 (1.00)	476 (0.38)	0.075
Interval between the first and second dose of vaccination-days						
Mean (SD)	30.10 (7.04)	30.21 (7.09)	0.015	31.36 (7.37)	31.99 (8.48)	0.080
Median (Q1–Q3)	28 (28–30)	28 (28–30)	-	29 (28–32)	29 (28–32)	-

Q1: Quartile 1, Q3: Quartile 3, SD: Standard deviation

between each entire cohort and its pair. Such a difference was also noted in the interval between two doses of Gam-COVID-Vac (standardized mean difference = 0.152).

The sufficiency of the matching processes is presented in Table 2, where the distribution of the above characteristics is well balanced. Although the standardized difference in the distribution of healthcare workers between the BIV1-CovIran matched cohorts was 0.084, which meant favorably matched, it could not be reduced to as much as the standardized differences in other characteristics. This was probably due to the small number of healthcare workers who had received the BIV1-CovIran vaccine.

Infection incidences

At the end of the study censoring date, more than 6 months had elapsed since the start of the follow-up for Gam-COVID-Vac. For ChAdOx1-nCoV-19, Sinopharm BIBP, and BIV1-CovIran, this time had been <2, <5, and <2 months, respectively.

Cumulative incidence

The cumulative infection incidences at 30-day intervals of follow-up and the total cumulative incidence at the end are shown for each matched cohort [Table 3], further reporting the breakthrough infection HRs for each cohort pair within the monthly intervals and at the end of the follow-up.

Table 2: Demographic characteristics of matched cohorts

Characteristics	Gam-COVID-Vac			ChAdOx1-nCoV-19		
	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference
Sample size	2722	8166		14,470	43,410	
Gender-Female *n* (%)	1457 (53.5)	4371 (53.5)	0.000	6190 (42.8)	18,570 (42.8)	0.000
Age groups *n* (%)						
<20	0 (0)	0 (0)	0.000	6 (0.04)	18 (0.04)	0.000
20–29	342 (12.7)	1026 (12.6)		636 (4.4)	1908 (4.4)	
30–39	834 (30.7)	2503 (30.7)		1951 (13.5)	5853 (13.48)	
40–49	762 (28.0)	2286 (28.0)		1838 (12.7)	5514 (12.7)	
50–59	508 (18.7)	1524 (18.7)		1801 (12.45)	5403 (12.45)	
60–69	82 (3.0)	246 (3.0)		1121 (7.75)	3363 (7.75)	
≥70	194 (7.1)	582 (7.1)		7117 (49.18)	21,351 (49.18)	
Healthcare worker *n* (%)	2406 (88.4)	7218 (88.4)	0.000	1711 (11.8)	5133 (11.8)	0.000
Interval between the first and second dose of vaccination-days						
Mean (SD)	31.1 (7.4)	31.1 (7.4)	−0.004	82.9 (13.6)	83.0 (13.8)	0.006
Median (Q1–Q3)	29 (28–31)	29 (28–31)	-	84 (72–90)	84 (71–90)	-
Characteristics	**Sinopharm BIBP**			**BIV1-CovIran**		
	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference	Individual with a prior PCR-confirmed infection	Individual with no prior PCR-confirmed infection	Standardized Difference
Sample size	101,377	304,131		11,433	34,299	
Gender-Female *n* (%)	47,548 (46.9)	142,644 (46.9)	0.000	4011 (35.1)	12,033 (35.1)	0.000
Age groups *n* (%)						
<20	1416 (1.4)	4248 (1.4)	0.000	52 (0.45)	156 (0.45)	0.000
20–29	10,568 (10.42)	31,704 (10.42)		817 (7.15)	2451 (7.15)	
30–39	23,431 (23.11)	70,293 (23.11)		2604 (22.78)	7812 (22.78)	
40–49	19,438 (19.17)	58,314 (19.17)		2893 (25.3)	8679 (25.3)	
50–59	17,345 (17.11)	52,035 (17.11)		3383 (29.59)	10149 (29.59)	
60–69	20,962 (20.68)	62,886 (20.68)		1321 (11.55)	3963 (11.55)	
≥70	8217 (8.1)	24,651 (8.1)		363 (3.18)	1089 (3.18)	
Healthcare worker *n* (%)	2956 (2.9)	8868 (2.9)	0.000	114 (0.01)	109 (0.032)	0.084
Interval between the first and second dose of vaccination-days						
Mean (SD)	30.0 (5.8)	29.9 (5.6)	0.007	31.3 (7.0)	31.4 (7.2)	0.026
Median (Q1–Q3)	28 (28–30)	28 (28–30)	-	29 (28–32)	29 (28–32)	-

Q1: Quartile 1, Q3: Quartile 3, SD: Standard deviation

Generally speaking, except for ChAdOx1-nCoV-19, the absolute difference in the ultimate cumulative incidences was significant for each vaccine's cohort pair. Furthermore, again with the exception of ChAdOx1-nCoV-19, these absolute differences had evident upward trends during the study period for each vaccine. The HR analysis in this table is described in Section 3.2.3.

Cumulative breakthrough infection incidences for each pair of the matched cohorts are graphically demonstrated against follow-up time in Figure 2; failure functions were found not to be equal between each pair of cohorts ($P < 0.0001$ for each pair). In accordance with Table 3 results, absolute differences between monthly cumulative incidences tended to increase as time passed, evidently observed as divergent lines within the mentioned figure.

Incidence rate

As the follow-up time for each individual was unique, the total incidence rate for each cohort was calculated using the person-week unit. The breakthrough infection IRRs for previously infected matched cohorts compared to infection-naïve ones were 0.35 (0.23–0.54), 0.37 (0.32–0.41), 0.38 (0.31–0.47), and 0.44 (0.33–0.57) for the BIV1-CovIran, Sinopharm BIBP, Gam-COVID-Vac, and ChAdOx1-nCoV-19 vaccines, respectively [Table 4].

Table 3: Hazard ratios of breakthrough infection by month of follow-up in matched cohorts of vaccinated individuals with vs. without prior infection

Follow-up time, months	Individual with a prior PCR-confirmed infection			Individual with no prior PCR-confirmed infection			Absolut difference of cumulative incidence (%95CI)	Hazard Ratio (%95CI) Virus variant before vaccination		
	n	Infected	Cumulative incidence (%95 CI)	*n*	Infected	Cumulative incidence (%95 CI)		All Variants	Alpha Variant	Delta Variant
Gam-COVID-Vac										
1	14	5	0.001 (0.0003–0.003)	54	27	0.002 (0.001–0.003)	0.001 (−0.002–0.0027)	0.61 (0.23–1.58)	0.61 (0.23–1.58)	NA
2	33	21	0.004 (0.002–0.007)	205	168	0.011 (0.008–0.012)	0.007 (0.001–0.011)*	0.72 (0.45–1.12)	0.72 (0.45–1.12)	NA
3	87	47	0.008 (0.006–0.012)	473	352	0.021 (0.019–0.025)	0.013 (0.006–0.020)*	0.65 (0.48–0.89)*	0.65 (0.48–0.89)*	NA
4	482	69	0.013 (0.009–0.017)	1740	542	0.033 (0.030–0.037)	0.010 (0.009–0.029)*	0.48 (0.37–0.61)*	0.48 (0.37–0.61)*	NA
5	1833	85	0.016 (0.012–0.021)	5665	666	0.042 (0.038–0.046)	0.026 (0.024,0.035)*	0.38 (0.30–0.48)*	0.38 (0.30–0.48)*	NA
6	2676	90	0.017 (0.013–0.022)	8069	720	0.046 (0.042–0.051)	0.029 (0.027–0.038)*	0.36 (0.29–0.45)*	0.36 (0.29–0.45)*	NA
>6 (Total)	2722	92	0.019 (0.013–0.028)	8166	736	0.053 (0.046–0.059)	0.034 (0.025–0.042)*	0.37 (0.30–0.46)*	0.37 (0.30–0.46)*	NA
ChAdOx1-nCoV-19										
1	4274	14	0.001 (0.0004–0.002)	12,959	130	0.002 (0.001–0.003)	0.001 (−0.001–0.0026)	0.37 (0.21–0.64)*	0.37 (0.21–0.64)*	NA
2	13,397	56	0.007 (0.002–0.015)	40,583	391	0.008 (0.006–0.011)	0.001 (−0.009–0.009)	0.44 (0.33–0.58)*	0.44 (0.33–0.58)*	NA
>2 (Total)	14,470	61	0.026 (0.005–0.045)	43,410	420	0.020 (0.012–0.028)	−0.006 (−0.031–0.018)	0.43 (0.32–0.56)*	0.43 (0.32–0.56)*	NA
Sinopharm BIBP										
1	55,664	81	0.001 (0.0006–0.001)	164,272	704	0.002 (0.002–0.003)	0.001 (0.001–0.0024)*	0.35 (0.28–0.44)*	0.34 (0.27–0.43)*	0.45 (0.18–1.17)
2	74,636	181	0.002 (0.0015–0.0023)	244,976	1596	0.006 (0.0053–0.006)	0.004 (0.003–0.0045)*	0.34 (0.29–0.40)*	0.34 (0.28–0.29)*	0.52 (0.24–1.09)
3	93,334	255	0.003 (0.0025–0.0035)	280,394	2347	0.010 (0.009–0.011)	0.007 (0.0065–0.0075)*	0.33 (0.29–0.37)*	0.32 (0.27–0.37)*	0.54 (0.27–1.10)
4	94,794	303	0.004 (0.003–0.005)	284,864	2727	0.014 (0.013–0.015)	0.01 (0.008–0.012)*	0.33 (0.30–0.38)*	0.33 (0.29–0.37)*	0.54 (0.27–1.10)
5	100,130	346	0.006 (0.005–0.007)	300,516	2983	0.017 (0.016–0.018)	0.011 (0.011–0.013)*	0.34 (0.31–0.38)*	0.34 (0.30–0.38)*	0.54 (0.27–1.10)
6	100889	363	0.007 (0.006–0.008)	302,723	3068	0.019 (0.018–0.020)	0.012 (0.010–0.014)*	0.35 (0.31–0.39)*	0.35 (0.30–0.39)*	0.54 (0.27–1.10)
>6 (Total)	101377	372	0.012 (0.009–0.015)	304,131	3094	0.021 (0.019–0.023)	0.009 (0.004–0.014)*	0.35 (0.32–0.40)*	0.35 (0.31–0.39)*	0.54 (0.27–1.10)
BIV1-CovIran										
1	4840	11	0.0007 (0.0003–0.0015)	14,533	74	0.0018 (0.0014–0.0025)	0.0011 (−0.001–0.0023)	0.43 (0.23–0.81)*	0.47 (0.24–0.89)*	NA
2	11095	20	0.0019 (0.0008–0.0044)	33,277	166	0.0045 (0.0036–0.0056)	0.040 (−0.008–0.0048)	0.36 (0.23–0.56)*	0.38 (0.24–0.62)*	NA
>2 (Total)	11433	23	0.0034 (0.0013–0.0082)	34,299	198	0.029 (0.017–0.038)	0.0256 (0.009–0.0365)*	0.36 (0.23–0.55)*	0.38 (0.25–0.59)*	NA

Follow-up time was analyzed in days. *P<0.05. NA: In the Gam-COVID-Vac cohort, no one was previously infected with the delta variant; in the ChAdOx1-nCoV-19 cohort, no case with a previous delta-variant infection was reinfected after the vaccine; and in the BIV1-CovIran cohort, the number of previously infected cases with delta variant was not sufficient for analysis. CI: Confidence interval, PCR: Polymerase chain reaction

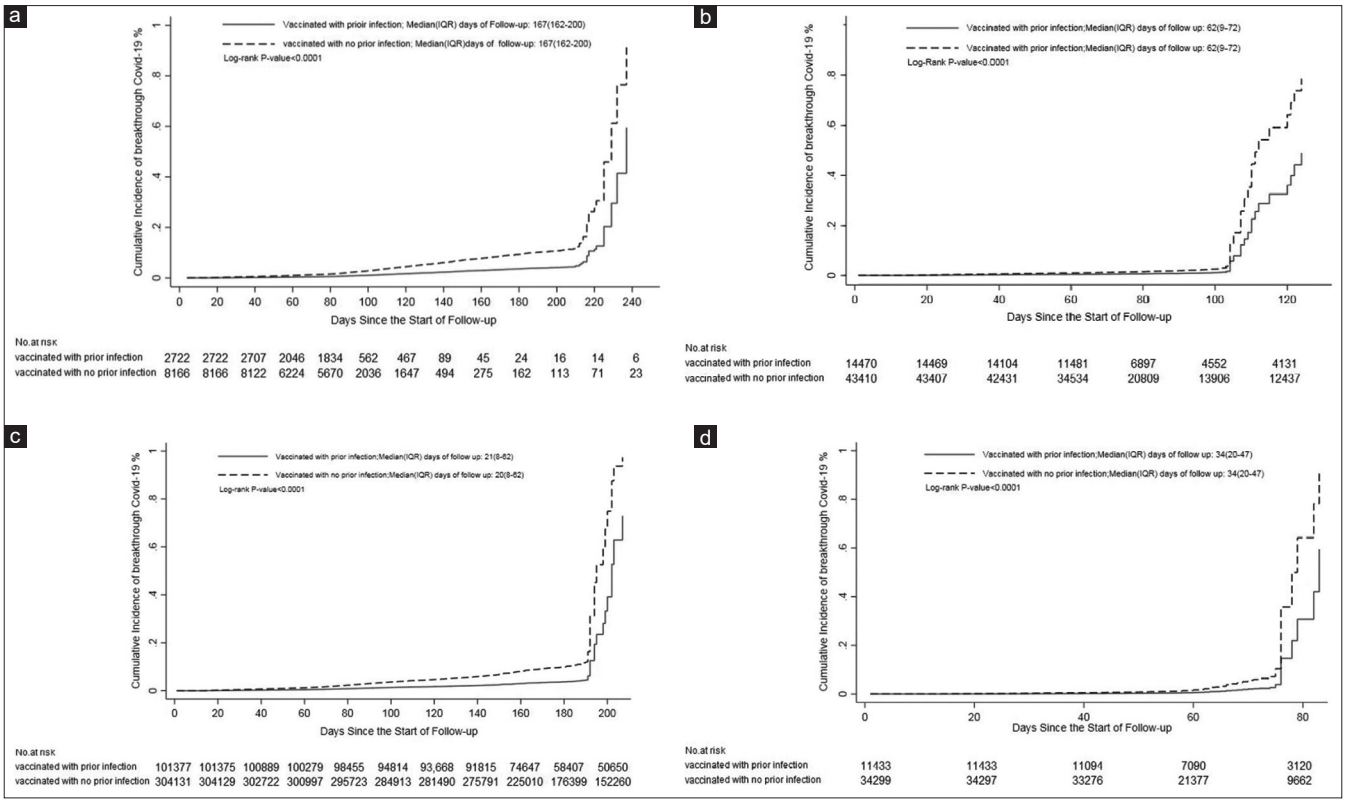

Figure 2: Cumulative breakthrough infection incidence curves for each pair of the matched cohorts: a) Gam-COVID-Vac, b) ChAdOx1-nCoV-19, c) Sinopharm BIBP, d) BIV1-CovIran. IQR: interquartile range

Table 4: Incidence rate ratios of breakthrough infection in matched cohorts of vaccinated individuals with vs. without prior infection

	Incidence Rate Ratio of Reinfection after Vaccination (95% CI)		
	All variants	**Alpha Variant**	**Delta Variant**
Gam-COVID-Vac	0.38 (0.31–0.47)*	NA	NA
ChAdOx1-nCoV-19	0.44 (0.33–0.57)*	0.44 (0.33–0.57)*	NA
Sinopharm BIBP	0.37 (0.32–0.41)*	0.36 (0.32–0.39)*	0.54 (0.26–1.09)
BIV1-CovIran	0.35 (0.23–0.54)*	0.38 (0.24–0.58)*	NA

*P<0.05. NA: In the Gam-COVID-Vac cohort, no one was previously infected with the delta variant; in the ChAdOx1-nCoV-19 cohort, no case with a previous delta-variant infection was reinfected after the vaccine; and in the BIV1-CovIran cohort, the number of previously infected cases with delta variant was not sufficient for analysis. CI: confidence interval, PCR: polymerase chain reaction

Hazard ratio

Total breakthrough infection HRs (previously infected over infection-naïve cohort) for the BIV1-CovIran, Sinopharm BIBP, Gam-COVID-Vac, and ChAdOx1-nCoV-19 vaccine groups were estimated to be 0.36 (0.23–0.55), 0.35 (0.32–0.40), 0.37 (0.30–0.46), and 0.43 (0.32–0.56), respectively [Table 3]. These ratios were approximately similar to the IRRs mentioned above.

The interval between previous SARS-CoV-2 infection and the first dose of vaccination

The mean ± standard deviation (SD) time interval between the prior PCR-confirmed COVID and the first dose of vaccination was 184.9 ± 70.5, 199.6 ± 99.4, 200.6 ± 118.2, and 216.1 ± 119.5 days for Gam-COVID-Vac, ChAdOx1 nCoV-19, Sinopharm BIBP, and BIV1-CovIran, respectively. This interval correlated with the calendar date on which the specific brand of the vaccine was first injected (the earlier the vaccine brand was opened, the shorter the mentioned interval).

An analysis of crude odds ratios demonstrated that for reinfected vaccinated individuals, the odds (95%CI) of a prior infection with the alpha variant having occurred more than 6 months before the first vaccination were 2.98 (2.18–4.08), 2.11 (1.38–3.21), 2.49 (2.13–2.92), and 2.31 (1.22–4.36) folds than 6 months or less than this interval for Gam-COVID-Vac, ChAdOx1-nCoV-19, Sinopharm BIBP, and BIV1-CovIran, respectively.

Stratified analysis of the previous infection variant of concern

In the Gam-COVID-Vac cohort, no one was previously infected with the delta variant; in the ChAdOx1-nCoV-19

cohort, no case with a previous delta-variant infection was reinfected after the vaccine; and in the BIV1-CovIran cohort, the number of previously infected cases with delta variant was not sufficient for analysis. Thus, only for Sinopharm's BIBP vaccine cohort, we could provide a separate analysis for the delta variant.

HRs and IRRs demonstrated that a previous infection with the alpha variant could confer significant additional immunity in all four cohort pairs. Nevertheless, the delta variant did not result in significantly more protection against reinfection [Table 3 and Table 4].

Discussion

The role of SARS-CoV-2 vaccinations and natural infections as determinants of herd immunity has yet to be explored in low- and middle-income countries. The current cohort study was conducted to answer how vaccination in a middle-income country provided immunity against breakthrough SARS-CoV-2 infection among previously infected adults. Obviously, a prior infection conferred incremental immunity against breakthrough infection after vaccination, no matter which vaccine brand was injected. Moreover, this incremental value was stronger if the prior infection had occurred less than 6 months previous to the first dose of vaccination.

Similar studies in other countries have concluded the same for people vaccinated with BNT162b2, mRNA-1273, or ChAdOx1-nCoV-19 vaccine.[19,23-26] Such a concordance proves that, regardless of the vaccine type, a combination of natural infection and vaccination (so-called hybrid immunization) infers a more robust immunity against SARS-CoV-2 breakthrough infections. It has been shown that a history of SARS-CoV-2 infection before or after vaccination provokes a significantly larger boost to the neutralizing antibody response compared with two doses of vaccine alone.[27] On the contrary, natural infection just results in short-lived protection from reinfection in real-world studies,[28] while the humoral response continues to develop long after vaccination, with memory B-cells showing the significance of vaccination, irrespective of SARS-CoV-2 infection history.[29] A physiological view would suggest that the recurrent stimulation of the immune system may speed the proliferation of memory cells and promote the production of specific neutralizing antibodies regardless of the brand of vaccine injected.[30,31] Further molecular studies may clarify how previously triggered memory cells react toward each specific vaccine brand.

The monthly cumulative infection incidences showed increasing trends during follow-up for each cohort. This finding was also concordant with previous studies that implicated waning immunity during time as the culprit.[12,32-34] In addition, the stronger immunity among vaccinated people who had been infected less than 6 months prior to the first vaccine dose, which was a result of this study and concordant with Abu-Raddad *et al*.,[19] further supports the reduced responsiveness of the immune system after 6 months of infection. SARS-CoV-2 vaccination protocols suggest booster doses after 5 months for healthy adults, in line with the available findings and consistent with this study.[18]

The waning immunity phenomenon accelerated faster among infection-naïve vaccinated people compared to previously infected ones.[19,26] Earlier studies have come to the conclusion that recurrent immune system stimulation promotes longevity and interaction between memory T and B-cells.[35-37] Therefore, future studies may reveal that booster doses will be unnecessary or can be administered at longer intervals than suggested now by the Center for Disease Control and Prevention.[18]

This study also provided results that could be utilized to compare how much immunity different SARS-CoV-2 vaccine brands infer if they were administered to formerly infected people. The total HR and IRR for previously infected people compared to infection-naïve ones were approximately the same among each cohort pair except for ChAdOx1-nCoV-19, which seemed to be higher. However, the short follow-up period for the ChAdOx1-nCoV-19 vaccine may be a confounding result that should be borne in mind. Medigeshi *et al*.[20] evaluated the antibody response against the Omicron variant of SARS-CoV-2 during this variant's breakthrough among previously infected and infection-naïve individuals who were vaccinated with ChAdOx1-nCoV-19 in India. At least 6 months had elapsed since the full vaccination of the participants in their study. Among 20 infected people, five infection-naive and nine formerly infected individuals developed neutralizing antibodies. Although their follow-up was longer and their variant of concern was different from this study, their result was fairly concordant.

Our analyses demonstrated that an earlier infection caused by the alpha variant provided more robust protection against reinfection than a previous delta infection. Conversely, Powell *et al*.[38] reported 86.1% and 92.3% protection against delta-variant infection for people previously infected with alpha and delta variants, respectively. We assume that such a discordance contributes to several factors: our limited follow-up time for individuals with previous delta-variant infection—a maximum of 4 months; an approved breakthrough infection as our outcome, regardless of its underlying variant; and the lower sensitivity of our PCR test kits for detecting the delta variant. Conclusively, we may not generalize our results regarding people previously infected with the delta variant; however, by excluding these cases, we could provide unbiased results for people formerly affected by the alpha variant.

To the extent of our knowledge, examining the protective effect of a mixture of natural and artificial immunity in a middle-income country with a unique availability of

various vaccine brands brings novelty to this study and makes it worth considering in future implementations. The study's large sample size, exact cohort matching, considering the dominant circulating variant of the virus, and month-by-month calculations provide robust conclusions in the end.

We could not eliminate some limitations during the study:

1. We could not verify if participants with no positive test results were surely uninfected, especially for delta-variant infections, for which the test kits had questionable sensitivity.
2. The registry database harbored insufficient information about nationalities other than Iranian, compelling us to ignore them in this study.
3. The follow-up time was short for the ChAdOx1-nCoV-19 and BIV1-CovIran vaccine brands and could not be as informative as the other studied brands. With the introduction of booster doses in Iran (October 2021), we could not efficiently continue studying participants who had received no booster doses beyond the study censoring date.
4. The studied sample was confined to one province in Iran.
5. Variant-specific PCR kits were not available to detect the exact previous infection's variant of concern; thus, we had to use the calendar date of infection to guess the probable variant.
6. We could only include people receiving two vaccine doses in the study.
7. The end of censorship was due before the Omicron variant breakthrough in Iran. Therefore, protection against this variant could not be assessed.
8. Previously infected individuals were people who had survived an infection. Henceforth, they are expected to be healthier than a normal community and develop stronger immunity. This fact may bias the results of this study.

By virtue of the abovementioned limitations and considering the extracted results from this study, the authors suggest:

1. Extending the results of this study to other nationalities and cities of Iran or other countries;
2. Evaluating if the same results will be achieved after administering booster doses;
3. Conducting reviews or multicentric studies to compare the effectiveness of different vaccine brands that are not available simultaneously in one country; and
4. Conducting this study over a larger population to achieve a sufficient sample size for one-by-one matching.

In conclusion, Prior SARS-CoV-2 infection conferred incremental immunity against breakthrough after vaccination, no matter which vaccine brand was injected. This incremental value was stronger if the prior infection had occurred less than 6 months previous to the first dose of vaccination. Such results could guide health authorities in middle-income countries to codify low-cost high-benefit vaccination protocols and protect the community's well-being.

Ethics of approval

The study was carried out in accordance with the Helsinki Declaration (IV Adaptation). The study protocol was approved by the Research Ethics Committees of Vice-Chancellery in Research, the Medical University of Isfahan (Approval ID: IR.MUI.MED.REC.1400.483).

Patient consent

In view of the retrospective nature, the need for individual patient consent was waived by the research ethics committee as data protection safeguard was in place.

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Conflicts of interest

There are no conflicts of interest.

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