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Prevalence of COVID-19 vaccines (*Sputnik V*, *AZD-1222*, and *Covaxin*) side effects among healthcare workers in Birjand city, Iran

Hamed Zare [a], Hadis Rezapour [b], Sara Mahmoodzadeh [b], Mohammad Fereidouni [a,b,*]

[a] Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran
[b] Department of Immunology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

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ABSTRACT

Background: The prevalence of vaccine side effects plays an important role in public perception about vaccination programs. This study was designed to investigate the side effects of the first dose of COVID-19 vaccine; Sputnik-V, AZD-1222, and Covaxin.

Methods: A study was performed to evaluate the side effects of these vaccine among 503 health care workers in Birjand (Iran). Our study used the questionnaire consisted of 4 main categories including demographic data, previous COVID-19 infection, vaccine information, and local and systemic side effects of vaccines.

Results: 81.9%, 88.8%, and 92.9% of people who have been vaccinated with Sputnik-V, AZD1222, and Covaxin vaccines, respectively, have reported at least one side effect. The prevalence of systemic side effects in AZD-1222 vaccine was higher than Sputnik V and Covaxin vaccines. Injection site pain (62.1%), fatigue (43.9%), muscle pain (42.5%), and fever (40.6%) were the most common side effects in all three vaccines. Side effect frequency was higher in the female group (90.6%) than the male group (79.5%). The prevalence of side effects with Sputnik V and Covaxin vaccines was reduced in the elderly. Moreover, the prevalence of side effects was higher in the case of convalescent patients (92.4 %) than in the group with no history of infection. The prevalence of side effects was higher in person with a BMI above 25 in the AZD-1222 and Covaxin vaccines.

Conclusions: The most common side effects of the Sputnik-V, AZD-1222, and Covaxin vaccine among Birjand (Iran) healthcare workers were injection site pain, muscle pain, fatigue, fever, and headache. Age and gender were the most important variables in the prevalence of vaccine side effects.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified as the causative agent of COVID-19 in December 2019 [1–3]. SARS-CoV-2 is capable of spreading rapidly among humans and at present (September 2021) had infected over 224 million people across worldwide and has been responsible for over 4.6 million deaths due to COVID-19 [4]. There is a broad clinical spectrum of SARS-CoV-2 infection ranging from asymptomatic and mild cases to severe manifestations with increased risk of death [5]. In addition, a significant share of convalescent, particularly those who survived a more severe form of COVID-19, suffer from long-term consequences known as a post-COVID-19 syndrome [6]. The most common of these problems are: muscle pains, fatigue, cough and shortness of breath, joint aches, chest pain, and headache [6,7]. In addition to the long-term COVID-19 syndrome, post-COVID-19 syndrome can be considered in three other categories: post-viral fatigue, permanent organ injury, and PICS (post-intensive care syndrome) [6]. Moreover, Cardiovascular problems, other infections (viral, bacterial, and fungal), side effects of medications, and psychological problems are other issues that occur in convalescent patients [6–8]. Consequently, the COVID-19 pandemic has put significant strain on health-care systems and posed major challenges to the global economy [9]. Therefore, effective COVID-19 vaccines are required to decrease the massive burden of death due to SARS-CoV-2 infection [10]. After Turkey, Iran was the second country in the Middle East to be affected by COVID-19 [11].

At present (September 2021) and according to the information of the World Health Organization, the total number of COVID-19 infections amounted to 5,129,407 with 110,674 fatal cases in Iran. Moreover, 29,152,527 doses of vaccine have been injected so far (September 2021), and the distribution of the vaccine in the study area is similar to other parts of Iran. By September 2021, about 7.5 million person (10%

* Corresponding author at: Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran.
E-mail addresses: hamed.zare1363@gmail.com (H. Zare), Dr.m.fereidouni@gmail.com (M. Fereidouni).

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of the total population) had received both doses of the vaccine and about 15 million (20% of the total population) had received one dose of the vaccine. The rate of vaccine acceptance in Birjand is very high and most people go to the designated centers to receive the vaccine according to the prioritization. Moreover, with the low population density in the eastern regions of Iran, a high percentage of people in this region have been vaccinated against coronavirus.

Sputnik V (Gamaleya Research Institute) and AZD-1222 (Oxford/AstraZeneca) vaccines were available at the time of this study (February to March 2021). However, a limited number of Covaxin or BBV152 (Bharat Biotech) vaccine were also injected.

Sputnik V and AZD-1222 are both non-replicating adenoviral vector vaccines. The first use of viral vectors began in 1972 with the production of recombinant DNA of the SV40 virus. After that, the vaccinia virus was presented in 1982 as a transient gene expression vector [12,13]. Sputnik V and AZD-1222 are based on adenoviruses that have been deactivated by eliminating the E1A and E1B gene region. The spike antigen cDNA is inserted into their genome, and these recombinant viruses carries a sequence encoding spike protein enabling its expression in the infected cell. Both vaccines contain adenoviruses that infect cells and provide the genetic code of the spike protein to infected cells, leading to the expression of spike protein by infected cells. Then, infected cells do present spike on the surface to T-cells [14]. These vaccines (Sputnik V and AZD-1222) increase both cellular and humoral immunity and triggers strong immune responses [14]. Clinical trial results demonstrated that Sputnik V and AZD-1222 have considerable safety and immunogenicity and induces antibody production against spike protein [2,15].

Inactivated vaccines such as Covaxin are one of the oldest and fastest alternatives to antiviral vaccines, first developed in 1940 using embryonic eggs to produce influenza vaccines [16]. Nevertheless, this approach is not suitable for all viruses, and may lead to serious safety concerns, if the molecular and structural understanding of the antigen is incomplete [17]. Firstly, virus particles are traditionally obtained from virus-infected cells, then using a variety of physical and chemical procedures, including the use of β-propiolactone and UV, coronaviruses are deactivated [14,16]. The polio vaccine, as a classic example of a whole killed virus vaccine, has been in the global vaccination program for many years [18]. Considering that the immunity produced by inactivated vaccines is less than that of live vaccines; they should be injected with adjuvants (Alum adjuvant) to achieve an effective immune response [19]. However, a main problem with these vaccines is the choice of virus type [20].

Moreover, one of the main concerns with inactivated vaccines is a change of proteins on the virus surface. For example, Liu and colleagues demonstrated that isolated SARS-CoV-2 viruses show most of the spikes in the postfusion conformation after treatment with the inactivating agent beta-propiolactone, and transformation from prefusion conformation to postfusion can lead to antibody-dependent enhancement as once seen with RSV vaccines [17]. Covaxin (BBV-152) is produced by means of Bharat Biotech, India [18]. Phase 3 clinical trial results confirmed that this vaccine is effective and safe and Covaxin vaccine can stimulate both cellular and humoral immunity [21].

Presently, most vaccines that are injected in the study area are: BBIBP-CorV (Sinopharm, China), AZD-1222, Sputnik V, and COVIran Barekat (Shafa Pharmed Pars, Iran).

Unlike conventional vaccine production methods, which often lasted for years, COVID-19 vaccine production progressed rapidly [2]. This is due to the accelerated development of all aspects of the COVID-19 vaccine, including: a) development of innovative vaccine platforms b) ability to use the extensive vaccine-development knowledge of academia and industry, c) rapid response to pandemics due to general pressure, d) scientific partnerships and collaboration, e) unparalleled funding for COVID-19 vaccine research and development, f) numerous clinical trials to assess the safety, immunogenicity, and efficacy, g) generating billions of doses of vaccines before licensing (a very costly action for a manufacturer), and h) accelerate the approval of COVID-19 vaccines, while maintaining consistent standards [22].

However, it is crucial to study the side effects of vaccines during the general vaccination phase. Moreover, due to the existence of genetic diversity in different population of the world, the study of the efficacy and side effects of different vaccines among different populations is necessary. In addition, fear of side effects is the most important reason for reduced vaccine readiness [23]. Clinical trial studies of the AZD-1222 and Sputnik V have shown that the injection of these vaccines has no serious side effects. In a clinical trial related to the AZD-1222, pain, fever, chills, muscle pain, headache and fatigue were the most common side effects of the vaccine [2]. The side effects of the Sputnik V were almost the same. The most common side effects of Sputnik V are: injection site pain, fever, headache, fatigue, and muscle and joint pain [15]. However, so far there have been no reports of side effects of these vaccines in Iran and this study seems very necessary. Moreover, unusual thrombotic cases have rarely been reported during the use of vector vaccines [24]. The most important reasons involved in causing this rare complication are platelets and PF4 (platelet factor 4). The mechanisms that may be behind thrombotic thrombocytopenia after COVID-19 vaccination are: a) antibodies against PF4, b) the cross-reactivity of anti-spike antibodies and PF4, c) cross-reactivity of antibodies against adenovirus with PF4, d) interaction between spike protein and platelets, e) the direct interaction between adenoviral vector and platelets [24].

This study aimed to evaluate the local and systematic side effects of the first dose of the three COVID19 vaccines including Sputnik V (Gamaleya Research Institute, Russia), AZD1222 (AstraZeneca company, British-Swedish), and Covaxin (Bharat Biotech company, India) vaccines among 503 healthcare workers in Birjand (Southern Khorasan province, Iran), to determine the risk factors for having post vaccination symptoms and to compare between the three vaccine manufacturers as well.

2. Methods

2.1. Participants of the study

This cross-sectional study was performed on health care workers employed at different hospitals of Birjand University of Medical Sciences, Iran from February 7 to March 7, 2021. To evaluate the side effects of the first dose of vaccines, list of vaccine recipients was received daily from vaccine registry system and an online questionnaire was sent for them. The questionnaire consisted of 4 main categories: (A) demographic data including age, gender, height, weight, profession, education rate, smoking, underlying diseases, vitamin D intake, and use of corticosteroids; (B) previous COVID-19 infection, severity of symptoms and time of infection; (C) vaccine information including vaccine type, vaccination date and number of doses; (D) vaccines' side effects including local and systemic adverse reactions. The participants were able to modify their response during first seven days post vaccination.

2.2. Inclusion/exclusion criteria

Criteria for inclusion in this study were the injection of the first dose of one of the three vaccines AZD-1222, Sputnik V, and Covaxin. Participants had one week to report the side effects of the vaccine on special forms. Exclusion criteria were: Failure to complete the side effects report form on time, and positive COVID-19 test during the study period.

2.3. Eethical approval

This study was approved by the Ethics Committee of the Birjand University of Medical University on April 17, 2021 (IR.BUMS.REC.1400.027). All participants filled out the informed consent form.

2.4. Statistical analysis

The statistical analysis was performed by the SPSS version 22.0 (SPSS Inc. Chicago, IL, USA). The sample size with 95% confidence level was calculated by Cochrane formula. Initially, descriptive statistics were performed for the demographic variables (Age, Sex, and BMI), previous COVID-19 infection, and first dose vaccine side effects to determine the percentages, frequencies, and means. Then, inferential statistics were performed to evaluate the relationship between side effects and various variables including type of vaccine, gender, age, previous COVID-19 infection, Body Mass Index (BMI), underlying disease, use of corticosteroids, and vitamin D intake by the Student's *t*-test and Chi-square test with a significance value $p < 0.05$. Comparison of more than two group was performed by one-way and Tukey test as post-hoc test with a significance value $p < 0.05$. Finally, multiple regression was performed in order to find the variables that most likely affect the prevalence of side effect for each vaccine separately.

3. Results

3.1. Demographic characteristics

In total 503 participants (Mean age: 35.7 ± 10.18, Age range: 20–67 years, Mean BMI: 23.45 ± 4.1, BMI range: 13–38, and Females constituted 57 %) were enrolled in this study. The total population of health care workers employed in the hospitals under consideration, was about 2500 and at the time of this study about 1,200 person had received the first dose of COVID-19 vaccine. According to the number of participants in this study (503), about 42% of vaccinated people were included in this study. Moreover, using Cochrane formula, the sample size with 95% confidence level was 428 persons. Details of demographic information were summarized in Table 1. In total 9.7% of participants had at least one underlying disorder and the hypertension was the most common one. There was no significant difference in the percentage of underlying disorders in female and male group ($p = 0.1$). About 38% and 2.4% of participants receiving vitamin D and corticosteroids respectively in the last month before vaccination (Table 2).

Table 2
Underlying disease, vitamin D intake, and corticosteroids consumption in Birjand medical staff who received COVID-19 vaccine.

	Female	Male	Total
Underlying disease	31 (10.8%)	18 (8.8%)	49 (9.7%)
Hypertension	11	8	19 (3.7%)
Cardiovascular disease	5	3	8 (1.6%)
Cancer	3	2	5 (1%)
Respiratory disease	4	1	5 (1%)
Hepatologic disease	2	1	3 (0.6%)
Allergy	2	1	3 (0.6%)
Renal disease	1	1	2 (0.4%)
Rheumatoid arthritis	2	0	2 (0.4%)
Diabetes mellitus type-2	1	1	2 (0.4%)
Vitamin D intake	132 (45.8%)	63 (29.3%)	195 (38.8%)
Use of Corticosteroids	8 (2.8%)	4 (1.9%)	12 (2.4%)

3.2. COVID-19 vaccine side effects

3.2.1. Status of side effects in different vaccines

There were no side effects reported by 71 participants after the first dose of the vaccine. The amount of persons who had no side effects after the first dose was 18.1, 11.2, and 7.1 percent in the Sputnik V, AZD1222, and Covaxin vaccines, respectively. It should be noted that the prevalence and frequency of the side effects (in 4 cases of injection site pain, muscle pain, fatigue, and fever and chills) in Sputnik V, AZD1222, and Covaxin groups, were different which was shown in Fig. 1.

Although, the most common side effect in three vaccine groups was "injection site pain", but the prevalence and frequency of the other side effects were reported differently in these three groups. In the case of sputnik V, "muscle pain" (41.6 %) was the second most common side effect, but in the case of AZD-1222 and Covaxin, "fatigue" was the second most common side effect of the vaccine (68.4 % and 41.9 %, respectively). In addition, "fever and chills" (as an important side effect) were reported as the third most common side effect in Sputnik V (37.4 %) and AZD-1222 (67.1 %), but ranked fourth in the case of Covaxin (16.3 %). Moreover, the incidence of side effects between three vaccines group was not significantly different in female ($p = 0.135$) and male ($p = 0.110$). The prevalence of local side effects (injection site pain) was

Table 1
Demographic characteristics of the vaccines' recipients.

Variable	Outcome	AZD-1222	Sputnik V	Covaxin	*pValue*	Sig*
Type of vaccine		223 (44%)	238 (47%)	42 (9 %)		
Gender	Female (57 %)	118 (53%)	141 (59%)	28 (66%)	0.1368	n.s.
	Male (43 %)	105 (47%)	97 (41%)	14 (34%)		
Age	≤ 40 years (69 %)	162 (72%)	149 (63%)	37 (88%)	0.0828	n.s.
	> 40 years (31 %)	61 (28%)	90 (37%)	5 (12%)		
BMI	< 25 (64 %)	145 (65%)	147 (61%)	32 (76%)	0.0561	n.s.
	≥ 25 (36 %)	78 (35%)	91 (39%)	10 (24%)		
		All three vaccines				Total (%)
Profession	Physician	103				20.5 %
	Nurse	88				17.5 %
	Medical students	71				13.9 %
	Administrative staff	54				10.8 %
	Laboratory expert	50				10 %
	Dentist	28				5.5 %
	Faculty member	22				4.4 %
	Hospital staff	22				4.4 %
	Paramedical experts	21				4.2 %
	hygiene expert	18				3.6 %
	Midwife	15				3 %
	Pharmacist	11				2.2 %
Education level	Diploma & Associate's degree					
	Bachelor	39				7.7 %
	Masters	265				52.6 %
	Doctor of Medicine	36				7.2 %
	PhD	130				25.9 %
		24				6.6 %

* One way ANOVA were used with a significance level of < 0.05.

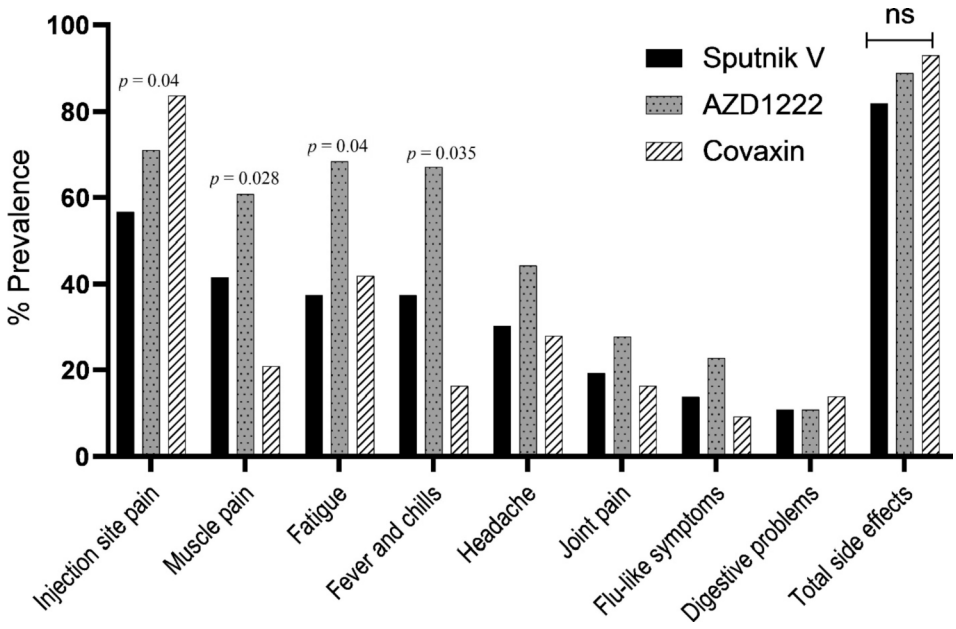

Fig. 1. Prevalence of the most common symptoms after vaccination based on the vaccine type. The difference in the prevalence and frequency 4 side effects of injection site pain, muscle pain, fatigue and fever and chills between the three groups of vaccine (Sputnik V, AZD1222 and Covaxin) was examined by One-way ANOVA, *pValue*<0.05 was considered as a significant level (ns referred to non-significant difference).

almost similar among the three vaccine groups; however, the prevalence of systemic side effects in AZD-1222 vaccine was higher than Sputnik V and Covaxin vaccines. In general, injection site pain, fatigue, muscle pain, and fever and chills were the most common side effects in all three vaccine groups.

3.2.2. Status of side effects based on gender

Side effect frequency was higher in the female group (90.6%) than the male group (79.5%) (Fig. 2). Moreover, the prevalence and frequency of these side effects were different in female and male groups, which was shown and Fig. 2. Among the reported side effects, only injection site pain was significantly different between female (69.5 %) and male (51.1 %) groups (p = 0.03), while the prevalence of other side effects was not significantly different between female and male group (Table 3).

Furthermore, Sputnik V had more side effects reported in the female group than in the male group (p = 0.04), but this ratio was nearly equal for the AZD1222 and Covaxin vaccine groups (Table 4). Moreover, the relationship between vaccine side effects and vitamin D intake, underlying disease and corticosteroids usage was also investigated. According to the results, there was no significant difference between the prevalence of side effects in the group receiving vitamin D compared to the group that did not receive vitamin D (87% vs. 86%). However, the prevalence of side effects was significantly different in the underlying disease group (77.5% vs. 88%; p = 0.03) and the corticosteroids usage group (78% vs. 88%; p = 0.04) compared to groups who did not have the underlying disease and did not take corticosteroids, respectively (Fig. 3).

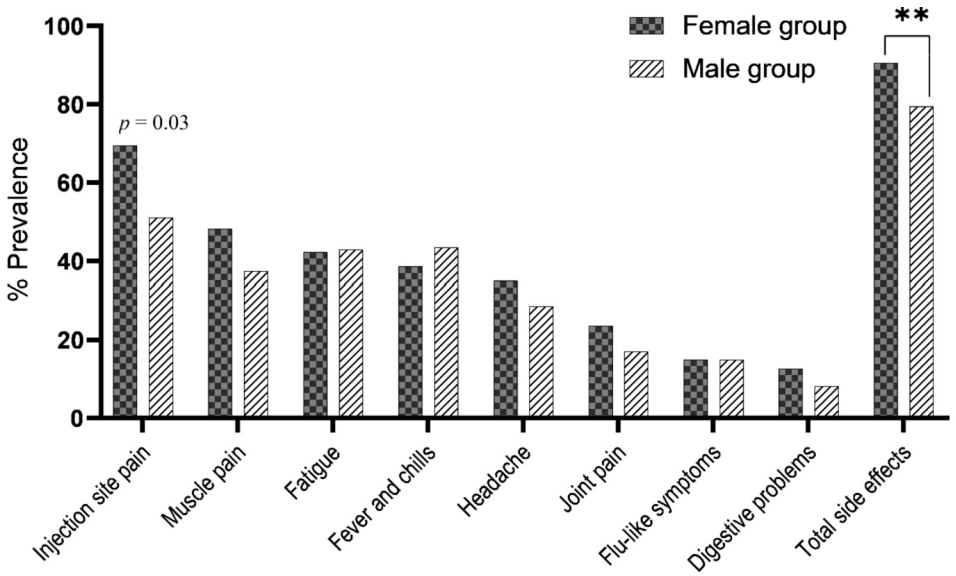

Fig. 2. Prevalence of different side effects among male and females. The difference in the prevalence and frequency of injection site pain between the two gender group (female and male) was examined by Chi-square test, *pValue*<0.05 was considered as a significant level.

Table 3
Prevalence of the COVID-19 vaccines side effects based on gender in the Birjand medical staff vaccination.

Side effects	Female	Male	*p-Value**
Injection site pain	69.5 %	51.1 %	0.03*
Fatigue	48.2 %	37.4 %	0.08
Muscle pain	42.3 %	42.9 %	0.3
Fever and chills	38.6 %	43.5 %	0.1
Headache	35 %	28.6 %	0.1
Joint pain	23.6 %	17 %	0.09
Flu-like symptoms	15 %	14.9 %	0.3
Digestive problems	12.7 %	8.2 %	0.1
Redness or swelling at the injection site	3.6 %	4.8 %	0.2
Shortness of breath	3.2 %	1.4 %	0.2
Hives and rashes	1.8 %	1.4 %	0.3
Severe allergies	0 %	0.7 %	0.1

* Chi-squared test were used with a significance level of < 0.05.

Table 4
Prevalence of the side effects in the three type of vaccines in the Birjand medical staff vaccination.

Side effects	Sputnik V	AZD1222	Covaxin	*p-Value**
Total	**81.9 %**	**88.8 %**	**92.9 %**	**0.119**
Side effects in female group	88.7 %	89.1 %	93.1 %	0.1351
Side effects in male group	72.2 %	88.5 %	92.3 %	0.1101

* One way ANOVA were used with a significance level of < 0.05.

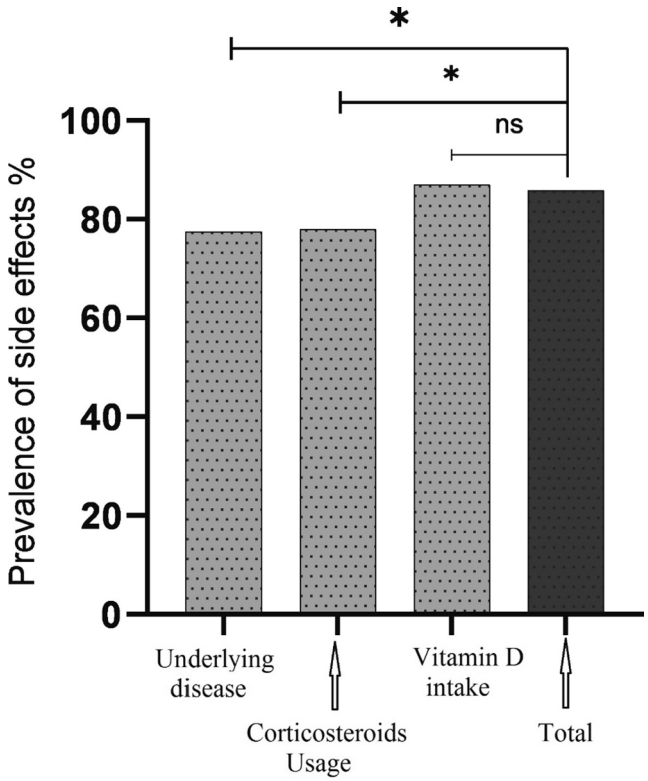

Fig. 3. Prevalence of side effects in underlying disease, corticosteroids usage, and vitamin D intake groups. The difference between the prevalence and frequency of vaccine side effects in the underlying disease groups, corticosteroid usage, and vitamin D intake was examined by Chi-square test, *pValue*<0.05 was considered as a significant level.

3.2.3. Status of side effects by age

In another analysis, the prevalence of vaccine side effects was compared in two age groups, less and>40 years. The frequency of side effects in the age group<40 years old (91.1%) was higher than the age group over 40 years old (76.8%); p = 0.04 (Fig. 4). Moreover, the amount and frequency of these side effects varies in different age groups, which was shown in Table 5. In addition, the difference in the prevalence of side effects in groups under 40 years and over 40 years was significant in Sputnik V (p = 0.03) and Covaxin vaccines (p = 0.02).

3.2.4. Relationship between previous COVID19 infection and the prevalence of vaccines side effects

The prevalence and severity of vaccine side effects was assessed based on a history of previous COVID-19 infection. The frequency of side effects was higher in the case of convalescent patients (the group with a history of COVID-19) (92.4 %) than in the group with no history of COVID-19 infection (85.1 %), and this difference was significant (p = 0.045) (Fig. 5). Furthermore, the prevalence and frequency of these side effects varies in these groups, which was shown in Table 6. In addition, the difference in the prevalence of side effects in group with a history of COVID-19 and group without a history of COVID-19 (85.1 %) was significant in Sputnik V (p = 0.048) and Covaxin vaccines (p = 0.04).

3.2.5. Relationship between BMI and the prevalence of vaccine side effects

In the following, the prevalence and severity of vaccine side effects was assessed based on BMI. The mean BMI among participants was 23.45 ± 4.1. The frequency of COVID-19 vaccine side effects was significantly difference in the case of the AZD-1222 (p = 0.04) and Covaxin vaccines (p = 0.04) and prevalence of side effects was higher in person with a BMI above 25. This difference was not observed with the Sputnik V vaccine (Fig. 6). According to Table 7, there was no significant difference between two groups (BMI above and below 25) in the prevalence and frequency of side effects, except for two cases (Headache and Flu-like symptoms).

3.3. Multiple regression for finding truly variable that impact on COVID-19 vaccine side effects

Multiple regression was performed in order to find the variables that really affect the prevalence of side effect for three vaccines separately. The results were summarized in Table 8. According to these results, in the case of Sputnik V, the effect of age and gender variables on the prevalence and frequency of post-vaccine side effects was significant. In the case of the Covaxin and AZD-122, no significant relationship was

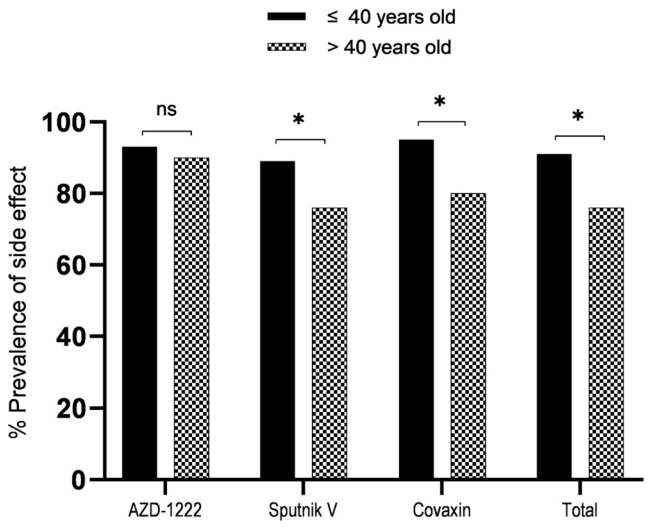

Fig. 4. Prevalence of the COVID-19 vaccines side effects based on age in three vaccine groups in the Birjand medical staff vaccination (Reported at least one side effect after vaccination). The difference in the prevalence of side effects between the groups under 40 years and over 40 years was examined by Chi-square test, *pValue*<0.05 was considered as a significant level (ns referred to non-significant difference).

Table 5
Prevalence of the COVID-19 vaccines side effects based on age in the Birjand medical staff vaccination.

Side effects	≤ 40 years Number = 348	> 40 years Number = 155	*p-Value**
Injection site pain	66 %	54 %	0.03*
Fatigue	49 %	34 %	0.04*
Muscle pain	44 %	39 %	0.08
Fever and chills	47 %	29 %	0.04*
Headache	37 %	23 %	0.02*
Joint pain	22 %	19 %	0.1
Flu-like symptoms	16 %	13 %	0.2
Digestive problems	14 %	5 %	0.06
Redness or swelling at the injection site	5 %	4 %	0.4
Shortness of breath	2.5 %	2.7 %	0.4
Hives and rashes	2.5 %	1.7 %	0.4
Severe allergies	0.5 %	0 %	0.3

* Chi-squared test were used with a significance level of < 0.05.

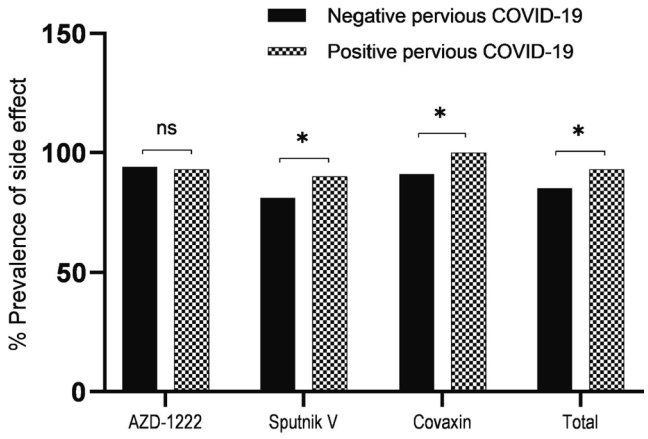

Fig. 5. Prevalence of the COVID-19 vaccines side effects based on previous COVID-19 infection in three vaccine groups in the Birjand medical staff vaccination (Reported at least one side effect after vaccination). The difference in the prevalence of side effects between the groups with a history of COVID-19 and group without a history of COVID-19 was examined by Chi-square test, *pValue*<0.05 was considered as a significant level (ns referred to non-significant difference).

Table 6
Prevalence of the COVID-19 vaccines' side effects based on previous COVID-19 infection among study population.

Side effects	Negative pervious COVID-19 Number = 391	Positive pervious COVID-19Number = 112	*p-Value**
Injection site pain	83 %	73 %	0.04*
Fatigue	43 %	54 %	0.03*
Muscle pain	40 %	59 %	0.02*
Fever and chills	42 %	44 %	0.2
Headache	34 %	30 %	0.1
Joint pain	20 %	29 %	0.04*
Flu-like symptoms	17 %	15 %	0.3
Digestive problems	10 %	15 %	0.1
Redness or swelling at the injection site	3 %	7 %	0.08
Shortness of breath	2 %	4 %	0.1
Hives and rashes	1.5 %	2.5 %	0.1
Severe allergies	0.3 %	0 %	0.3

* Chi-squared test were used with a significance level of < 0.05.

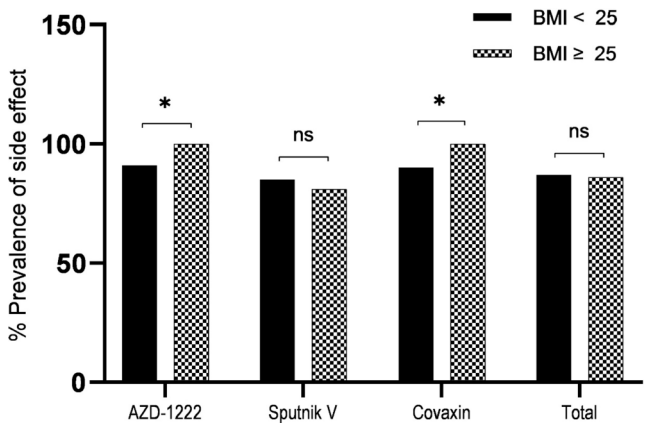

Fig. 6. Prevalence of the COVID-19 vaccines side effects based on BMI in three vaccine groups in the Birjand medical staff vaccination (Reported at least one side effect after vaccination). The difference in the prevalence of side effects between the groups (BMI above and below 25) was examined by Chi-square test, *pValue*<0.05 was considered as a significant level (ns referred to non-significant difference).

Table 7
Prevalence of the COVID-19 vaccines side effects based on BMI in the Birjand medical staff vaccination.

Side effects	BMI < 25 Number = 332	BMI ≥ 25 Number = 121	*p-Value**
Injection site pain	66 %	60 %	0.1
Fatigue	46 %	44 %	0.2
Muscle pain	45 %	44 %	0.2
Fever and chills	43 %	40 %	0.3
Headache	37 %	26 %	0.02*
Joint pain	22 %	21 %	0.2
Flu-like symptoms	12 %	21 %	0.01*
Digestive problems	12 %	10 %	0.1
Redness or swelling at the injection site	4 %	7 %	0.08
Shortness of breath	3 %	1 %	0.1
Hives and rashes	0.8 %	3 %	0.09
Severe allergies	0 %	0.8 %	0.1

* Chi-squared test were used with a significance level of < 0.05.

found for any of the variables.

4. Discussion

AZD-1222 (ChadOx1 nCoV-19) consists of replication-deficient simian adenovirus vector (ChAdOx1) with replication deficiency. This non-replicating virus carries the optimal codon sequence for the spike protein. Studies show that the vaccine is better tolerated in the elderly than in the young, and after a booster dose, develops similar immunogenicity in all age groups [25]. The Sputnik V vaccine (rAd26-S and rAD5-S), made by a Russian company, contains the glycoprotein S gene of the SARS-CoV-2 virus. The first and second doses of this vaccine are based on two different types of adenoviruses. Phase 1/2 studies indicated that both formulations of this vaccine (rAd26-S and rAD5-S) were safe and tolerable [25]. Covaxin (BBV152) is an inactivated whole virion which is produces by Bharat Biotech Company, and formulated with a TLR (toll-like receptor) 7/8 agonist molecule adsorbed to alum. This vaccine was established using an isolated strain (NIV-2020–770) from a patient with COVID-19 in India. Studies have shown that this vaccine has acceptable safety and can stimulates humoral and cellular responses [25].

Among all studied vaccines, injection-site pain was the most common local reactions, and muscle pain, fatigue, fever and chills, and headache were the most common systemic reactions. The current study

Table 8
Multiple regression to investigate the relationship between age, gender, BMI, previous infection, vitamin D, and corticosteroid with the prevalence of side effects in three vaccines AZD-1222, Sputnik V, and Covaxin (Dependent Variable: Side effect).

Model (AZD-1222)		t	Sig.
	Age	−1.075	0.286
	Gender	0.112	0.911
	BMI	0.351	0.726
	Previous infection	−0.077	0.939
	Vitamin D	0.551	0.583
	Corticosteroid	0.337	0.737
Model (Sputnik V)		t	Sig.
	Age*	−4.482	0.000
	Gender*	−2.368	0.019
	BMI	0.956	0.340
	Previous infection	0.397	0.691
	Vitamin D	−0.192	0.848
	Corticosteroid	0.131	0.896
Model (Covaxin)		t	Sig.
	Age*	−1.117	0.272
	Gender	0.262	0.795
	BMI	0.376	0.709
	Previous infection	0.191	0.850
	Vitamin D	0.700	0.488
	Corticosteroid	0.155	0.878

* Significance level of < 0.05.

reported a statistically significant difference in the prevalence of injection site pain, muscle pain, fatigue, and fever and chills between the three vaccine groups (Fig. 1). Muscle pain, fatigue, and fever and chills were significantly more common in people who received the AZD-1222 vaccine. This indicates that the AZD-1222 vaccine has more systemic side effects than Sputnik V and Covaxin. However, the rate of other complications, including headache, joint pain, flu-like symptoms, and gastrointestinal problems, was not statistically significant between the three vaccine groups. Although, the main common side effect in three vaccine groups was "injection site pain", but the prevalence and frequency of the other side effects were reported differently in these three groups. The frequency of important side effects of AZD-1222 is as follows: Fatigue > Muscle pain > Fever and chills. The frequency for Sputnik V is as follows: Muscle pain > Fatigue > Fever and chills; and the frequency for Covaxin is as follows; Fatigue > Muscle pain > Fever and chills. The prevalence of local side effects (injection site pain) was almost similar among the three vaccine groups; however, the prevalence of systemic side effects in AZD-1222 vaccine was higher than Sputnik V and Covaxin vaccines.

In our study, 85% of participants reported at least one adverse reaction (local or systemic reaction), that was significantly different between the female group and the male group. Among the reported side effects, injection site pain was significantly different between female and male groups ($p = 0.002$), while fatigue, muscle pain, fever and chills, and other systemic side effects were not significantly different between these groups (Fig. 2). The difference in the prevalence of injection site pain between male and female possibly is due to differences in the threshold of pain tolerance rather than any biological causes.

A study from Saudi Arabia, the safety of the AZD-1222 vaccine was evaluated after the first dose in 1592 vaccinated volunteers (37.4 ± 9.6 years and 81% male). About 35% of receivers of AZD1222, reported at least one side effect after vaccination. The most common side effects were: injection site pain (30.5%), fever (31.3%), muscle symptoms (27.5%), gastrointestinal symptoms (23.8%), and skin rash (19.2%), which consistent with our result [26]. Similar to our study female more likely to report injection site pain, and men were more likely to report skin rash (81.1%), fever (76.9%), and injection site pain (77.3%) [26]. Similar to our finding, Cerino et al., reported muscle symptoms (28.2 %), headache (26.8 %), fatigue (20.8 %), fever (17.9 %), chills (14.9 %), and injection site pain (8.9 %) as the most common side effects among a group of adults who received one dose of AZD1222 [27]. As can be seen in these two studies, muscle symptoms, fever, and fatigue are more common AZD-1222 side effects, which are consistent with our study. In the case of injection site pain, the results of our study were similar to the results of Al Bahrani et al., (70% vs. 77.3%), although they were clearly different from the results of Cerino et al., (70% vs. 8.9%) [26,27]. Variances in the definition of pain in various areas can cause these differences. However, the location of Iran and Saudi Arabia in the same geographical area and the similarity of the pain percentage of the injection site is also interesting.

As many studies have shown, younger people are more likely than older people to experience side effects after vaccination [28,29]. In the present study, the frequency of side effects was higher in the people under 40 years old. Although, this difference was not significant in all side effects; but complications such as injection site pain, fatigue, headache, and fever were more common in young people than in the elderly. When the vaccine groups were examined separately, it was found that in the case of the AZD-1222 vaccine, there was no significant difference in the frequency of side effects between the two age groups. But in the case of Sputnik V and Covaxin vaccines, this difference was significant. In Al Bahrani study, the AZD-1222 vaccine caused less side effects among those aged 45–54 years, demonstrating lower events compared to younger people [26].

Fatigue, headache, injection site pain, muscle pain and fever were the most common side effect for AZD 1222 in the study of Folegatti [5]. In general the common side effects of AZD 1222 are similar although there are some changes in the rank of some side effects among different studies possibly because of difference in the study population and evaluation methods.

In a study by Logunov et al., the side effects of Sputnik V vaccine were evaluated in 76 participant. The prevalence of side effects was reported as follows; 58% injection site pain, 50% fever and chills, 42% headache, 28% fatigue, and 24% muscle pain [30]. A similar trend was observed in our study, where injection site pain was more prevalent than the adverse effects (58% vs. 56.7%), and the same pattern was reported for fever and chills (50% vs. 37.4%), and headache (42% vs. 30.3%). Nevertheless, there was no similarity prevalence between fatigue (28% vs. 37.4%), and muscle pain (24% vs. 41.6%) [30]. In line with our study, Babamahmoodi reported injection site pain (56.9% vs. 56.7%), fatigue (50.9% vs. 37.4%), muscle pain (43.9% vs. 41.6%), headache (35.7% vs. 30.3%), fever and chills (31.4% vs. 37.4%), and joint pain (30.3% vs. 22.1%) as the most common side effects after receiving Sputnik V among a large group of healthcare workers in Iran [31]. Interestingly, similar to our study, the side effects were significantly more common in women and younger people [31].

In case of Covaxin data are scarce. The most common Covaxin vaccine side effects in our study were: injection site pain (83.7%), fatigue (41%), headache (27.9%), muscle pain (20%), and fever (16%), While the amount of side effects reported in Ella's study was<10% for all side effects [32]. In the another report by Kamal and colleagues, the most common side effects were: headache (17.4%), fever (12.5%), fatigue (12.3%), and muscle pain (11.2%) [33]. In both studies, the rate of side effects was lower than our study possibly because of difference in the study participants or data collection method.

The frequency and severity of vaccine side effects in the case of convalescent patients was another factor that was examined in this study. According to the results, having a history of COVID-19 infection also affects the incidence of post-vaccine complications. But, this difference was not significant in all side effects. However, the prevalence of some side effects such as injection site pain, fatigue, muscle aches and joint pain is higher in the case of convalescent patients. Regarding the effect and role of BMI on the prevalence of post-vaccine complications, the results showed that this factor does not have a significant effect on the incidence of vaccine side effects. However, the headache complication was an exception and persons with low BMI are more likely to have headaches.

Moreover, there was no significant difference in the prevalence of side effects in the vitamin D intake group compared to the group that did not receive vitamin D. However, the prevalence of side effects was significantly different in participants with underlying diseases or receivers of the corticosteroid drugs compared to other groups who did not have the underlying diseases and did not take corticosteroids. Corticosteroids drugs are well known for reducing the inflammation and therefore the finding is expectable [34]. In case of people with underlying disease, using analgesic and anti-inflammatory drugs or have higher threshold for enduring pain or discomforts are possible reasons for our finding.

Lastly, it should be noted that no serious and severe side effects were observed in any of the participants and all side effects disappeared after a maximum of 7 days.

The results of multiple regressions were significant only for Sputnik V vaccine. The results showed that there is a linear regression between age and incidence of side effects. The prevalence of side effects in Sputnik V with age has a coefficient of −0.12 (inverse correlation). This suggests that side effects of this vaccine are more common at younger ages. This is consistent with other studies. However, this correlation was not observed for AZD-1222 and Covaxin. Similar correlations with age have been reported in similar studies for the AZD-1222 vaccine. The lack of available samples for these vaccines seems to be one of the reasons for the lack of correlation.

This study has some limitations including recall bias or individuals' biases in reporting side effects, incomplete answers to questionnaire and small sample size for Covaxin which was due to the low number of imported Covaxin. Male can admit less to side effects following the vaccination in a similar fashion that they may report lower fear of vaccination. Examining side effects with more participants and examining side effects in different vaccines can be interesting goals in future studies.

5. Conclusion

The most common side effects of the Sputnik V, AZD-1222, and Covaxin vaccine among Birjand (Iran) healthcare workers were injection site pain, muscle pain, fatigue, fever and chills, and headache. These data were highly consistent with clinical studies performed by vaccine manufacturers. The incidence of side effect was generally higher in female than in male, but the correlation was more pronounced in the case of Sputnik V. The prevalence of side effects was also inversely related to age, and older people were less likely to develop post-vaccination complications. Further research is needed to strengthen public confidence in the vaccine and to better understand the possible side effects in different populations on approved COVID-19 vaccines.

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CRediT authorship contribution statement

Hamed Zare: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Hadis Rezapour:** Methodology, Writing – review & editing. **Sara Mahmoodzadeh:** Methodology, Writing – review & editing. **Mohammad Fereidouni:** Conceptualization, Writing – review & editing, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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