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Original Article

Factors influencing COVID-19 vaccine breakthrough infections: an analysis of healthcare workers in Ardabil, Iran

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Abstract

***Background & Aims*:** Investigating re-infection with COVID-19 is necessary due to the existence of genetic differences among populations after a general vaccination plan. In addition to genetic differences, gender, age, the presence of underlying diseases, and the type of vaccine are factors that affect the rate and severity of re-infection after vaccination.

***Materials & Methods*:** Demography, physical activity and nutrition, underlying diseases, the period of involvement with the COVID-19 pandemic, and the percentage of re-infection before and after each stage of vaccination of the medical staff at Imam Khomeini Hospital in Ardabil (Iran) were evaluated. Our study was performed in a descriptive-analytical manner among 149 healthcare workers. The data were collected using a valid and reliable questionnaire and analyzed using SPSS version 26.

***Results*:** According to the results, 69.1% of healthcare workers had a positive PCR test or symptoms of COVID-19 before the first injection of the vaccine. The types of injected vaccines included AstraZeneca, Sinopharm, Sputnik V, Bharat, Barekat, Spicogen, and PastoCovac. After the injection of the first dose of the vaccine, the number of severe cases decreased from 30.9% to 10.7%, which indicates the effectiveness of the vaccination.

***Conclusion*:** The lowest rate of re-infection was observed in people with good physical activity compared to those who were less active (9.6% versus 59.6%). The highest rate of re-infection with COVID-19 between the first and second doses of the vaccine was related to Sinopharm, Sputnik V, and AstraZeneca. The highest rate of re-infection (82.7%) was in the age group under 40 years old.

***Keywords*:** AstraZeneca, Breakthrough infection, COVID-19, Vaccine

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Introduction

The widespread spread of the COVID-19 virus caused the World Health Organization to declare it a public health emergency around the world. With the death rate increasing day by day, the COVID-19 pandemic has become one of the biggest threats to human health in the last century, and it has created vast political, economic, and social consequences in the

world and in Iran (1, 2). Since the outbreak of the COVID-19 pandemic, its worldwide impact on all aspects of human health and social and economic life has been evident. As of June 21, 2021, the number of infected people in the world was more than 180, 654, 652, and the number of deaths due to COVID-19 was more than 4.6 million (1, 2).

Vaccination against infectious diseases such as COVID-19 is the most cost-effective health intervention. Due to the rapid spread of the COVID-19 virus and the high death rate it caused, the production and development of a vaccine for this disease was a necessity in terms of implementation. Today, mass vaccination against COVID-19 could limit the spread and transmission of the disease, as well as reduce the death rate caused by it (3, 4).

Among the foreign vaccines that are allowed to be administrated in Iran are the Sinopharm vaccine (made in China and an inactivated vaccine), the AstraZeneca vaccine (made in England and a vaccine based on a viral vector), the Sputnik V vaccine (made in Russia and also based on viral vector), and the Covaxin vaccine (produced by Bharat India and an inactivated vaccine type). COVIran Barekat, SpicoGen, and PastoCovac vaccines are among the Iranian vaccines that have obtained the license for administration (5).

The prevalence of re-infection in some parts of the world (Mississippi and Alabama, which are part of the United States) has been reported to be more than 30%. In these areas, conditions such as close contact, cramped work-spaces, and presence in enclosed spaces like restaurants may have caused a significant increase in the number of relapses. Also, re-infection is more common among healthcare staff who are in frequent contact with patients with COVID-19. For unknown reasons, women account for 63% of re-infection cases (6). Vaccines elicit a weaker immune response in the elderly, and the probability of re-infection, as assessed by the CDC, is 75% in people 65 years and older. Immune deficiency and underlying diseases such as high blood pressure, diabetes, heart disease, lung disease, cancer, etc., increase the risk of re-infection after vaccination (7).

Since India is one of the countries where the mutation of the COVID-19 virus is very high, several studies have been published on re-infection after vaccination due to the emergence of new virus strains. In one of these studies, consecutive blood samples were collected from 1,858 Indian medical staff who had received the AstraZeneca-Oxford vaccine to determine the levels of SARS-CoV2-IgG and neutralizing antibodies. They reported the results as follows: about 65.13% of the recipients of the first two doses of the vaccine and 62.8% of the recipients of both doses experienced re-infection after vaccination. This statistic shows that complete vaccination with two doses provides higher safety and efficacy. Genome analysis of PCR-positive samples in this study shows an alarming increase in delta variants of the COVID-19 virus (6).

Another study was conducted to investigate the rate of re-infection after vaccination with the AstraZeneca-Oxford vaccine in India. In this study, at least 2 months had passed since the injection of the first or second dose. The participants were mostly doctors or hospital health personnel. In the subsequent steps, the non-healthcare employees of the hospital who had visited the center for vaccination were also registered. The sample size in this study was reported to be 1,650. In order to collect information, each participant was supervised by an expert over the phone. The information required in this study included demographic characteristics, history of underlying diseases, symptoms of COVID-19, positive PCR test or positive antigen test at any time after vaccination, need for hospitalization, and details of the person's need for oxygen. In the event of the recipient's death, the cause of death was asked from the family members (8). In this study, positive cases of COVID-19 are divided into two categories: Confirmed and Suspected. Any person with laboratory confirmation and a positive PCR test, regardless of clinical symptoms, was considered a Confirmed case. Suspected cases also have a spectrum of clinical symptom patterns and were exposed to confirmed or probable cases of COVID-19 in the past 14 days. In the group that received only one dose (65

people), 27 cases (41.5%) were confirmed, and 2 cases (3.1%) were reported as suspected cases. In 70% of cases, the infection was mild, and only 3 people (10%) needed hospitalization and oxygen. Additionally, 2 deaths due to underlying diseases were recorded in this group. Among the people who received both doses of the vaccine (1,435 people), a total of 388 cases (27%) of confirmed and suspected infections were reported, of which 271 cases (18.9%) were PCR-positive. Most cases (85%) were mild, and only 1.3% required hospitalization. In this group, 2 deaths were recorded, both of which had underlying diseases (8).

Bergwerk et al. in a large medical center, investigated the possibility of re-infection after COVID-19 vaccination with the Pfizer-BioNTech vaccine. In order to evaluate re-infection in this study, PCR tests, rapid antigen detection methods, serological methods, and genomic analysis were used to collect information. The results of the study are as follows: Among the 1,497 personnel of the health center, 39 cases of re-infection (PCR positive) with COVID-19 after vaccination were recorded (9). According to the results, a higher titer of neutralizing antibodies before re-infection is associated with a lower probability of infection with the virus. Most cases of re-infection were asymptomatic or mild; however, 19% of relapses had persistent symptoms for more than 6 weeks. In 85% of the cases, the alpha variant of the COVID-19 virus was recorded in the samples. In general, the occurrence of reinfection with COVID-19 after vaccination is related to the titer of neutralizing antibodies during the infection period (9).

Taygi et al. published the following data during a study of re-infection with COVID-19 after vaccination among health workers of a medical care center in New Delhi: 113 people were vaccinated among 123 personnel who worked in this center. 94.7% of them had received both doses of the vaccine, and the rest had received only one dose. Information related to personnel vaccination (type of vaccines were Covaxin and Covishield), health status, symptoms of COVID-19, and PCR test results of participants were recorded from January 16, 2021 (10). In this study, vaccine breakthrough infection is defined as the occurrence of infection after 14 days (or more) after completing the recommended standard doses of the vaccine. The project expert has been in contact with people with re-infection by phone, and descriptive expressions were used to express the history of the patients. Among the 113 vaccinated people, 15 cases of symptomatic disease were reported, only one case required hospitalization, and the rest were mild cases (10).

One of the limitations of previous studies in this field is not taking into account the role of a person's nutrition, weight, physical activity and exercise, and the use of supplements and vitamins in the severity of side effects or not considering the timing of each occurrence (10, 11). The main goals of this study were to determine the prevalence of side effects after COVID-19 vaccination in the medical staff of Imam Khomeini Hospital in Ardabil and to investigate the effect of demographic factors, nutrition and medication consumed by the individual, the type of vaccine after three stages of vaccination, and previous infection with COVID-19.

Materials & Methods

Participants of the Study:

This study was performed among health care workers employed at Imam Khomeini Hospital of Ardabil University of Medical Sciences, Iran, from May 7 to June 7, 2022. The current study was designed and implemented during the years 2021-2022, with the aim of investigating the prevalence of side effects of various injected vaccines in an interdepartmental and descriptive-analytical manner among 149 health care workers of Imam Khomeini Hospital in Ardabil.

Based on the information obtained from the hospital management, the number of health personnel was estimated to be around 500. The sample size in this statistical population was calculated by taking into account a side effect percentage of 50, a 5% margin error, and a confidence interval of 95%, resulting in at least 200 people. The site (http:.www.raosoft.com.samplesize.html) was used.

Questionnaires were distributed in two ways: printed forms and online link sharing. Each person was only allowed to complete the online questionnaire once. The data were coded and received as an Excel file. The data collection tool was a questionnaire compiled by the researcher according to previous studies, examining their strengths and weaknesses, and was divided into four main sections: demographic information of the volunteers (age, gender, height, weight, level of education, expertise, smoking), previous infection with COVID-19 and severity of symptoms in each infection, sports activities and nutrition quality, underlying diseases, severity and time of symptoms, infection with COVID-19 after the injection of the first and second doses of the vaccine, and the severity and symptoms of the infection and the hospitalization status of the participants.

Ethical Approval:

After receiving approval from the university's ethics committee (number: IR.ARUMS.REC.1401.008), the questionnaire for this research was distributed among the hospital's medical staff. All the information and medical histories of the participants were obtained through coding, and the names and information of the participants remained confidential throughout all stages of the research, and will continue to remain so.

Inclusion/Exclusion Criteria:

The inclusion criteria in this study were the administration of three doses of one of the available vaccines in Iran and a positive COVID-19 test before and after each stage of vaccination. The exclusion criterion was the failure to complete the questionnaire on time.

Statistical Analysis:

The collected information was entered into an Excel file and then analyzed using SPSS.26 statistical software. Quantitative variables were described using either the mean (Mean ± SD) or the median (first quartile and third quartile), depending on the conditions. For qualitative demographic variables (age, gender, body mass index, vaccine side effects, underlying diseases, and their relationship), frequency reports (%), agreement tables, chi-square tests, and t-tests were used when necessary. For quantitative variables, after evaluating the normality of the data with the Kolmogorov-Smirnov test, comparisons between two groups were performed using a t-test for parametric data and a Mann-Whitney U test for non-parametric data. For statistical analyses involving more than two groups, a one-way analysis of variance (ANOVA) test and Tukey's mean comparisons were used at a significance level of $p \leq 0.05$. Cluster analysis was employed to reduce data and group vaccine complications. Pearson's correlation analysis was used to identify correlations between variables. In all analyses performed, p value of less than 0.050 was considered significant.

Results

Demographic Characteristics:

The details of the demographic characteristics of the studied population are summarized in Table 1. According to the results, 77.2% of the studied population were women. The age range of the participants varied between 27 and 55 years, with 52% of them being in the 30-39 age group. About 50% of the participants had a healthy body mass index, while approximately 43.6% had a body mass index higher than 25 and were classified as overweight. Regarding underlying diseases, 76.5% of the studied subjects had no underlying conditions. However, 33% had at least one or more underlying diseases. The highest frequency of underlying diseases is as follows: allergy (6.7%), high blood pressure (HTN) (4%), asthma and COPD (1.3%), diabetes (1.3%), and other conditions as angina and heart failure (Figure 1). There is also a history of heart attack, gestational diabetes, deep vein thrombosis, hypothyroidism, lumbar disc issues, anemia, psoriatic arthritis, thalassemia minor, arthritis, osteomalacia, and irritable bowel syndrome.

Table 1. The important characteristics of studied population

Variable	Level	Frequency	Percentage
Sex	Male	34	32.8
	Female	115	77.2
Age	< 29 yrs.	41	27.5
	30-39 yrs.	78	52.3
	> 40 yrs.	30	20.1
Smoking	Yes	7	4.7
	No	142	95.3
Regular use of medical supplement	Yes	56	37.6
	No	93	62.4
Regular sport activities	Low	91	61.1
	Medium	43	28.9
	High	15	10.1
BMI	Healthy	67	44.9
	Overweight	65	43.6
	Obese	11	7.38
	Thin	6	4.0

The percentage and frequency of underlying diseases were different between male and female groups, with the highest rates observed among women and the elderly. In terms of smoking, more than 95% of the studied population were non-smokers. Regarding the consumption of food supplements, especially vitamin D, and engagement in sports activities, only 30-40% of the studied population were at the optimal levels. Additionally, 61% of the participants were inactive in terms of sports activities. One and two tenths of the participants had taken corticosteroid drugs one month before vaccination, which were effective in the treatment of COVID-19 due to their anti-inflammatory effects. In this study, 105 participants (70.5%) were nurses, 20 (13.4%) were residents, 14 (9.4%) were nursing assistants, 6 (4%) were general practitioners or specialists, and 4 subspecialists (2.6 %) participated. In terms of the workplace, 30.9% of the participants worked in the ICU department of the hospital, 18.1% in multiple departments (simultaneous activity in different departments), 16.1% in the infectious disease department, and 11% in the general department of the hospital (Figure 2). More than 87% of the studied staff have been working in departments dedicated to the hospitalization of COVID 19 patients since the beginning of the pandemic. Additionally, 60.8% of these individuals have been active in this sector for more than 6 months.

Also, 69.1% (103 people) of the participants had a positive PCR test or symptoms of COVID-19 before the first dose of the vaccine was administrated. 31%, 20.4% and 52.4% of the patients reported their COVID-19 symptoms as mild, moderate, and severe, respectively. Of severely infected patients, 41.7% were admitted to the hospital, and 2% were admitted to the ICU. The duration of symptoms persistence before the first dose of the vaccine was reported as 16.5% for less than 5 days, 45.6% for 5-10 days, and 39.8% for more than 10 days.

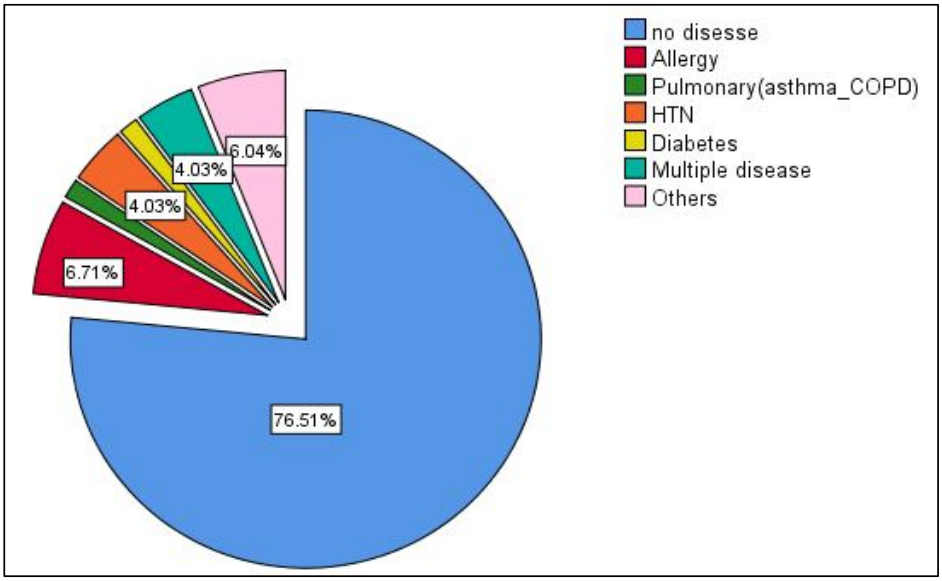

Fig. 1. The condition of the participants in terms of having underlying diseases.

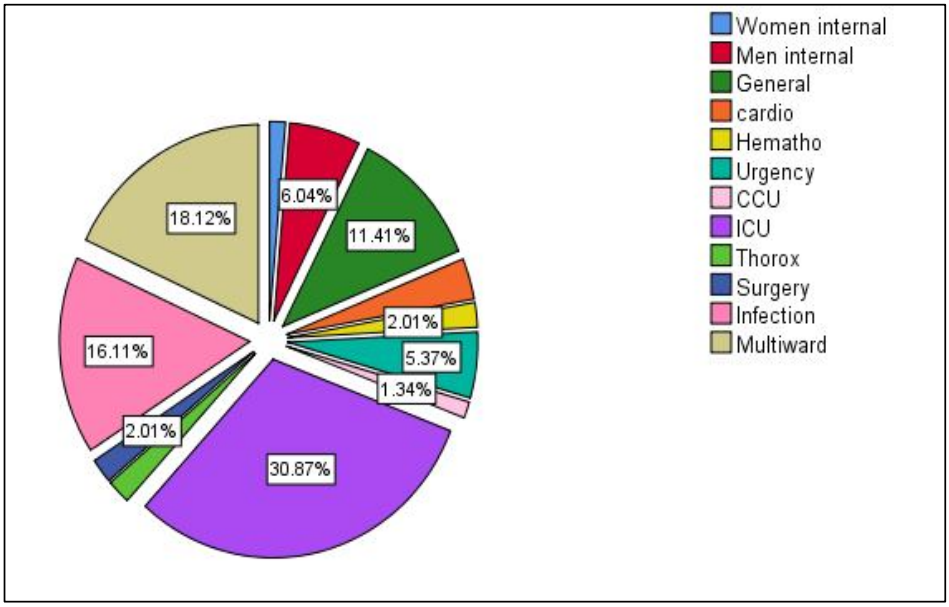

Fig. 2. Participant activity department in the hospital

The types of vaccines administrated included AstraZeneca, Sinopharm, Sputnik V, Bharat, Barekat, SpicoGen, and PastoCovac. The frequency of each type of vaccine administered in the first, second, and third doses is summarized in Table 2.

Table 2. The frequency of vaccines injected in three vaccination periods

Type of vaccine	Dose 1 and 2 (%)	Dose 3 (%)
AstraZeneca	18.1	52.3
Sinopharm	28.2	26.2
Sputnik V	45.6	8.7
Bharat	5.4	1.3
COVIran Brekat	2.7	3.4
SpicoGen	-	2
PastoCovac	-	6

Status of Previous COVID-19 Infection before Vaccination:

In this study, 103 participants, equivalent to 69% of the total, were infected with COVID-19 before vaccination. The severity and range of symptoms in these individuals are presented in Tables 3-20. Based on the obtained information, about 35% of these individuals experienced severe COVID-19 symptoms, with 26.7% being admitted to a regular hospital ward and some (2%) requiring admission to the intensive care unit. Other information, such as the severity and duration of the disease, type, and duration of hospitalization, is included in Table 3. In terms of gender, 75.7% of the primary patients were women and the rest were men (Table 4). In terms of age, 80% of the individuals were under 40 years old (Table 4). Additionally, 55.3% of the affected individuals had a BMI equal to or higher than 25 (Table 4). Furthermore, 65% of the patients did not take supplements, 98% were non-smokers, 58.3% did not engage in regular sports activities, and 80.6% of the patients were hospital staff, including nurses and assistant nurses (Table 4).

Table 3. Status of previous COVID-19 infection before first dose injection among studied people

		N (%)
Status of infection	Positive	103 (69.1)
	Negative	46 (30.9)
Severity of disease	< 5 days	17(11.4)
	5-10 days	47 (31.5)
	> 10 days	41 (27.5)
Hospitalization	No hospital	60 (71.1)
	Normal	40 (26.8)
	ICU	3 (2.0)
Duration of hospitalization	< 5 days	29 (19.5)
	5-10 days	10 (6.7)
	> 10 days	2 (1.3)

Table 4. Previous infection with COVID-19 before first dose as affected by studied factors

Factor	Level	Infection status (%)		Significance
		Positive	Negative	
Sex	Female	78 (75.7)	37 (80.4)	0.049
	Male	25 (24.3)	9 (19.6)	
Age	< 40	83 (80.6)	36 (78.3)	0.049
	> 40	20 (19.4)	10 (21.7)	
BMI	BMI < 25	46 (44.7)	27 (58.7)	0.049
	BMI ≥ 25*	57 (55.3)	19 (41.3)	
Smoking	+	5 (4.9)	2 (4.37)	0.060
	-	98 (95.1)	44 (95.1)	
Regular exercise	Low	60 (58.3)	31 (67.4)	0.042
	Medium	33 (32.0)	10 (21.7)	
	High	10 (9.7)	5 (10.9)	
Supplement	+	36 (35.0)	20 (43.5)	0.209
	-	67 (65.0)	26 (56.5)	
Hospital sector	Physician …	20 (19.4)	83 (80.6)	0.451
	Nurse and nurse aide	10 (21.7)	36 (78.3)	

After receiving the first dose of the vaccine, 52 people, equivalent to 34.9% of the population, were infected with COVID-19. The severity, spectrum, and duration of symptoms as well as the type and timing of hospitalization, are presented in Table 5. Despite the peak of COVID-19, after the first dose of the vaccine, the number of severely infected people decreased from 30.9% in the first stage to 16 people, equivalent to 10.7% of the population, demonstrating the effectiveness of the vaccination program (Table 6).

Table 5. Status of COVID-19 infection among studied people after first dose of vaccination

		N (%)
Status of infection	+	52 (34.9)
	-	97 (65.1)
Severity of disease	Low	23 (15.5)
	Medium	16 (10.7)
	High	16 (10.7)
Duration of disease	< 5 days	26 (17.4)
	5-10 days	18 (12.1)
	> 10 days	16 (10.7)
Hospitalization	No hospital	28 (53.8)
	Normal	21 (44.2)
	ICU	3 (2.0)
Duration of Hospitalization	< 5 days	18 (21.1)
	5-10 days	5 (3.4)
	10 days	1 (0.7)

Table 6. COVID-19 breakthrough after first dose as affected by sexuality, age and BMI among studied people.

Factor	Level	Reinfection status (%)		Significance
		Positive	Negative	
Sex	Female	45 (86.5)	75 (77.2)	0.034
	Male	7 (24.3)	27 (27.8)	
Age	< 40	43 (82.7)	76 (78.4)	0.343
	> 40	9 (17.3)	21 (21.6)	
BMI	BMI < 25	28 (53.8)	45 (46.4)	0.243
	BMI ≥ 25*	24(46.2)	52 (53.6)	
Smoking	+	2 (3.8)	2 (5.4)	0.534
	-	50 (96.2)	92 (94.8)	
Regular exercise	Low	31 (59.6)	60 (61.9)	0.089
	Medium	16 (30.8)	27 (27.8)	
	High	5 (9.6)	10 (10.3)	
Supplement	+	18 (34.6)	38 (39.2)	0.357
	-	34 (65.4)	59 (60.8)	
Hospital sector	Physician …	4 (7.7)	26 (26.8)	0.011
	Nurse and nurse aide	48 (92.3)	71 (73.2)	

Table 7. Status of COVID-19 infection among studied people after second dose of vaccination

		N (%)
Status of infection	+	78 (52.3)
	-	71 (47.7)
Severity of disease	Low	32 (22.0)
	Medium	17 (11.4)
	High	30 (20.1)
Duration of disease	< 5 days	31 (20.8)
	5-10 days	26 (17.4)
	> 10 days	20 (13.4)
Hospitalization	No hospital	119 (79.9)
	Normal	22 (14.8)
	ICU	0 (0.00)
Duration of Hospitalization	< 5 days	18 (21.1)
	5-10 days	4 (3.4)
	> 10 days	1 (0.7)

Table 8. COVID-19 breakthrough after second dose as affected by sexuality, age and BMI among studied people

Factor	Level	Reinfection status (%)		Significance
		Positive	Negative	
Sex	Female	45 (86.5)	75 (77.2)	0.034
	Male	7 (24.3)	27 (27.8)	
Age	< 40	43 (82.7)	76 (78.4)	0.343
	> 40	9 (17.3)	21 (21.6)	
BMI	BMI < 25	28 (53.8)	45 (46.4)	0.243
	BMI ≥ 25*	24 (46.2)	52 (53.6)	
Smoking	+	4 (5.1)	3 (4.2)	0.552
	-	74 (94.9)	68 (95.8)	
Regular exercise	Low	48 (61.5)	43 (60.6)	0.958
	Medium	22 (28.2)	21 (29.6)	
	High	8 (10.3)	7 (9.9)	
Supplement	+	28 (35.9)	50 (64.1)	0.032
	-	28 (39.4)	43 (60.6)	
Hospital sector	Physician …	17 (21.8)	13 (18.3)	0.373
	Nurse and nurse aide	61 (78.2)	58 (81.7)	

Status of Breakthrough Infection after First Dose of Vaccine:

The re-infection rate between the first and second injections of the COVID-19 vaccine was higher in women than in men. Therefore, due to the predominance of women in this study, more investigations with more men are needed. After the first dose of the vaccine, there is a positive correlation between age and the re-infection rate. The highest rate of infection was in the age group under 40 years old, which, due to the predominance of young staff working in the hospital, requires more studies to draw precise conclusions. The re-infection rate between the first and second dose injections was higher in people with a body mass index less than 25 (53.8% vs. 46.2%). There is a relationship between the reinfection rates after the first and second doses of the COVID-19 vaccine, but this relationship was not statistically significant at the desired probability level.

In terms of social habits such as the level of physical activity (regular sports activities), smoking, and the consumption of medicinal and dietary supplements, differences were observed among the participants. Smoking and, consequently, chronic pulmonary complications negatively affect cardiovascular function and the body's immune system. In this study, the rate of relapses was higher in the non-smoking group. Considering that 95% of the studied subjects were non-smokers, definitive conclusions in this case require additional tests with a larger number of smokers and non-smokers. Regular sports activities have a significant positive effect on reducing re-infection. The lowest re-infection was observed in people with regular sports activities compared to inactive people (9.6% vs. 59.6%). On the other hand, the use of medicinal supplements had a positive effect on reducing re-infection with COVID-19. The lowest rate of re-infection was related to people with

supplement use (34.6%) vs. people without supplement use (65.4%). The rate of re-infection between the first and second dose of the COVID-19 vaccine was significant, particularly among hospital professionals, with the highest number of cases reported among nurses and assistant nurses.

Based on the obtained data, the highest rate of re-infection with COVID-19 between the first and second doses of the vaccine was related to Sinopharm, Sputnik V, and AstraZeneca. Considering that a small number of people had injected Bharat and Barekat vaccines, drawing a definite conclusion about these two vaccines requires further investigation (Tables 9 and 10).

Table 9. COVID-19 breakthrough as affected by type vaccine after first dose

Vaccine type	Response		Total	Negative/Total ratio*
	+	-		
AstraZeneca	10 (19.2%)	17 (17.5%)	27	63.0%
Sinopharm	13 (25.0%)	29 (29.9%)	42	69.0%
Sputnik V	22 (42.3%)	46 (47.4%)	68	67.6%
Bharat	4 (7.7%)	4 (4.1%)	8	50.0%
Barekat	3 (5.8%)	1 (1.0%)	4	25.0%

*Higher ratios indicating better effectiveness of vaccine

Table 10. COVID-19 breakthrough as affected by type vaccine after second dose

Vaccine type	Response		Total	Negative/Total ratio*
	+	-		
AstraZeneca	16 (20.5%)	11 (15.5%)	27	40.7%
Sinopharm	17 (21.8%)	25 (35.3%)	42	59.5%
Sputnik V	36 (46.2%)	32 (47.4%)	68	47.0%
Bharat	6.0 (7.7%)	2.0 (2.8%)	8	25.0%
Barekat	3.0 (3.8%)	1.0 (1.4%)	4	25.0%

*Higher ratios indicating better effectiveness of vaccine p value (< 0.05); sig: 0.373

Status of Breakthrough Infection after Second Dose of Vaccine:

According to Table 7, among the 149 participants, 78 people were re-infected with COVID-19 after the second dose of the vaccine, which is more than the 52 people who were re-infected after the first dose. However, the severity of the disease, the symptoms, and the rate of hospitalization decreased significantly compared to the previous infection. The rate of re-infection with COVID-19 after the second dose of the vaccine was higher in men than in women. According to Table 8, the re-infection rate after the second dose of the vaccine was higher in the age group below 40 years. Additionally, the rate of re-infection was almost the same in people with a BMI of less than 25 and those with a BMI greater than 25.

The relationship between re-infection with COVID-19 after the second dose of the vaccine in the study population was also investigated. As previously mentioned, social habits such as the level of physical activity (regular sport activities), smoking, and the use of medicinal and nutritional supplements influence the

rate of infection with COVID-19. The relationship between these variables and the re-infection rate is presented in Table 8. Smoking and, consequently, chronic pulmonary complications negatively affect cardiovascular function and the body's immune system. In this study, the rate of relapses was higher in the non-smoking group. Considering that 95% of the studied subjects were non-smokers, definitive conclusions in this case require additional tests with a larger number of smokers and non-smokers.

Regular sports activities have a significant positive effect on reducing re-infection. The lowest re-infection was related to people who engaged in regular sports activities compared to inactive individuals (9.9% vs. 60.6%). The use of medicinal supplements had a positive effect on reducing re-infection with COVID-19. The lowest re-infection was related to people who used supplements (39.4%) compared to those who did not (60.6%). The rate of re-infection with COVID-19 after the second dose was higher among nurses and assistant nurses than among doctors. According to Table 7, the rate of re-infection with COVID-19 after the second dose of the vaccine was varied depending on the vaccine administrated. The lowest re-infection rates were associated with the Sinopharm, Sputnik V, and AstraZeneca vaccines. The rate of infection was the same for the Bharat and Barekat vaccines.

The most underlying diseases in the study population were allergies (10 people) and high blood pressure (6 people). Before the first dose of the vaccine, 7 out of 10 individuals with allergies were infected, and after the injection of the vaccine, between the first and second doses, only 2 people were infected again. Regarding blood pressure, out of 6 patients, 5 were infected with COVID-19 before the injection, but only one person tested positive for COVID-19 after the injection. A similar trend can be seen for other underlying diseases, but the difference between the sick and healthy groups was not statistically significant (Table 11).

According to Table 11, in the healthy study population (without underlying disease), almost half of the people were re-infected with COVID-19 after the second dose injection, but in people with a history of underlying disease, this figure was about 70%. However, no statistically significant relationship was observed between underlying disease and re-infection with COVID-19 at this stage.

Table 11. COVID-19 breakthrough as affected by ground disease before and after vaccination

	Before first dose		**Between first and second dose**		**After second dose**	
Infection status	+	-	+	-	+	-
Without underlying disease	76 (66.7%)	38 (33.3%)	39	75	61	53
Allergy	7	3	2	8	3	70
Pulmonary	1	1	1	1	0	2
Hypertension	5	1	1	5	5	1
Diabetes	2	0	0	2	0	2
Multiple dis.	5	1	5	1	4	2
Others	7	2	4	5	5	4
Significance	*p* value (< 0.05); sig: 0.198		*p* value (< 0.05); sig: 0.112		*p* value (< 0.05); sig: 0.158	

Discussion

Based on the results obtained, the community studied in this research was predominantly young, with most participants being women. The occurrence of COVID-19 symptoms or a positive PCR test 14 days or more after the first dose of the vaccine is considered re-

infection after vaccination. Previous infection with the COVID-19 virus is a sign of a person's vulnerability to other people.

Multinational studies have reported that race is an influencing factor in the course of the disease and its recovery. In patients with COVID-19, individuals of yellow and black races are more vulnerable than those of the white race. Even different nationalities, such as Brazilian, Chinese, and Italian, have been effective in contracting COVID-19 (11).

In terms of underlying diseases, one-third of the people in this community had at least one, and some had multiple underlying conditions. These underlying diseases can accelerate infection, slow down treatment, and increase the severity and weakness of side effects. It has been reported that high blood pressure can aggravate the side effects of vaccines. Based on the results of this project, there is a strong and significant relationship between underlying diseases, and initial infection with COVID-19, as well as the severity and spectrum of disease symptoms.

The results of a study by Butt et al. showed that in cases of re-infection with SARS-CoV-2, increasing age is associated with a higher risk of severe disease or death, while vaccination is associated with a lower risk. The presence of underlying diseases was not associated with severe disease or death among those with breakthrough infections (12). Among the group consisting of 456 cases of re-infection after vaccination, compared to the control group of 456 unvaccinated cases, severe COVID-19 was reported in 48 vaccinated individuals (10.5%) and 121 individuals (26.5%) in the unvaccinated group. The average age of re-infected cases was 45 years, and 60.7% of them were men. In summary, according to the results of this study, age over 60 years, male gender, and lack of COVID-19 vaccination were among the risk factors associated with re-infection (12).

Ku Yu et al. (2023) reported that long-term use of glucocorticoids increases the mortality and severity of COVID-19 and emphasizes the need to vaccinate these individuals and use preventive methods to avoid infection (13).

Profession and place of work had a significant relationship with the rate of infection, hospitalization, and length of treatment for COVID-19. In this study, the majority of the community belonged to the working group of nurses and assistant nurses, and they were infected with COVID-19 due to working in different departments of the hospital. About 60% of these individuals had been working in departments involved with COVID-19 for more than 6 months, and about 70% of them had a positive PCR test or symptoms of COVID-19 infection before the first dose of the vaccine was injected. Of the severely infected patients, 41.7% were hospitalized in the general department of the hospital, and 2% were hospitalized in the ICU department. The duration of symptoms of COVID-19 infection before the first dose of the vaccine was 16.5% less than 5 days, 45.6% between 5-10 days, and 39.8% more than 10 days.

Previous infection with the COVID-19 virus is a sign of the vulnerability of the studied subjects compared to the other group. In this study, 103 people, equivalent to 69% of the participants, were infected with COVID-19 before vaccination. The severity and range of symptoms of these individuals varied. Based on the information, about 35% of the participants had severe symptoms of COVID-19, with 26.7% admitted to the general department of the hospital, and some others (2%) admitted to the intensive care unit. In terms of gender, 75.7% of the initial patients were women, and the rest were men. In terms of age, 80% of the participants were under 40 years old and 55.3% of the affected individuals had a BMI equal to or greater than 25. Additionally, 65% of the patients did not take supplements, 98% were non-smokers, 58.3% did not have regular sports activities, and 80.6% of the patients were nurses and assistant nurses.

After the injection of the vaccine, some side effects usually appear in the person's body, indicating that the immune system is activated to defend itself, and these side effects are often short-term and harmless. The types of vaccine administrated in this study included AstraZeneca, Sinopharm, Sputnik V, Bharat, Barekat, SpicoGen, and PastoCovac. The results of this research

showed that the frequency of infection, the frequency of re-infection, the severity and occurrence of symptoms, the duration of hospitalization, and the type of hospitalization decreased significantly after the first dose of vaccine. The obtained results demonstrated, to a large extent, the effectiveness of vaccines in controlling COVID-19.

In the present study, the highest rate of re-infection (82.7%) was in the age group below 40 years. In a study examining the re-infection rate of people over 40 years of age with the same gender and initial test time, it showed that older people have 1.5 times more re-infection than younger people. The reason for this discrepancy is the majority of people under 40 years old in the present research (14).

A study by Enayatrad et al., published in the bulletin of the World Health Organization, showed that among the four vaccines AstraZeneca, Sputnik V, Sinopharm, and Barekat, in general and especially in single-dose form, AstraZeneca provides the most protection, while the Sinopharm vaccine offers the least protection against infection, hospitalization, and death due to COVID-19 (15). At the same time, another study on healthcare personnel was published in vaccines magazine and showed that people who experienced symptoms and complications related to Pfizer and Moderna vaccines had a longer antibody response. It has previously been shown that fever or other systemic symptoms may be associated with higher levels of antibodies after vaccination (16).

Tran et al. (2021) reviewed 22 cases of SARS-CoV-2 infection among more than 14,000 fully vaccinated nursing facility residents and staff and found that most of these infections were asymptomatic or had mild symptoms. This report suggests that the risk of re-infection after vaccination against COVID-19 is rare but also confirms that vaccines do not provide 100% protection, even in hosts with a favorable and unsuppressed immune system (17).

Butt et al.'s study showed that in re-infection with SARS-CoV-2, increasing age was associated with a higher risk of severe disease or death, while vaccination was associated with a lower risk. The presence of underlying diseases was not associated with severe disease or death among those with progressive infection. Among the group consisting of 456 cases of re-infection after vaccination, in contrast to the control group consisting of 456 cases of non-vaccination, severe COVID-19 disease was reported in 48 people (10.5%) in the vaccinated group and 121 people (26.5%) unvaccinated group. The average age of re-infected cases was 45 years, and 60.7% of them were men. In summary, according to the results of this study, age over 60 years, male gender, and lack of COVID-19 vaccination injection were among the risk factors associated with re-infection (18).

In this research, after receiving the first dose of the vaccine, re-infection with COVID-19 was observed. However, despite the peak of COVID-19, the infection rate was much lower, which demonstrates the effectiveness of the vaccination program. These results are consistent with the data from Gohil et al.'s study (19). They showed that both symptomatic and asymptomatic infections of the COVID-19 virus decreased steadily after vaccination of healthcare workers. These findings are consistent with past experiences with other viral respiratory infections, such as influenza and measles, in which vaccination reduces the overall rate of infection (19).

The results of Lee et al.'s study showed that unvaccinated individuals were more vulnerable to contracting COVID-19 than vaccinated individuals. However, after infection, there was no statistically significant difference in the risk of hospitalization, the need for invasive mechanical ventilation, or the mortality rates between the two vaccinated and unvaccinated groups. Nonetheless, unvaccinated subjects required more oxygen supplementation (20).

Lim et al. found that over time following vaccination, the rate of COVID-19 reinfection increases; however no statistically significant difference in reinfection rates was observed between hospital workers vaccinated with the AstraZeneca vaccine and those who received mRNA-based vaccines (21).

In this study, the relationship between the risk factors of COVID-19 and demographic factors was investigated. In general, there was a strong relationship between age, body mass index, level of education, employment status in the hospital, underlying diseases, number of supplements, and sports activities with the rate of infection with COVID-19 and the severity and type of complications. It is important to understand the different aspects of COVID-19 in various ways. The degree of influence of demographic characteristics on the severity of the disease in different countries varies depending on different races. According to previous studies, people with higher education are less susceptible to infection, as higher education reflects a greater level of awareness and knowledge, which is important for following prevention principles of and implementing treatment protocols. As a result, the infection rate is lower in this group. In addition, despite the many disputes in the hospital environment, there is a possibility of quick treatment for hospital staff due to timely visits to the hospital. In the present study, there is a significant relationship between old age and contracting COVID-19. This finding is consistent with recent reports that young people, especially children, are less affected by COVID-19 (22).

Lippi et al. (2020) compared the demographics and mortality of people in Italy and China in a study. In this study, the severity of illness, hospitalization, and even mortality increased with age. According to studies, the reasons for the increase in elderly patients can be two things: a decrease in the immune system and the presence of accompanying diseases due to increasing age (22).

Islam et al. (2022) in Bangladesh investigated re-infection with COVID-19 and reported that 98% of people experienced re-infection after 3 to 6 months, and 98% of them were from densely populated urban areas. According to this report, physical distancing caused the infection rate to decrease (23).

Re-infection in a hospital environment is common due to frequent exposure to patients, and the results of this project showed that re-infections were often limited to hospital nurses. Regarding underlying diseases, the result of the present study showed that the presence of underlying conditions such as high blood pressure, diabetes, and respiratory diseases increased the duration of hospitalization, which is consistent with other studies (24). Based on the studies of Besharat et al. (2020), which aimed to determine the demographic and clinical characteristics of patients who died after being hospitalized in the COVID-19 department of Modarres Hospital in Tehran, most of the recorded deaths were among those who were overweight, over 60 years old, and suffering from multi-organ failure. Fever, chills, fatigue, cough, and shortness of breath were evident in most of the patients before death. Also, there was no difference between men and women in having an underlying disease, symptoms of COVID-19, and death afterward (24).

Examining the gender factor in patients with COVID-19 in this study showed that the severity and duration of the disease were greater in women. Of course, most of the hospital staff in this study were women, which shows that more women participated in the present study. Interactions were also seen between re-infection with gender, body mass index, and type of vaccine. This means that people with a higher body mass index, and underlying disease were the most involved in contracting COVID-19. Also, due to the high vulnerability of women to extreme stress, their immune systems are weakened, exacerbating the severity of the disease. According to reports from other sources, the amount of stress on women working in private hospitals is even higher than in public hospitals. People who were employed in public centers were hospitalized for less time than those who were employed in private centers. The results of the present study are in line with the study of other researchers (24).

Conclusion

In people who received the AstraZeneca, Sputnik V, and Sinopharm vaccines, the rate of re-infection after vaccination was lower. Also, a direct relationship was observed between female gender, low body mass index, and young age with re-infection after COVID-

19 vaccination. The prevalence of re-infection and the severity of the disease decreased significantly after the administration of booster doses of the COVID-19 vaccine.

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Authors' Contributions

The authors confirm sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results. All authors read and approved the final manuscript.

Data Availability

The data used to support the findings of this study are included within the article.

Conflict of Interest

The authors have no conflicts of interest related to the material presented in this article.

Ethical Statement

This study protocol was reviewed and approved by Ardabil university of medical science , approval number IR.ARUMS.REC.1401.008.

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