COVID-19 vaccines breakthrough infection and adverse reactions in medical students: A nationwide survey in Iran

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Abstract

Purpose: This study aimed to investigate the rate of COVID-19 breakthrough infection and adverse events in medical students.

Methods: Iranian medical students receiving two doses of COVID-19 vaccines were included in this retrospective cohort study. The medical team gathered the demographic characteristics, comorbidities, type of vaccine, adverse events following vaccination, and history of COVID-19 infection data through a phone interview. The frequency of adverse events and breakthrough infection was stratified by vaccine type (ChAdOx1-S, Gam-COVID-Vac, and BIBP-CorV).

Results: A total of 3591 medical students enrolled in this study, of which 57.02% were females, with a mean age of 23.31 + 4.87. A PCR-confirmed and suspicious-for-COVID-19 breakthrough infection rate of 4.51% and 7.02% was detected, respectively. There was no significant relation between breakthrough infection and gender, BMI, blood groups, and comorbidities. However, there was a significant difference in breakthrough infection rate among different types of vaccines (P=0.001) and history of COVID-19 infection (P=0.001). A total of 16 participants were hospitalized for COVID-19 infection, and no severe infection or death was observed in the studied population.

Conclusion: Vaccination prevented severe COVID-19 infection, although a high breakthrough infection rate was evident among Iran medical students during the Delta variant's peak. Vaccine effectiveness may be fragile during emerging new variants and in high-exposure settings. Moreover, adverse events are rare, and the benefits of vaccination outweigh the side effects. However, many limitations challenged this study, and the results should be cautious.

Introduction

The rapid spread of the coronavirus disease 2019 (COVID-19) caused 235 million infected cases, and 4.8 million lives claimed globally [1]. Many countries decided to use COVID-19 vaccines under Emergency Use Authorization (EUA) to prevent further fatality and disruption caused by the pandemic [2, 3]. COVID-19 vaccines dramatically reduced the disease's mortality; some concerns were raised regarding their safety and effectiveness [4].

Although COVID-19 vaccines can cause various complications, they are usually safe. The adverse events are mild and self-limiting in most of the cases [5]. However, COVID-19 vaccines are under emergence use approval, and some adverse reactions may remain obscure. Anaphylaxis can occur after vaccination and has a reporting rate of about 1 case in 1 million but gets much attention due to its severity and importance [6]. Also, vaccines passed different regulations for approval, and types administrated in developed countries are more closely investigated in the literature than in developing countries. Therefore, surveillance programs are needed better to evaluate the adverse events of the COVID-19 vaccines.

In addition to the fact that COVID-19 vaccines do not provide complete protection, individuals are also at the risk of post-vaccination breakthrough infection due to the development of mutations and different variants of SARS-CoV-2. Vulnerable subjects, including immunosuppressed transplant recipients, are at higher risk of post-vaccination breakthrough infections and further mortalities and morbidities than the average risk [7]. Still, there is a paucity of evidence regarding the safety and efficacy of vaccines in large populations. Since no national studies focus on vaccine-related adverse reactions and breakthrough cases, this study aimed to investigate the rate of adverse events and COVID-19 infection in medical students.

Material And Methods

Ethics statement

The institutional Review Board of Shahid Beheshti University of Medical Sciences approved this study protocol (reference code: IR.SBMU.RETECH.REC.1400.947). Informed consent was obtained through phone calls, and confidentiality of data was concerned during the study.

Study design

In this retrospective cohort study, medical students who received two doses of COVID-19 vaccines were enrolled from 5 provinces (Tehran: 2899, Shiraz:333, Kerman: 121, Yazd: 74, Hamedan: 31, other: 133). Subjects' information including their demographic data, comorbidities, history of COVID-19 infection (before, after, and during (from first one to 21 days after receiving the second dose) immunization period), blood group, body mass index (BMI), history of influenza vaccination, and adverse events following vaccination was gathered by a medical team via a follow-up call from 28 August to 22 September 2021 (the delta variant was the dominant strain of the virus at that time). Participants with two unanswered phone calls with a minimum of 24-hour intervals between calls and subjects who received two different types of vaccines were excluded. The study's outcome was a breakthrough infection rate among medical students after full immunization and adverse reactions to COVID-19 vaccines.

Definitions and grades

The method of COVID-19 diagnosis was based on self-report during the call and then verification of the provided information with the database provided by the health authorities. Moreover, subjects with COVID-19 symptoms but did not undergo PCR tests (COVID-19 suspected patients) were also included. Suspicious-for-COVID-19 is defined by Iran's ministry of health as a patient with respiratory symptoms, exposure to COVID-19, and no other robust explanation for the symptoms. In the case of two negative PCR tests, the COVID-19 infection was ruled out. Categories of severity for COVID-19 infection were as follows: Mild: any sign of COVID-19 infection without any dyspnea or abnormal imaging, Moderate: patient experiencing dyspnea or hospitalization or abnormal imaging, Severe: decrease in oxygen saturation (< 94%), or intensive care unit admission. A severe adverse event after vaccination is a side effect that needs hospitalization for further evaluation or treatment.

Statistical analysis

R software version 3.6.3 was used for the statistical analysis. Descriptive statistics were provided as mean ± standard deviation or number and percentage. Mann–Whitney U test was used to evaluate the difference between the means of the two groups. Categorical variables were compared using the chi-square test. A P-value < 0.05 was considered significant.

Results

A total of 3591 medical students with a mean age of 23.31 ± 4.87 that 57.02% of whom were female, were investigated. Mean BMI was 22.9 + 3.71, and O, A, B, and AB blood group was evident in 35.85%, 31.67%, 22.48%, and 10% of students, respectively. Of 180 reported comorbidities, asthma (31) and thyroid gland disorders (26) were among the most frequent underlying diseases.

As depicted in Fig. 1, a PCR-confirmed breakthrough infection rate of 4.51% was detected. In addition, the suspicious-for-COVID-19 breakthrough infection rate was 7.02%. Breakthrough infection was lower in students who experienced COVID-19 infection vaccination more than once compared to students infected with COVID-19 once (1.55%, 2/129 vs. 2.32%, 23/990).

Table 1 describes the relation of breakthrough infection with underlying factors and different types of COVID-19 vaccines. There was no significant relation between breakthrough infection and gender, BMI, blood groups, and comorbidities. However, there was a significant difference in breakthrough infection rate among different types of vaccines (P = 0.001), history of COVID-19 infection (P = 0.001), and history of influenza vaccination (p = 0.001). The severity of COVID-19 after vaccination is presented in Table 2, stratified by type of vaccine. The breakthrough rate was higher for ChAdOx1-S (6.22%) than Gam-COVID-Vac (3.13%) and BIBP-CorV (4.23%) vaccines. A total of 16 participants were hospitalized because of COVID-19 infection after vaccination. No severe infection was evident in the studied population.

Table 1
COVID-19 Vaccine breakthrough in medical students

	% PCR positive (Number)	% Suspicious for COVID-19 (Number)
Total	4.51% (162)	7.02% (252)
Gender	P = 0.117	P = 0.860
Female	4.99% (102)	7.09% (145)
Male	3.89% (60)	6.93% (107)
Body mass index (kg/m2)	P = **0.385**	P = **0.566**
< 18.5	3.78% (13)	5.23% (18)
18.5–24.9	4.78% (111)	7.31% (170)
25-29.9	4.55% (35)	7.01% (54)
> 30	1.99% (3)	6.62% (10)
Blood Group	P = **0.715**	P = **0.864**
A	4.14% (47)	6.51% (74)
AB	4.18% (15)	6.96% (25)
B	5.2% (42)	7.19% (58)
O	4.51% (58)	7.38% (95)
Rh	P = 0.310	P = 0.118
Positive	4.65% (145)	7.28% (227)
Negative	3.61% (17)	5.31% (25)
History of COVID-19 infection	P = 0.001	P = 0.001
Positive	2.4% (25)	3.27% (34)
Negative	5.38% (137)	8.56% (218)
Vaccine	P = **0.001**	P = 0.001
Gam-COVID-Vac (1181)	3.13% (37)	4.74% (56)
ChAdOx1-S (916)	6.23% (57)	9.95% (91)
BIBP-CorV (1419)	4.23% (60)	6.56% (93)
COVIran Barekat t (48)	6.25% (3)	12.5% (6)
BBV152 (27)	18.52% (5)	22.22% (6)

	% PCR positive (Number)	% Suspicious for COVID-19 (Number)
Comorbidities	P = 0.747	P = 0.430
Yes	5% (9)	5.56% (10)
No	4.49% (153)	7.1% (242)
Thyroid Disorder	P = 0.433	P = 0.893
Yes	7.69% (2)	7.69% (2)
No	4.49% (160)	7.02% (250)
Allergy/Asthma	P = 0.729	P = 0.406
Yes	3.23% (1)	3.23% (1)
No	4.53% (161)	7.05% (251)
Vaccination against influenza	P = 0.001	P = 0.003
Yes	7.79% (30)	10.65% (41)
No	4.12% (132)	6.59% (211)

Table 2
The breakthrough infection among different COVID-19 vaccines

	Gam-COVID-Vac	ChAdOx1-S	BIBP-CorV	All vaccines	P-value
Number of vaccines administrated	1181	916	1419	3591	
History of COVID-19 infection	28.79% (340)	29.91% (274)	28.49% (404)	29.03% (1042)	0.586
Breakthrough infection (PCR positive)	3.13% (37)	6.22% (57)	4.23% (60)	4.51% (162)	0.003
ICU admission/death	0	0	0	0	NA
Moderate - Hospitalized	0.25% (3)	0% (0)	0.78% (11)	0.45% (16)	NA
Moderate - outpatient	1.86% (22)	2.4% (22)	1.62% (23)	1.89% (68)	0.400
Mild	1.02% (12)	3.82% (35)	1.83% (26)	2.17% (78)	0.001
Breakthrough infection (Suspicious for COVID-19)	4.74% (56)	9.93% (91)	6.55% (93)	7.02% (252)	0.001
ICU admission/death	0	0	0	0	NA
Moderate - Hospitalized	0.34% (4)	0.33% (3)	0.92% (13)	0.67% (24)	0.079
Moderate - outpatient	2.12% (25)	4.37% (40)	2.61% (37)	3.04% (109)	0.007
Mild	2.29% (27)	5.24% (48)	3.03% (43)	3.31% (119)	0.001
During immunization (PCR positive)	0.51% (6)	2.18% (20)	0.7% (10)	0.89% (32)	0.001
During immunization (Suspicious for COVID-19)	0.59% (7)	6.88% (63)	1.41% (20)	1.89% (68)	0.001

“During immunization” is defined as a period from the first dose to 14 days after receiving the second dose. “After immunization” is defined as a period from 14 days after receiving the second dose to a follow-up call, which eq breakthrough infection. Abbreviations: PCR: polymerase chain reaction, ICU: intensive care unit, NA: not applicable.

Figure 2 shows the adverse reactions after COVID-19 vaccine administration (Numbers of events are also presented in Supplementary File 1). Fever (31.22%), myalgia (12%), injection site pain and swelling (11.08%), weakness (6.45%), and headache (4.3%) were the most common adverse events after receiving a dose of vaccine. Severe complications occurred in 9 participants (Anaphylaxis: 3, Rash: 1, heartthrob: 2, severe weakness, and fever:4).

Discussion

Newly emerged Covid-19 variants are of great concern since they can be highly transmissible, severe, or fatal. The mutations can also help evade detection or reduce the effectiveness of treatments or vaccines [1]. Vaccination in the COVID-19 pandemic is the only known effective means to prevent COVID-19 spread and prospect mutations; however, any fully vaccinated subject may experience COVID-19 infection yet. Thus, understanding the complications and effectiveness of the available vaccines will aid us in developing better policies. This study was conducted on healthcare students more exposed to COVID-19 infection. The study was performed during the most violent peak of COVID-19 in Summer in Iran, with 30,519 reported fatalities and 71,297 excess deaths, [8] while only 16.2% of the general population were fully vaccinated by the end of summer [9].

Among the 3591 medical and paramedical students, our study reported a PCR-confirmed vaccine breakthrough of 5.13%, which is significantly higher than most previous studies. High exposure risk of participants, low vaccine coverage, administrated types of vaccines, dominancy of delta variant, or coincidence with pandemic wave may explain some extent of this high vaccine breakthrough infection rate.

This study was performed on the earliest fully vaccinated population and coincided with the emergence of the Delta variant and the greatest COVID-19 waves in Iran. The estimated initiation time of the follow-up period was mid-April, when only 0.12% of the national population were fully vaccinated [10]. At that time, countries with mostly unvaccinated populations (such as Iran and India) experienced a brutal coronavirus wave. As in a single-center study in India, 13.3% of healthcare workers experienced breakthrough infections during a massive COVID-19 wave with the Alpha and Delta dominancy period [2]. At the time of Delta variant dominancy in the USA, when 50.2% of the population were immunized, the weekly incidence rate of breakthrough infections rose from 6.94 to 130.23 per 100000 fully vaccinated [11]. Therefore, the effect of the Delta variant on delineating vaccine effectiveness is indisputable [4, 5]. Although not enough data is available regarding the share of variants in Iran, the immune escape by Delta variant may play a role in the high breakthrough infection rate in countries with low vaccination rates.

In the latest official available data, the efficacy of Gam-COVID-Vac, ChAdOx1-S, and BIBP-CorV were reported to be 91.6%, 72%, and 79%, respectively [12–14]. Our study observed the lowest breakthrough infection rate in participants vaccinated with Gam-COVID-Vac. Vaccines have been proven to prevent contracting severe COVID-19 effectively. Despite administering the BIBP-CorV vaccine to less exposed healthcare students, ChAdOx1-S and Gam-COVID-Vac were significantly more effective in preventing severe COVID-19. In addition, COVID-19 infection after the first dose was significantly more prevalent among participants vaccinated with ChAdOx1-S than other vaccines. This can be justified by the long interval between its first and second dose (8 to 12 weeks for ChAdOx1-S relative to 4 weeks for other vaccines). The best vaccine in pandemic waves should be decided based on the efficacy and shortest time to reach maximum effectiveness.

Recent studies suggested a history of COVID-19 infection and healthcare jobs as factors for breakthrough infections. Higher breakthrough rates were reported in participants with higher neutralizing antibody titers [15, 16]. Vaccine breakthrough was less common in our participants experiencing COVID-19 infection before vaccination which is in line with previous studies [17]. According to serological studies, individuals with a history of COVID-19 infection have significantly high anti-spike antibody levels [18]. In our study, about 29% of the participants had a history of COVID-19 infection, yet the breakthrough infection rates were high. A study on 126,586 vaccine recipients reported that working in healthcare centers is associated with a higher risk of breakthrough infection [19]. Although exposure is an essential factor, our study's rate of 5.13% breakthrough cases is very high compared to previous studies on healthcare workers [15, 19].

Since no study has assessed the side effects of different types of vaccines in Iran, we also studied this issue. The most commonly reported side effects were fever, lethargy/fatigue, weakness, myalgia, and pain at the injection site. Inconsistent with previous studies, vaccines without adjuvant (Gam-COVID-Vac and ChAdOx1-S) were accompanied by a higher incidence of systemic adverse events, while vaccines with excipients consisting of Aluminum compounds (COVIran Barekat, BBV152, and BIBP-CorV) caused local reactions [20]. In our study, fever was the most reported adverse event of the COVID-19 vaccine and most probable in the first dose administration. Severe post-vaccination adverse events were present in 0.25% (n = 9) of our population, in which ChAdOx1-S and Gam-COVID-Vac were more likely to develop such events. A previous report on 1954 healthcare workers showed a 0.4% (n = 9) severe post-vaccination adverse incident leading to hospital attendance; BIBP-CorV (n = 1), Gam-COVID-Vac V (n = 3), and ChAdOx1-S (n = 5) [21]. Overall, among vaccine recipients, adverse events were rare and non-life-threatening.

This study investigated breakthrough infection and adverse events at young ages. There are some significant limitations to this study. This was a retrospective study with no control group, and investigation of vaccine effectiveness was impossible. In addition, this study does not include asymptomatic COVID-19 breakthrough infections; hence, underestimating breakthrough infection cases is possible. Comparison between the types of vaccines should be avoided since the time and administration settings were not similar. At first, Gam-Cov-Vac and ChAdOx1-S were more available for administration to front-line medical interns whereas BIBP-CorV was mainly administered to students with less exposure. Also, our study may miss a fatality ratio because of its retrospective nature. However, we checked authorities for any mortality report, which was found to be zero. Further prospective cohorts and active surveillance programs are warranted to investigate complications of COVID-19 vaccines.

Conclusion

Vaccination prevented severe COVID-19 infection, although a high breakthrough infection rate was evident among Iran medical students during the Delta variant's peak. Vaccine effectiveness may be fragile during emerging new variants and in high-exposure settings. Simple preventive actions such as wearing a face mask and social distancing should be continued until complete control of the pandemic.

Moreover, adverse events are rare, and the benefits of vaccination outweigh the side effects. However, many limitations challenged this study, and the results should be cautious.

Declarations

Acknowledgment

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Conflict of Interests

The authors declared no conflict of interests related to this work.

Author Contribution

Amirreza Allahgholipour: Methodology, Project administration; **Mohammad Rosstami-Nejad:** Methodology; **Seyed Amir Ahmad Safavi-Naini:** Formal analysis, Data Curation, Writing - Original Draft; **Hossein Nazary:** Data collection; **Mohamad Javad Honarvar:** Writing - Original Draft, Writing - Review & Editing; **Mohammad Mohammadi:** Investigation, Writing - Review & Editing; **Parnian Khalili:** Data collection, Investigation; **Mehran Ilaghi:** Data collection, Investigation; **Hossein Afshar:** Data collection; **Ali Amini Baghbadorani:** Data collection; **Hamid Reza Moghimi:** Data collection; **Alireza Chamani Goorabi:** Data collection; **Amirreza Mehrparvar:** Data collection; **Mehdi Safari:** Data collection; **Ashraf Sadat Nakhli:** Data collection; **Mohammad Mahmoudabadi:** Data collection; **Adib Seifadini:** Data collection; **Sobhan Shaikhansari:** Data collection; **Sadaf Khojastehfar:** Data collection; **Parisa Mahdavi:** Data collection; M**aede Mohammadi:** Data collection; **Siyamak Ashrafi Barzideh:** Data collection; **Nadia Akbarzadeh:** Data collection; **Adel Ahmadigol:** Data collection; **Alireza Zali:** Data collection, Writing - Review & Editing; **Seyed Hosein Delavarpour Moghadam:** Data collection; **Mohammad Barary:** Data collection, Writing - Review & Editing; **MohammadAli Emamhadi:** Methodology, Project administration, Writing - Review & Editing

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Figures

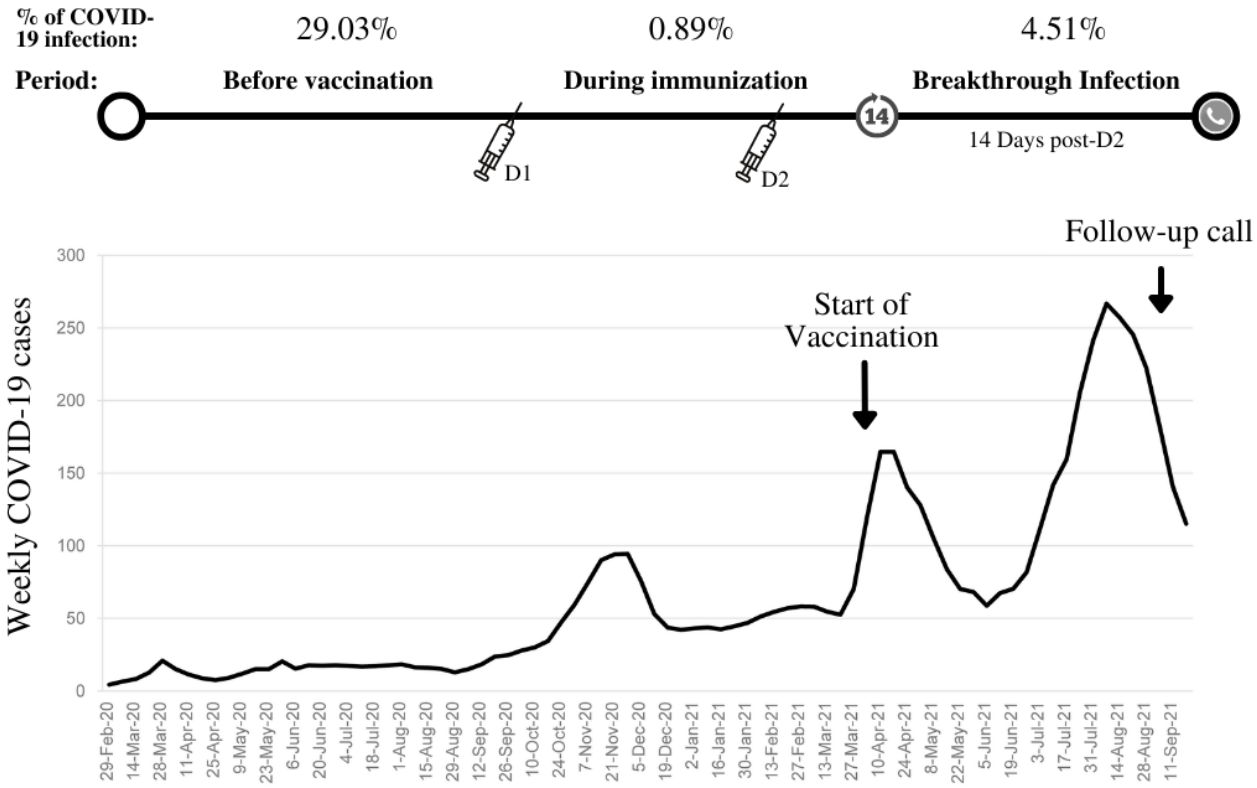

Figure 1

Weekly COVID-19 cases in Iran, start of COVID-19 vaccination program in medical students, history of COVID-19 infection, and breakthrough infection rate (confirmed by polymerase chain reaction).

Figure 2

Percentage and number of adverse events among medical students who received two doses of COVID-19 vaccine, stratified by type of vaccine (A: more frequent adverse reactions; B: rare adverse reactions)

Supplementary Files

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- SupplemantaryFile1.docx