

# Side Effects of COVID-19 Vaccination Following First and Second Doses: A Cross-Sectional Survey Based on Vaccine-associated Factors

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**Background:** Due to the rapid launch and development of vaccines (the most ideal protocol for countering COVID-19), monitoring of post-vaccination side effects is essential. This study aimed to assess symptoms and side effects of three types of COVID-19 vaccines (Sputnik, AstraZeneca, and Sinopharm) and the details of their relationship with demographic characteristics in Iran.

**Materials and Methods:** A cross-sectional and telephonic interview-based study was conducted from May 12 to July 11, 2021, among 420 university staff who received both doses of the COVID-19 vaccine. The association of vaccination behavior-related symptoms after the first and second doses with age, gender, vaccine type, blood type, underlying medical situation, and past infection and reinfection with SARS-CoV-2 was analyzed.

**Results:** The majority of participants were men (58.7%), the median age was 41.30+11.208 years, and 18.6% were vaccinated with the Sputnik vaccine, 75.1% with Sinopharm, and 6.3% with AstraZeneca. In addition, 47.3% and 41.8% were symptomatic after first and second dose vaccination, respectively. The frequency of symptoms was higher in younger individuals, women, and AstraZeneca recipients ( $p = 0.001$ ). The most frequently reported symptoms were fever, weakness, and muscular and injection site pain. These symptoms were more reported after the first dose than the second one. There was no significant connection between blood types, underlying medical situations, past infection and reinfection with SARS-CoV-2, and the prevalence of symptoms.

**Conclusion:** AstraZeneca, Sputnik, and Sinopharm COVID-19 vaccines were found to be safe and the lowest incidence of symptoms was seen in Sinopharm recipients.

**Keywords:** SARS-CoV-2; COVID-19 Vaccines; Iran; Sputnik; AstraZeneca; Sinopharm; Symptom; Side Effects

## INTRODUCTION

COVID-19 is a new strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged in China in late December 2019 (1-3). The novel disease was declared a global pandemic by the World Health Organization (WHO) in March 2020 (4,5). Due to the repeated genome recombination and high genetic diversity, the transmission rate of COVID-19 disease is very high. It may be asymptomatic or cause symptoms such as fever, cough, shortness of breath, gastrointestinal disorders, and nausea. Severe complications of the disease can lead to hospitalization and even death (6,7). Iran is one of the countries that has been severely affected by COVID-19 and has a high incidence and mortality rate (8,9).

A well-performing vaccine is considered the most effective means to fight against COVID-19 and control the pandemic. Boost the level of immunization, building protection, and developing herd immunity are the benefits of vaccination which enable the immune system to fight the virus effectively and fast in the future (10,11). With the release of multiple vaccines at the end of 2020, new hope has emerged for the eradication of COVID-19. Iran started the COVID-19 vaccination program in February 2021 with the medical staff as the main first-line workers and high-risk groups including the elderly population and individuals with underlying medical conditions (12). The common vaccines in Iran's COVID-19 vaccination program were Sputnik V (Gam-COVID-Vac), Sinopharm (BBIBP-CorV), and AstraZeneca (ChAdOx1 nCoV-19; AZD1222) vaccines that were imported into the country. These vaccines got requisite international approval for public use and have indicated proper efficacy in clinical trials.

Sputnik V (Gam-COVID-Vac) is a vaccine based on the adenovirus vectors that utilizes two types of adenoviruses (Ad5 and Ad25) to cause a humoral and cellular immune response against COVID-19. Two doses of this vaccine are injected with different materials at 21-day intervals for stronger and longer immunity. The efficacy of this vaccine was reported 91.6% with no unusual complicacy (13,14).

Another vaccine that uses an adenovirus vector against COVID-19 is AstraZeneca (ChAdOx1 nCoV-19; AZD1222), which targets spike proteins to induce immunity. The maximum effectiveness of this vaccine is 81% and the specific interval between two doses is 4 to 12 weeks (15,16).

Sinopharm (BBIBP-CorV), an inactivated vaccine containing killed copies of SARS-CoV-2, targets the whole virus and produces a humoral immune response. Safety and 86% efficiency of Sinopharm were reported in the experiments. In addition, acceptable protection against SARS-CoV-2 has been demonstrated in animal studies with Sinopharm. Xia et al. studied that Sinopharm vaccination using a two-dose schedule, with doses given three or four weeks apart, produces higher neutralizing antibody titers and yields better results (17,18).

The abovementioned vaccines can sometimes cause side effects during the process of immunization after the first and/or second dose. These vaccine-induced side effects can range from mild to severe, including fever, chills, cough, rhinorrhea, olfaction loss, muscular pain or pain at the injection site, joint pain, nausea, diarrhea, stomachache, weakness and tiredness, and other symptoms (19). Therefore, studies are needed to describe the side effects and risks of vaccines because they help to reduce public concern about these types of vaccines and increase public trust.

The current study aimed to report the occurrence of the side effects after receiving the first and second doses of three types of COVID-19 vaccines, as well as the detail of their association with demographic characteristics among Shahid Beheshti University of Medical Sciences staff, in Iran.

## MATERIALS AND METHODS

### Participants and data collection

This cross-sectional study was performed among staff who received the COVID-19 vaccine at Shahid Beheshti University of Medical Sciences, a public university in Iran. Participants comprised 420 university staff from different administrative departments who completed the

questionnaire through telephonic interviews. Shahid Beheshti University of Medical Sciences started vaccinating its staff against COVID-19 with the Sputnik V (Gam-COVID-Vac), the Sinopharm (BBIBP-CorV), and the AstraZeneca (ChAdOx1 nCoV-19; AZD1222) vaccines on May 12, 2021. From this time to July 11, three weeks after receiving the second dose of the COVID-19 vaccine, the data was collected.

The questionnaire included sections and the questions were multiple-choice. The first section covered demographic characteristics such as age, gender, blood type, and presence of underlying medical conditions (cancer, asthma, chronic respiratory diseases, autoimmune diseases, diabetes, cardiovascular disease, liver diseases, and kidney diseases). The second section included information about the previous infection of COVID-19 and their present symptoms. Items in the third and fourth sections focused on vaccination details like the vaccine type and the symptoms of the first and second doses of the COVID-19 vaccine. To protect the confidentiality of participants' information, all precautions were taken.

### Study ethics

Ethical approval was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences (ID: IR.SBMU.RETECH.REC.1400.357) and all participants expressed their verbal consent before the start of the study.

### Data management and statistical analysis

Data from the fully completed questionnaires were entered into IBM SPSS software version 23 for analysis. The characteristics of the study participants were summarized with descriptive statistics (mean, standard deviation, frequency, and percentage). A chi-squared test was performed for statistical analysis and to assess the associations between independent and dependent variables. The considered significance level was a p-value of less than 0.05.

## RESULTS

### Demographic information

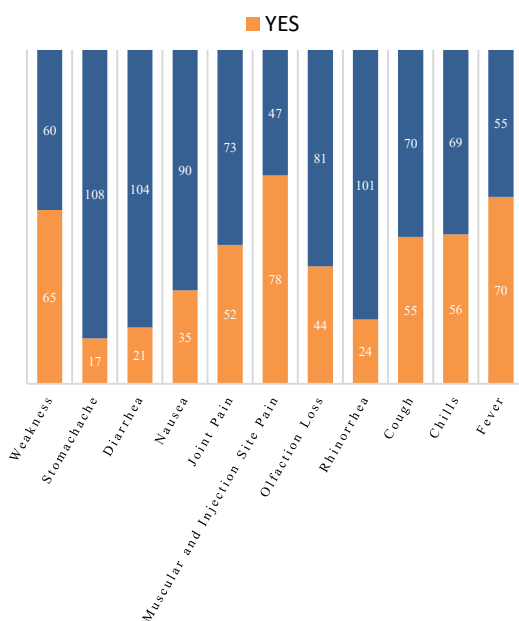
The survey included 420 staff of Shahid Beheshti University of Medical Sciences, of whom, 414 were quite vaccinated with two doses and were enrolled in this study. Participants who reported COVID-19 infection after the first dose and did not receive the second dose of the vaccine were excluded from the study (n=6). The demographic information of the participants is presented in Table 1.

Table 1. Demographic information of the participants

Variable	Number (n)	Percentage (%)	
<b>Gender</b>	Men	243	58.7
	Women	171	41.3
<b>Age</b> 41.30±11.208 (mean ± SD)	20-30	75	18.1
	31-40	122	29.5
	41-50	114	27.5
	51-60	93	22.5
	≥ 61	10	2.4
	A*	121	29.2
<b>Blood group type</b>	A-	21	5.1
	B*	72	17.4
	B-	8	1.9
	AB*	28	6.8
	AB-	1	0.2
	O*	148	35.7
	O-	15	3.6
	Yes	52	12.6
<b>Underlying medical situations</b>	No	362	87.4
	Yes	125	30.2
<b>COVID-19 past infection</b>	No	289	69.8
	0	289	69.8
	1	110	26.6
<b>Frequency of COVID-19 infection</b>	2	11	2.7
	≥ 3	4	1

The majority of participants were men (243, 58.7%). The median (SD) age was 41.30 (11.208) years and ranged from 20 to 73 years. It was found that 362 (87.4%) of participants were healthy, while 52 (12.6%) had a history of underlying medical situation, and among them, cardiovascular disease, especially hypertension and diabetes were the most common underlying diseases. The previous infection of COVID-19 before vaccination occurred in 125 (30.2%)

participants. Of these, 110 (26.6%) participants once, 11 (2.7%) twice, and 4 (1%), three, or more times reported the COVID-19 infection. On the other hand, most participants (289, 69.8%) were previously uninfected. Muscular and injection site pain (78, 62.4%) and fever (70, 56%) were the most common symptoms reported by participants with COVID-19 infection (Figure 1). The frequency of other symptoms is shown in Figure 1. All other symptoms not mentioned in the survey (difficulty breathing, tachycardia, whole-body aches, back pain, and ...) were less common.



**Figure 1.** COVID-19 symptoms in participants before vaccination. A total of 125 participants (30.2%) reported symptoms of COVID-19, with muscular pain, injection site pain, and fever being the most common

## Reported symptoms

### Association of symptoms with the vaccine type

Among the study participants, 77 (18.6%) were vaccinated with the Sputnik vaccine, 311 (75.1%) with Sinopharm, and only 26 (6.3%) were vaccinated with AstraZeneca. The reported symptoms by participants after the first and second doses of the COVID-19 vaccine are listed in Table 2. 196 (47.3%) individuals experienced at least one symptom following the first dose of the COVID-19 vaccine and 218 (52.7%) individuals did not report any symptoms. Symptoms reported by individuals who received the AstraZeneca (76.9%) vaccine were higher than

those who received the Sputnik (71.4%) and Sinopharm (38.9%) vaccines following the first dose of the vaccine.

For the second dose, 173 participants (41.8%) reported side effects and individuals who received the Sputnik (53.2%) vaccine showed more symptoms. In both doses, individuals who received the Sinopharm vaccine reported the fewest (~38%) symptoms. The difference between symptomatic recipients of vaccines was significant after the first ( $p = 0.001$ ) and second ( $p = 0.039$ ) doses of vaccination.

The most commonly reported symptoms for both doses of all three vaccines were fever, weakness, and muscular and injection site pain. The prevalence of these symptoms for the AstraZeneca recipients was fever (61.5%), muscular and injection site pain (46.2%), weakness (42.3%) after the first dose, and muscular and injection site pain (30.8%), fever (23.1%), and weakness (15.4%) after the second dose of vaccination, respectively. For the first dose of Sputnik recipients, 45.5% reported fever and muscular and injection site pain, followed by 33.8% weakness. For the second dose, 32.5% reported muscle and injection site pain, 31.2% experienced fever, and 27.3% reported weakness. The most-reported symptoms at both doses for Sinopharm recipients were weakness (first dose: 28.9%, second dose: 24.4%), muscular and injection site pain (first dose: 17.7%, second dose: 19.6%), and fever (first dose: 17%, second dose: 10%), respectively. Some unusual symptoms not mentioned in the questionnaire, such as low back pain, fast heartbeat, palpitations, dizziness, swollen lymph nodes, and skin rash. They were expressed by AstraZeneca and Sputnik vaccine recipients but they were only reported by four participants.

### Association of symptoms with gender

Regarding gender, female participants reported more side effects than male participants at both doses ( $p = 0.001$ ) (Table 3). The presence of symptoms after vaccination in women compared to men was after the first dose: 60.2% vs. 38.3% and after the second dose: 58.5% vs. 30%, respectively. The most common symptoms in first dose (women vs. men) were weakness (43.9% vs. 21.4%,  $p=0.001$ ), fever (32.7% vs. 19.8%,  $p=0.004$ ), and muscular

and injection site pain (32.7% vs. 18.9%,  $p=0.001$ ), while in second dose were weakness (36.3% vs. 16%,  $p=0.001$ ), muscular and injection site pain (32.2% vs. 16%,  $p = 0.001$ ), and fever (20.5% vs. 10.7%,  $p=0.006$ ). The frequency of all symptoms was reduced in the second dose than in the first dose in both men and women.

#### Association of symptoms with the blood type

We collected data on participants' blood groups to investigate whether blood types could affect the presence of the COVID-19 vaccine symptoms. As seen in Table S1,

the frequency of symptom presence was higher among AB+ (64.3%) and B- (50%) blood types after the first and second doses of COVID-19 vaccination. Although, we did not find a significant difference between blood groups in the presence of symptoms after the first ( $p = 0.6$ ) and second ( $p=0.23$ ) doses of vaccination.

There was also no significant difference in the prevalence of different symptoms except cough ( $p = 0001$ ) between blood groups. Detail of the prevalence of symptoms according to blood type is listed in Table S1.

Table 2. Frequency of symptoms according to the type of vaccine after first and second doses of COVID-19 vaccine

Symptoms	First dose (n and %)			P- value	Second dose (n and %)			P- value
	AstraZeneca	Sputnik	Sinopharm		AstraZeneca	Sputnik	Sinopharm	
Symptoms following vaccination	20 (76.9)	55 (71.4)	121 (38.9)	<b>0.001</b>	13 (50)	41 (53.2)	119 (38.3)	<b>0.039</b>
Fever	16 (61.5)	35 (45.5)	53 (17)	<b>0.001</b>	6 (23.1)	24 (31.2)	31 (10)	<b>0.001</b>
Chills	10 (38.5)	20 (26)	25 (8)	<b>0.001</b>	4 (15.4)	14 (18.2)	16 (5.1)	<b>0.001</b>
Cough	4 (15.4)	3 (3.9)	6 (1.9)	<b>0.001</b>	1 (3.8)	2 (2.6)	2 (0.6)	0.166
Rhinorrhea	3 (11.5)	1 (1.3)	4 (1.3)	<b>0.001</b>	0 (0)	1 (1.3)	0 (0)	0.112
Olfaction loss	0 (0)	2 (2.6)	1 (0.3)	0.098	0 (0)	1 (1.3)	0 (0)	0.112
Muscular and injection site pain	12 (46.2)	35 (45.5)	55 (17.7)	<b>0.001</b>	8 (30.8)	25 (32.5)	61 (19.6)	<b>0.033</b>
Joint pain	6 (23.1)	16 (20.8)	17 (5.5)	<b>0.001</b>	2 (7.7)	8 (10.4)	14 (4.5)	0.129
Nausea	4 (15.4)	6 (7.8)	7 (2.3)	<b>0.001</b>	2 (7.7)	2 (2.6)	5 (1.6)	0.119
Diarrhea	0 (0)	2 (2.6)	2 (0.6)	0.255	0 (0)	1 (1.3)	2 (0.6)	0.752
Stomachache	6 (23.1)	3 (3.9)	3 (1)	<b>0.001</b>	3 (11.5)	1 (1.3)	1 (0.3)	<b>0.001</b>
Weakness	11 (42.3)	26 (33.8)	90 (28.9)	0.295	4 (15.4)	21 (27.3)	76 (24.4)	0.475

Table 3. Frequency of symptoms according to the gender after first and second doses of COVID-19 vaccine

Symptoms	First dose (n and %)			P- value	Second dose (n and %)			P- value
	Man	Woman	Total		Man	Woman	Total	
Symptoms following vaccination	93 (38.3)	103 (60.2)	196	<b>0.001</b>	73 (30)	100 (58.5)	173	<b>0.001</b>
Fever	48 (19.8)	56 (32.7)	104	<b>0.004</b>	26 (10.7)	35 (20.5)	61	<b>0.006</b>
Chills	21 (8.6)	34 (19.9)	55	<b>0.001</b>	13 (5.3)	21 (12.3)	34	<b>0.11</b>
Cough	7 (2.9)	6 (3.5)	13	<b>0.718</b>	2 (0.8)	3 (1.8)	5	<b>0.398</b>
Rhinorrhea	5 (2.1)	3 (1.8)	8	<b>0.825</b>	0 (0)	1 (0.6)	1	<b>0.183</b>
Olfaction loss	2 (0.8)	1 (0.6)	3	<b>0.778</b>	1 (0.4)	0 (0)	1	<b>0.302</b>
Muscular and injection site pain	46 (18.9)	56 (32.7)	102	<b>0.001</b>	39 (16)	55 (32.2)	94	<b>0.001</b>
Joint pain	22 (9.1)	17 (9.9)	39	<b>0.761</b>	10 (4.1)	14 (8.2)	24	<b>0.081</b>
Nausea	5 (2.1)	12 (7)	17	<b>0.12</b>	3 (1.2)	6 (3.5)	9	<b>0.121</b>
Diarrhea	0 (0)	4 (2.3)	4	<b>0.008</b>	1 (0.4)	2 (1.2)	3	<b>0.374</b>
Stomachache	7 (2.9)	5 (2.9)	12	<b>0.979</b>	4 (1.6)	1 (0.6)	5	<b>0.308</b>
Weakness	52 (21.4)	75 (43.9)	127	<b>0.001</b>	39 (16)	62 (36.3)	101	<b>0.001</b>

### Association of symptoms with age

Table 4 compares the distribution of COVID-19 vaccine-related symptoms according to the participants' ages. We observed statistically significant differences between age groups after the first ( $p = 0.005$ ) and second ( $p=0.001$ ) doses of the vaccine. The incidence of symptoms was more common in the youngest age group (3rd decade or 20-30 years) at each dose. The percentage of symptoms was 61.3% (20-30 years), 42.6% (31-40 years), 42.1% (41-50 years), 52.7% (51-60 years), 10% (61 years and older) after the first dose and 58.7% (20-30 years), 45.1% (31-40 years), 31.6% (41-50 years), 39.8% (51-60 years), and 10% (61 years and older) after the second dose. Besides, the most prevalent symptoms of the first and second doses were weakness, fever, and muscular and injection site pain. All of these adverse reactions at each dose were more common among the 20-30 years age group participants.

The distribution of reported symptoms for each vaccine by age of participants is shown in Tables S2, S3, and S4 and Figures S1, S2, and S3. Regarding the symptoms reported by Sputnik recipients, this study shows a significant difference between age groups after first dose ( $p=0.013$ ). However, no significant differences were seen between the age groups of AstraZeneca and Sinopharm vaccines recipients.

### Association of vaccination symptoms with the past infection

Of the 125 participants who reported a past history of COVID-19 infection, 52% and 44.8% suffered from the vaccine adverse reactions after first and second doses,

respectively. However, this was not significantly different to those who had never been infected (Table 5). Fever, chills, joint pain, and muscular and injection site pain symptoms were more reported by individuals who had been previously infected with the COVID-19 in comparison to not infected individuals.

### Association of vaccination symptoms with the underlying medical situations

The results regarding the medical history of the study population showed that participants with the underlying medical situation had more symptoms than healthy participants; although, this difference was not significant ( $p=0.125$  for the first dose and  $p = 0.406$  for the second dose, Table 6). Weakness, muscular and injection site pain, and fever were more frequent signs associated with participants with the underlying medical situation after the first and second doses of vaccination. However, stomachache, olfaction loss, and rhinorrhea were noted only in healthy participants, as presented in Table 6.

### Association of vaccination symptoms with the COVID-19 reinfection

Out of the 125 infections and reinfections (1, 2, 3, and more times), 65 participants reported symptoms following the first dose of vaccination, and intriguingly, no participants reported olfaction loss (Table 7). There was no significant association between infections and reinfections in individuals who had not previously been infected with COVID-19 regarding the presence of symptoms after the first ( $p=0.221$ ) and second ( $p=0.325$ ) doses.

Table 4. Frequency of symptoms according to the age groups after the first and second doses of COVID-19 vaccine

Symptoms	First dose (n and %)					P- value	Second dose (n and %)					P- value
	20-30	31-40	41-50	51-60	61≤		20-30	31-40	41-50	51-60	61≤	
Symptoms following vaccination	46 (61.3)	52 (42.6)	48 (42.1)	49 (52.7)	1 (10)	<b>0.005</b>	44 (58.7)	55 (45.1)	36 (31.6)	37 (39.8)	1 (10)	<b>0.001</b>
Fever	29 (38.7)	23 (18.9)	22 (19.3)	29 (31.2)	1 (10)	<b>0.005</b>	23 (30.7)	15 (12.3)	7 (6.1)	16 (17.2)	0 (0)	<b>0.001</b>
Chills	23 (30.7)	12 (9.8)	10 (8.8)	10 (10.8)	0 (0)	<b>0.001</b>	17 (22.7)	6 (4.9)	3 (2.6)	8 (8.6)	0 (0)	<b>0.001</b>
Cough	3 (4)	2 (1.6)	3 (2.6)	5 (5.4)	0 (0)	0.552	2 (2.7)	2 (1.6)	0 (0)	1 (1.1)	0 (0)	0.548
Rhinorrhea	2 (2.7)	0 (0)	4 (3.5)	2 (2.2)	0 (0)	0.363	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0.339
Olfaction loss	1 (1.3)	1 (0.8)	0 (0)	1 (10)	0 (0)	0.833	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.663
Muscular and injection site pain	26 (34.7)	28 (23)	24 (21.1)	23 (24.7)	1 (10)	0.185	25 (33.3)	35 (28.7)	15 (13.2)	18 (19.4)	1 (10)	<b>0.005</b>
Joint pain	15 (20)	4 (3.3)	10 (8.8)	9 (9.7)	1 (10)	<b>0.004</b>	3 (4)	10 (8.2)	6 (5.3)	5 (5.4)	0 (0)	0.656
Nausea	5 (6.7)	5 (4.1)	4 (3.5)	3 (3.2)	0 (0)	0.743	3 (4)	3 (2.5)	0 (0)	3 (3.2)	0 (0)	0.347
Diarrhea	0 (0)	2 (1.6)	0 (0)	2 (2.2)	0 (0)	0.422	0 (0)	1 (0.8)	1 (0.9)	1 (1.1)	0 (0)	0.934
Stomachache	4 (5.3)	1 (0.8)	3 (2.6)	4 (4.3)	0 (0)	0.351	2 (2.7)	0 (0)	1 (0.9)	2 (2.2)	0 (0)	0.441
Weakness	29 (38.7)	33 (27)	29 (25.4)	35 (37.6)	1 (10)	0.072	25 (33.3)	34 (27.9)	23 (20.2)	18 (19.4)	1 (10)	0.109

Table 5. Frequency of symptoms after the first and second doses of COVID-19 vaccine according to the previous infection of COVID-19

Symptoms	First dose (n and %)		P- value	Second dose (n and %)		P- value
	Infected	Not infected		Infected	Not infected	
Symptoms following vaccination	65 (52)	131 (45.3)	0.127	56 (44.8)	117 (40.5)	0.239
Fever	36 (28.8)	68 (23.5)	0.156	20 (16)	41 (14.2)	0.367
Chills	24 (19.2)	31 (10.7)	<b>0.017</b>	14 (11.2)	20 (6.9)	0.105
Cough	3 (2.4)	10 (3.5)	0.412	2 (1.6)	3 (1)	0.476
Rhinorrhea	1 (0.8)	7 (2.4)	0.249	1 (0.8)	0 (0)	0.302
Olfaction loss	0 (0)	3 (1)	0.339	1 (0.8)	0 (0)	0.302
Muscular and injection site pain	36 (28.8)	66 (22.8)	0.122	32 (25.6)	62 (21.5)	0.212
Joint pain	17 (13.6)	22 (7.6)	<b>0.044</b>	13 (10.4)	11 (3.8)	<b>0.01</b>
Nausea	4 (3.2)	13 (4.5)	0.378	4 (3.2)	5 (1.7)	0.273
Diarrhea	1 (0.8)	3 (1)	0.648	0 (0)	3 (1)	0.339
Stomachache	3 (2.4)	9 (3.1)	0.485	3 (2.4)	2 (0.7)	0.164
Weakness	38 (30.4)	89 (30.8)	0.517	31 (24.8)	70 (24.2)	0.496

Table 6. Frequency of symptoms according to presence of the underlying medical situations after the first and second doses of COVID-19 vaccine

Symptoms	First dose (n and %)		P- value	Second dose (n and %)		P- value
	Presence	Absent		Presence	Absent	
Symptoms following vaccination	28 (53.8)	168 (46.4)	0.125	23 (44.2)	150 (41.4)	0.406
Fever	14 (26.9)	90 (24.9)	0.432	8 (15.4)	53 (14.6)	0.512
Chills	5 (9.6)	50 (13.8)	0.278	5 (9.6)	29 (8)	0.428
Cough	2 (3.8)	11 (3)	0.502	0 (0)	5 (1.4)	0.509
Rhinorrhea	0 (0)	8 (2.2)	0.338	0 (0)	1 (0.3)	0.874
Olfaction loss	0 (0)	3 (0.8)	0.668	0 (0)	1 (0.3)	0.874
Muscular and injection site pain	15 (28.8)	87 (24)	0.276	10 (19.2)	84 (23.2)	0.329
Joint pain	6 (11.5)	33 (9.1)	0.362	5 (9.6)	19 (5.2)	0.170
Nausea	1 (1.9)	16 (4.4)	0.346	1 (1.9)	8 (2.2)	0.685
Diarrhea	2 (3.8)	2 (0.6)	0.079	0 (0)	3 (0.8)	0.668
Stomachache	0 (0)	12 (3.3)	0.195	0 (0)	5 (1.4)	0.509
Weakness	19 (36.5)	108 (29.8)	0.205	13 (25)	88 (24.3)	0.974

Table 7. Frequency of symptoms after the first and second dose of COVID-19 vaccine according to the number of reinfections with COVID-19

Symptoms	First dose (n and %)				P- value	Second dose (n and %)				P- value
	0	1	2	3 ≤		0	1	2	3 ≤	
Symptoms following vaccination	131 (45.3)	59 (53.6)	3 (27.3)	3 (75)	0.221	117 (40.5)	50 (45.5)	3 (27.3)	3 (75)	0.325
Fever	68 (23.5)	33 (30)	2 (18.2)	1 (25)	0.559	41 (14.2)	18 (16.4)	2 (18.2)	0 (0)	0.778
Chills	31 (10.7)	22 (20)	1 (9.1)	1 (25)	0.086	20 (6.9)	12 (10.9)	0 (0)	2 (50)	<b>0.008</b>
Cough	10 (3.5)	3 (2.7)	0 (0)	0 (0)	0.886	3 (1)	2 (1.8)	0 (0)	0 (0)	0.897
Rhinorrhea	7 (2.4)	1 (0.9)	0 (0)	0 (0)	0.736	0 (0)	1 (0.9)	0 (0)	0 (0)	0.428
Olfaction loss	3 (1)	0 (0)	0 (0)	0 (0)	0.727	0 (0)	1 (0.9)	0 (0)	0 (0)	0.428
Muscular and injection site pain	66 (22.8)	32 (29.1)	2 (18.2)	2 (50)	0.346	62 (21.5)	29 (26.4)	2 (18.2)	1 (25)	0.744
Joint pain	22 (7.6)	14 (12.7)	2 (18.2)	1 (25)	0.20	11 (3.8)	11 (10)	2 (18.2)	0 (0)	<b>0.029</b>
Nausea	13 (4.5)	3 (2.7)	1 (9.1)	0 (0)	0.68	5 (1.7)	3 (2.7)	1 (9.1)	0 (0)	0.393
Diarrhea	3 (1)	1 (0.9)	0 (0)	0 (0)	0.983	3 (1)	0 (0)	0 (0)	0 (0)	0.727
Stomachache	9 (3.1)	2 (1.8)	1 (9.1)	0 (0)	0.547	2 (0.7)	2 (1.8)	1 (9.1)	0 (0)	<b>0.08</b>
Weakness	89 (30.8)	36 (32.7)	1 (9.1)	1 (25)	0.442	70 (24.2)	28 (25.5)	1 (9.1)	2 (50)	0.409

## DISCUSSION

The symptoms of the investigated vaccines in this study were evaluated separately after the first and second doses. There were significant differences between the frequency of reported symptoms following receiving the first ( $p = 0.001$ ) and second ( $p = 0.039$ ) doses of each vaccine (Table 2). Out of 414 participants, most study respondents did not report any symptoms, and less than half reported symptoms after vaccination with the most occurrence post-first dose (196, 47.3%) compared to the second dose (173, 41.8%). This result was similar to a previous study in Iran on the Sputnik vaccine (12). In several literatures, a higher rate of side effects was seen in second-dose recipients contrary to our findings (20–22). This difference between these findings is due to the immune system response and immunogenicity of vaccines. Symptoms and signs are the body's natural reflexes to the entry of an external factor, which are interceded by the innate immune system. Cytokines are released upon detection of vaccine molecules by the body's neutrophils or macrophages and stimulate immune responses (23,24).

The most frequently reported symptoms associated with these three vaccines were fever, weakness, and muscular and injection site pain (Table 2). After the first dose, AstraZeneca was identified as the most relevant vaccine with the highest prevalence of symptoms and this is consistent with other studies (23,25). Our results showed that the prevalence of symptoms for AstraZeneca recipients (76.9%) is less than the side effects reported (88%) in the phase 2/3 clinical trial of the AZD1222 vaccine after the first injection (16). Among the reported symptoms experienced by recipients of the AstraZeneca vaccine, gastrointestinal symptoms were particularly notable. Participants who received the AstraZeneca reported significantly higher frequencies of nausea (15.4%) and stomachache (23.1%) than Sinopharm and Sputnik recipients. The explanation for this effect on the gastrointestinal tract may be attributed to the nature and mechanism of the vaccine (S glycoprotein).

In our study, individuals who received the Sputnik (53.2%) vaccine showed more adverse reactions after the second dose compared to the other two vaccines ( $p = 0.039$ , Table 2). Evidence from the Gam-COVID-Vac vaccine analysis in Phase 3, as well as the statements of the Centers for Disease Control and Prevention (CDC), suggests that the most common side effects for the Sputnik vaccine were fever, chills, muscle pain, weakness, and injection site pain, which are similar to our findings after the first and second doses (19,26,27). It was reported that after the second dose of the Sputnik vaccine, more adverse symptoms occurred compared to the first dose (28). But, in our study, side effects decreased from 71.4% after the first dose to 53.2% after the second dose. It's noteworthy that symptoms like rhinorrhea and loss of olfaction were reported after the second dose only by Sputnik recipients. However, it seems that these results need to be further confirmed by large-scale participants.

In addition to the above-listed findings, our result showed that the most asymptomatic individuals in both doses were related to the Sinopharm vaccine recipients (almost 61%). In line with other studies, we found that individuals who received the Sinopharm vaccine experienced a minimal rate of symptoms, indicating proper safety outlines for inactivated vaccines (20,22,29). Nevertheless, to create an adequate immune response, a booster program (repeated dose) is needed (30). Similar to AstraZeneca and Sputnik vaccines, the frequency of all symptoms after the second injection in Sinopharm recipients was lower than the post-first dose. Except for muscular and injection site pain, which was more frequent post-second dose (19.6% vs. 17.7%). These results were consistent with the side effects reported in the study by Xia et al., in phase I and II interim for the Sinopharm vaccine and were associated with no serious adverse reactions (31).

In the present study, the relationship between several demographic factors and COVID-19 vaccine side effects was investigated including gender, age, blood type, underlying medical situation, past infection, and

reinfection with COVID-19. According to the gender of the individuals, the male gender (243, 58.7%) participated more than the female gender (171, 41.3%) but the incidence of symptoms in women was significantly higher than in men in both doses ( $p = 0.001$ ) (Table 3), as it's also published in the literature (20,21,29,32,33). Women had symptoms more often than men 1.5 times after the first dose (60.2% vs. 38.3%) of vaccination and almost 2 times after the second dose (58.5% vs. 30%). This observation can be interpreted based on the stronger immune system of women than men, which gives the possibility of more symptoms.

The obtained data indicated age was significantly correlated with reported vaccination symptoms, with a higher frequency among the youngest group (20-30 years) than other groups at each dose (Table 4). This is in line with the published findings on the side effects of the Pfizer, AstraZeneca, and Sputnik vaccine (32-34). The incidence of symptoms in the youngest age group was 46, 61.3% after the first dose, and 44, 58.7% after the second dose. While in the oldest group (61 years and older) only 10% (1 person) experienced any symptoms at each dose. This finding may be due to the small number of older participants. However, in general, for the same reason mentioned for women, young people develop more frequent symptoms due to a stronger and more effective immune system. Vaccine reactogenicity is reduced with increasing age because it is associated with transient elevation of inflammatory cytokines, although it is not reflected as a valid signal of a favorable immune response (35).

Furthermore, reported symptoms based on the age of Sputnik recipients showed a significantly higher prevalence in the 20-30 years age group after the first injection ( $p = 0.013$ ), while post-second dose 51-60 years age group reported the most symptoms, although this was not significant ( $p = 0.225$ , Table S2). Additionally, there were no significant differences in symptom prevalence between the age groups of AstraZeneca and Sinopharm vaccine recipients (Tables S3 and S4).

It was noticed that there was no significant connection between blood types, underlying medical situations, past infection and reinfection with COVID-19, and the appearance of signs and symptoms. As a result, the appearance of symptoms does not appear to be affected by these issues. The precise reason for these findings is currently unknown, and further studies with larger sample sizes are needed to confirm these correlations. In participants with past COVID-19 infection, the prevalence of post-vaccine symptoms was approximately the same as the prevalence of COVID-19 symptoms and all COVID-19 symptoms were less common after the first and second doses of the vaccine. Moreover, similar to the results of previous studies, it was shown that symptoms were more common in individuals with a previous SARS-CoV-2 infection than in individuals without a previous infection (12,32,36-38).

## CONCLUSION

To the best of our knowledge, this survey was the first study that evaluated the symptoms and vaccine-associated factors in Iran. To sum up, the AstraZeneca, Sputnik, and Sinopharm vaccines were found to be safe given the results of the present study. Individuals who received the Sinopharm vaccine showed the lowest appearance of symptoms. Keeping with published reports of manufacturing companies, we found that fever, muscular and injection site pain, and weakness were the most common symptoms, and were more reported after the first dose than post second dose. Additionally, younger individuals, women, and AstraZeneca recipients had more adverse reactions. Our results help to alleviate concerns about adverse reactions associated with the COVID-19 vaccine and can be used to inform individuals about the potential for side effects based on gender, age, blood type, type of vaccine, underlying medical situations, and past infection and reinfection with COVID-19. In this study, there were limitations due to this issue that the analysis only relied on filled questionnaires, without our impact on participants, and psychological factors may have affected

participants' perceptions. It is recommended that further studies with larger sample sizes be performed to better understand side effects in vaccine recipients as well as to evaluate long-term side effects.

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### Conflict of interest

The authors declare no conflict of interest related to this paper.

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**SUPPLEMENTARY**

**Table S1.** Frequency of symptoms according to the blood types after COVID-19 vaccination

Symptoms	1st dose (n and %)								P- value	2nd dose (n and %)								P- value
	A+	A-	B+	B-	AB+	AB-	O+	O-		A+	A-	B+	B-	AB+	AB-	O+	O-	
Symptoms following vaccination	54 (44.6)	12 (57.1)	33 (45.8)	4 (50)	18 (64.3)	0 (0)	68 (45.9)	7 (46.7)	0.6	45 (37.2)	8 (38.1)	27 (37.5)	4 (50)	13 (46.4)	0 (0)	73 (49.3)	3 (20)	0.23
Fever	36 (29.8)	7 (33.3)	13 (18.1)	2 (25)	9 (32.1)	0 (0)	35 (23.6)	2 (13.3)	0.495	12 (9.9)	4 (19.0)	12 (16.7)	1 (12.5)	3 (10.7)	0 (0)	27 (18.2)	2 (13.3)	0.685
Chills	19 (15.7)	3 (14.3)	5 (6.9)	1 (12.5)	2 (7.1)	0 (0)	25 (16.9)	0 (0)	0.316	6 (5.0)	2 (9.5)	6 (8.3)	0 (0)	1 (3.6)	0 (0)	19 (12.8)	0 (0)	0.260
Cough	3 (2.5)	4 (19)	0 (0)	1 (12.5)	2 (7.1)	0 (0)	3 (2)	0 (0)	<b>0.001</b>	3 (2.5)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0.572
Rhinorrhea	2 (1.7)	1 (4.8)	0 (0)	1 (12.5)	1 (3.6)	0 (0)	3 (2)	0 (0)	0.352	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.932
Olfaction loss	2 (1.7)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)	0 (0)	0.479	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.932
Muscular and injection site pain	31 (25.6)	3 (14.3)	19 (26.4)	4 (50)	8 (28.6)	0 (0)	35 (23.6)	2 (13.3)	0.559	27 (22.3)	5 (23.8)	15 (20.8)	3 (37.5)	5 (17.9)	0 (0)	38 (25.7)	1 (6.7)	0.687
Joint pain	12 (9.9)	2 (9.5)	7 (9.7)	2 (25)	3 (10.7)	0 (0)	13 (8.8)	0 (0)	0.767	9 (7.4)	1 (4.8)	4 (5.6)	0 (0)	1 (3.6)	0 (0)	9 (6.1)	0 (0)	0.935
Nausea	6 (5)	1 (4.8)	0 (0)	1 (12.5)	2 (7.1)	0 (0)	7 (4.7)	0 (0)	0.511	2 (1.7)	1 (4.8)	2 (2.8)	0 (0)	0 (0)	0 (0)	4 (2.7)	0 (0)	0.942
Diarrhea	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	2 (1.4)	0 (0)	0.848	0 (0)	1 (4.8)	0 (0)	0 (0)	1 (3.6)	0 (0)	1 (0.7)	0 (0)	0.219
Stomachache	4 (3.3)	2 (9.5)	2 (2.8)	0 (0)	2 (7.1)	0 (0)	2 (1.4)	0 (0)	0.417	1 (0.8)	2 (9.5)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.4)	0 (0)	0.54
Weakness	37 (30.6)	8 (38.1)	18 (25)	3 (37.5)	12 (42.9)	0 (0)	46 (31.1)	3 (20)	0.657	28 (23.1)	2 (9.5)	17 (23.6)	2 (25)	10 (35.7)	0 (0)	41 (27.7)	1 (6.7)	0.303

**Table S2.** Frequency of symptoms according to the age groups after Sputnik vaccination

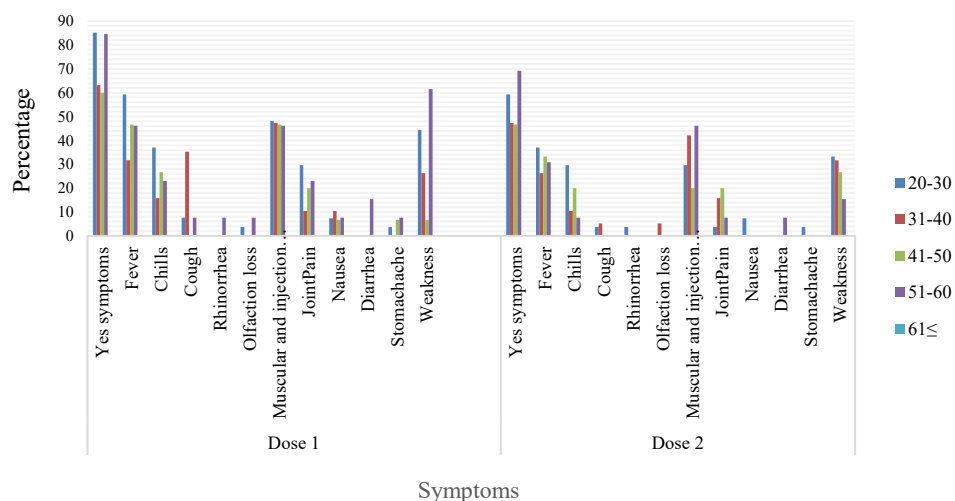
Symptoms	1st dose (n and %)					P- value	2nd dose (n and %)					P- value
	20-30	31-40	41-50	51-60	61≤		20-30	31-40	41-50	51-60	61≤	
Symptoms following vaccination	23 (85.2)	12 (63.2)	9 (60)	11 (84.6)	0 (0)	<b>0.013</b>	16 (59.3)	9 (47.4)	7 (46.7)	9 (69.2)	0 (0)	0.225
Fever	16 (59.3)	6 (31.6)	7 (46.7)	6 (46.2)	0 (0)	0.195	10 (37)	5 (26.3)	5 (33.3)	4 (30.8)	0 (0)	0.729
Chills	10 (37)	3 (15.8)	4 (26.7)	3 (23.1)	0 (0)	0.426	8 (29.6)	2 (10.5)	3 (20)	1 (7.7)	0 (0)	0.310
Cough	1 (7.7)	1 (35.3)	0 (0)	1 (7.7)	0 (0)	0.875	1 (3.7)	1 (5.3)	0 (0)	0 (0)	0 (0)	0.828
Rhinorrhea	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.289	1 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	0.759
Olfaction loss	1 (3.7)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.653	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	0.542
Muscular and injection site pain	13 (48.1)	9 (47.4)	7 (46.7)	6 (46.2)	0 (0)	0.624	8 (29.6)	8 (42.1)	3 (20)	6 (46.2)	0 (0)	0.340
Joint pain	8 (29.6)	2 (10.5)	3 (20)	3 (23.1)	0 (0)	0.504	1 (3.7)	3 (15.8)	3 (20)	1 (7.7)	0 (0)	0.430
Nausea	2 (7.4)	2 (10.5)	1 (6.7)	1 (7.7)	0 (0)	0.975	2 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)	0.433
Diarrhea	0 (0)	0 (0)	0 (0)	2 (15.4)	0 (0)	<b>0.039</b>	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.289
Stomachache	1 (3.7)	0 (0)	1 (6.7)	1 (7.7)	0 (0)	0.790	1 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	0.759
Weakness	12 (44.4)	5 (26.3)	1 (6.7)	8 (61.5)	0 (0)	<b>0.012</b>	9 (33.3)	6 (31.6)	4 (26.7)	2 (15.4)	0 (0)	0.604

**Table S3.** Frequency of symptoms according to the age groups after AstraZeneca vaccination

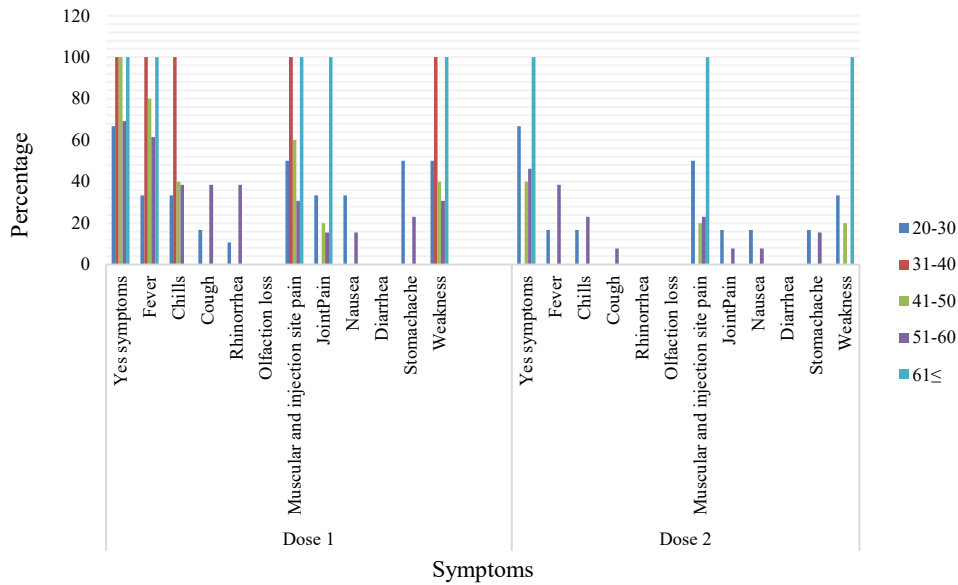
Symptoms	1st dose (n and %)					P- value	2nd dose (n and %)					P- value
	20-30	31-40	41-50	51-60	61≤		20-30	31-40	41-50	51-60	61≤	
Symptoms following vaccination	4 (66.7)	1 (100)	5 (100)	9 (69.2)	1 (100)	0.577	4 (66.7)	0 (0)	2 (40)	6 (46.2)	1 (100)	0.359
Fever	2 (33.3)	1 (100)	4 (80)	8 (61.5)	1 (100)	0.408	1 (16.7)	0 (0)	0 (0)	5 (38.5)	0 (0)	0.410
Chills	2 (33.3)	1 (100)	2 (40)	5 (38.5)	0 (0)	0.881	1 (16.7)	0 (0)	0 (0)	3 (23.1)	0 (0)	0.759
Cough	1 (16.7)	0 (0)	0 (0)	5 (38.5)	0 (0)	0.759	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.904
Rhinorrhea	1 (10.7)	0 (0)	0 (0)	5 (38.5)	0 (0)	0.917	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Olfaction loss	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Muscular and injection site pain	3 (50)	1 (100)	3 (60)	4 (30.8)	1 (100)	0.407	3 (50)	0 (0)	1 (20)	3 (23.1)	1 (100)	0.358
Joint pain	2 (33.3)	0 (0)	1 (20)	2 (15.41)	1 (100)	0.349	1 (16.7)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.867
Nausea	2 (33.3)	0 (0)	0 (0)	2 (15.4)	0 (0)	0.599	1 (16.7)	0 (0)	0 (0)	1 (7.7)	0 (0)	0.867
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Stomachache	3 (50)	0 (0)	0 (0)	3 (23.1)	0 (0)	0.337	1 (16.7)	0 (0)	0 (0)	2 (15.4)	0 (0)	0.869
Weakness	3 (50)	1 (100)	2 (40)	4 (30.8)	1 (100)	0.464	2 (33.3)	0 (0)	1 (20)	0 (0)	1 (100)	0.047

**Table S4.** Frequency of symptoms according to the age groups after 1st and 2nd doses Sinopharm vaccination

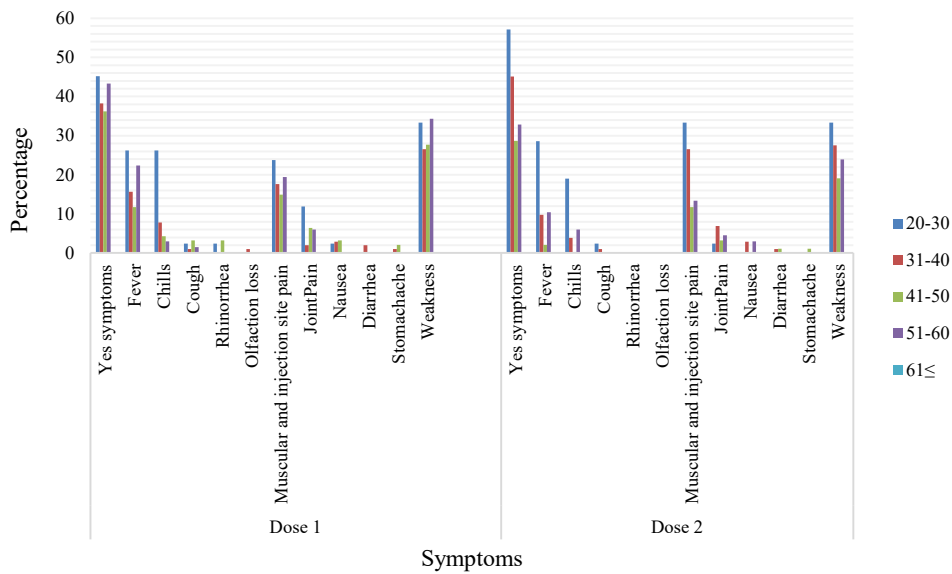
Symptoms	1st dose (n and %)					P- value	2nd dose (n and %)					P- value
	20-30	31-40	41-50	51-60	61≤		20-30	31-40	41-50	51-60	61≤	
Symptoms following vaccination	19 (45.2)	39 (38.2)	34 (36.2)	29 (43.3)	0 (0)	0.25	24 (57.1)	46 (45.1)	27 (28.7)	22 (32.8)	0 (0)	0.121
Fever	11 (26.2)	16 (15.7)	11 (11.7)	15 (22.4)	0 (0)	0.131	12 (28.6)	10 (9.8)	2 (2.1)	7 (10.4)	0 (0)	<b>0.001</b>
Chills	11 (26.2)	8 (7.8)	4 (4.3)	2 (3)	0 (0)	<b>0.001</b>	8 (19)	4 (3.9)	0 (0)	4 (6)	0 (0)	<b>0.001</b>
Cough	1 (2.4)	1 (1)	3 (3.2)	1 (1.5)	0 (0)	0.825	1 (2.4)	1 (1)	0 (0)	0 (0)	0 (0)	0.517
Rhinorrhea	1 (2.4)	0 (0)	3 (3.2)	0 (0)	0 (0)	0.252	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.311
Olfaction loss	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0.726	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.311
Muscular and injection site pain	10 (23.8)	18 (17.6)	14 (14.9)	13 (19.4)	0 (0)	0.556	14 (33.3)	27 (26.5)	11 (11.7)	9 (13.4)	0 (0)	<b>0.005</b>
Joint pain	5 (11.9)	2 (2)	6 (6.4)	4 (6)	0 (0)	0.176	1 (2.4)	7 (6.9)	3 (3.2)	3 (4.5)	0 (0)	0.659
Nausea	1 (2.4)	3 (2.9)	3 (3.2)	0 (0)	0 (0)	0.684	0 (0)	3 (2.9)	0 (0)	2 (3)	0 (0)	0.371
Diarrhea	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0.389	0 (0)	1 (1)	1 (1.1)	0 (0)	0 (0)	0.880
Stomachache	0 (0)	1 (1)	2 (2.1)	0 (0)	0 (0)	0.653	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0.678
Weakness	14 (33.3)	27 (26.5)	26 (27.7)	23 (34.3)	0 (0)	0.385	14 (33.3)	28 (27.5)	18 (19.1)	16 (23.9)	0 (0)	0.225



**Figure S1.** The distribution of reported symptoms for the Sputnik vaccine by age of participants  
 There was a significant difference between age groups after the first dose of the Sputnik vaccine ( $p = 0.013$ ).



**Figure S2.** The distribution of reported symptoms for the AstraZeneca vaccine by age of participants  
There was no significant difference between age groups post-AstraZeneca vaccine ( $p > 0.05$ ).



**Figure S3.** The distribution of reported symptoms for the Sinopharm vaccine by age of participants  
There was no significant difference between age groups post- Sinopharm vaccine ( $p > 0.05$ ).