Self-Reported Adverse Events after Primary COVID-19 Vaccination in Bulgarian Healthcare Workers

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Article

Self-Reported Adverse Events after Primary COVID-19 Vaccination in Bulgarian Healthcare Workers

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Abstract: The immunization of healthcare workers in the early stages of the rollout of COVID-19 vaccines was prioritized in order to ensure uninterrupted medical care provision. At the same time the increasing number of available COVID-19 vaccines may trigger hesitancy towards the decision to get vaccinated. Thus, accumulating reliable information on the adverse events following immunization may educate and urge the general population to receive a COVID-19 vaccine. The present study aimed to evaluate the adverse events (AEs) following immunization with any of the available COVID-19 vaccine among Bulgarian healthcare workers (HCWs). A cross-sectional study among HCWs in Plovdiv, Bulgaria was conducted in the period March – September 2021. Through a semi-structured online questionnaire, the participants reported the adverse events following the administration of the first and second dose of a COVID-19 vaccine. A total of 253 respondents, vaccinated with one of the available vaccines against COVID-19 took part in the study. Of them 71.9% were females, and 75.9% received mRNA-based vaccines, while 24.1% received a viral-vector based vaccine. Overall 91.6% and 82.6% of all participants reported at least one local AE after the first and second dose of a COVID-19 vaccine. The share of respondents reporting at least one systemic AE after the first and second dose of a COVID-19 vaccine was 59.7% and 62.4% respectively. The most common local AE was pain at the injection spot (84.0%), while the most common systemic AEs were fatigue (54.9%), chills (43.2%), and headache (41.7%). The mRNA-based vaccines versions seem to cause higher prevalence of local AEs, while the vector-based vaccines were linked with increased prevalence of systemic AEs. Female HCWs and the younger age group were associated with an increased risk of adverse events generally. Our results added more evidence that mRNA-based and viral-vector based vaccines are generally safe. The reported adverse events were mild, although they occurred in a high share of the respondents. No serious AEs attributable to the vaccines were reported.

Keywords: COVID-19; SARS-CoV-2; vaccine; mRNA vaccine; adenoviral vector vaccine; adverse event; local adverse event; systemic adverse event

1. Introduction

The emergence and global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 6.57 million deaths [1]. To control the pandemic various infection control measures including wearing masks, suspension of mass gatherings, school closures and travel restrictions were implemented; nonetheless it became obvious over time that defeating the pandemic could only be accomplished by widespread vaccination [2,3]. The first COVID-19 vaccine BNT1622, was conditionally approved by EMA on December 21, 2020 [4], and the immunization campaign in Bulgaria began on December 27th 2020. Of the six vaccines for primary immunization against COVID-19 authorized for use in the EU, five of them have been distributed and administered in

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Bulgaria, respectively from: December 27, 2020 – Comirnaty; from January 9, 2021 - Spikevax; from February 6, 2021 – Vaxzevria; from March 23, 2021 - Jcovden; from 01.11.2022 – Valneva [5].

In Bulgaria, 1,295,585 COVID-19 cases with 38,184 fatalities have been documented by February 5, 2023 in a population of 6 838 937 million [6]. By January 2023, 73% of the population of the EU had completed the primary COVID-19 vaccination course, compared to just 30% of Bulgarians [7].

Healthcare workers (HCW) and students in medical universities are regularly in direct contact with potentially infectious patients and are at a higher risk of being exposed to SARS-CoV-2. According to official data, as of February 5, 2023, there were 26,329 infected medical personnel in Bulgaria (doctors - 6,542, nurses - 8,520, paramedics - 4,948, paramedics - 489, others - 5,830) [8]. Exact data on those who died among them are not available.

COVID-19 immunization could reduce the incidence of severe COVID-19 and hospitalization, especially among high-risk populations including those over 65 years of age and healthcare [9,10]. The authorities in many countries have discussed making COVID-19 vaccination mandatory for eligible health professionals and medical students [11]. In Bulgaria, as in many other European countries, the national COVID-19 vaccination program prioritized the immunization of healthcare workers in the early stages of the rollout of COVID-19 vaccines in order to ensure uninterrupted medical care provision and due to the high risk of exposure in this specific group.

Public trust in vaccination is crucial for the successful immunization program, but the increasing number of available COVID-19 vaccines may trigger hesitancy towards the decision to get vaccinated. There are no publicly available research studies in Bulgaria that mention adverse events following immunization in HCWs. Thus, accumulating reliable information on the adverse events following immunization, their severity and their impact on the individual's life may educate and urge the general population to receive a COVID-19 vaccine. From the beginning of the vaccination campaign in Bulgaria until November 22, 2022, the total number of reports to the executive agency for medicines (AML) about post-vaccination reactions after administration of vaccines against COVID-19 was 4,188, with 4,592,347 doses of vaccines administered. This represents 0.91 reports for every 1000 doses administered [12].

2. Materials and Methods

2.1. Design

This survey was designed as a cross-sectional study among healthcare professionals in the city of Plovdiv, Bulgaria, during the months of March through September 2021. A semi-structured questionnaire was created and distributed online using the Microsoft Forms Platform (Microsoft Forms, Microsoft 365 Package). The intended audience included medical staff from UMHAT "St. George," Plovdiv, and Medical University Plovdiv who had received one of the COVID-19 vaccines that were available at the time. Potential respondents were asked for their willingness to participate and email addresses prior the administration of a COVID-19 vaccine.

The sample size was calculated using G*Power version 3.1.9.7 [13]. The maximum amount by which the sample results may differ from the full population (margin of error) and the probability that the sample accurately reflects the self-reported adverse events of the targeted population (confidence interval) were set to 5% and 95%, respectively. Based on similar studies, the expected frequency (outcome probability) is assumed to be 60% as the prevalence of side effects following COVID-19 vaccines ranged between 62% to 93% [14–16]. Thus, the number of people who need to take the survey was estimated to be 220. The total sample size achieved included 253 respondents, vaccinated with one of the available vaccines against COVID-19.

Participants in the study had to meet the following eligibility criteria: 1) age of 18 or above 2) immunization with any of the readily accessible vaccines, regardless of a prior COVID-19 infection 3) signed permission to participate voluntarily without payment and the right to withdraw at any time up until the submission of data.

2.2. Questionnaire

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The Microsoft Forms Platform was used to create the four-part self-administered survey, which was then disseminated through email with a link generated electronically. On the main page of the questionnaire, an informed consent form with an opt-out option was included for those who did not want to continue. The first section collected information on the individuals' demographics, professional occupation, comorbidities, prior COVID-19 infection, and adverse events following vaccination in the past.

The second section gathered data on the first dose of the COVID-19 vaccine, such as the type of vaccine: mRNA vaccine–Comirnaty (BNT162b2 (INN: tozinameran) by Pfizer-Biontech), Spikevax (mRNA-1273 (INN: elasomeran) by Moderna), adenoviral vector vaccine–Vaxzevria (INN: ChAdOx1-S [recombinant]) by Astra-Zeneca), COVID-19 Vaccine Janssen (INN: Ad26.COV2-S [recombinant] by Johnson & Johnson); adverse events following immunization–local reactions (pain, edema, redness, rash, nodule, infected abscess, sterile abscess, cellulitis), systemic reactions (chills, fatigue, headache, muscle pains, joint pains, nausea/vomiting, diarrhea, reduced appetite, lymphadenopathy), allergic reactions (anaphylaxis, angioedema, generalized urticaria), and reactions of interest in relation to COVID-19 vaccines (thrombocytopenia, blood disorders, syncope, arthralgia).

Additionally, participants were asked to rate the severity of the event (mild, moderate, or severe) and the time point of occurrence in terms of local and systemic reactions (24 hours after vaccination, 24–48 hours after vaccination, and more than 72 hours after vaccination). The third segment's questions focused on the second dose of the COVID-19 vaccine and were identical to those in the previous section. Participants were given the option of providing any extra details they thought were important but were not asked for in section four of the questionnaire (about reactions or complaints they had after receiving the vaccine).

In the data analysis, we examined the levels of post-vaccination adverse events (local and systemic), in two groups that had either received an mRNA vaccine or an adenoviral vector vaccine.

2.3. Statistical analysis

Standard descriptive statistics was used to summarize demographic characteristics. Quantitative variables were presented by the mean and standard deviation (mean ± SD) or median (25th percentile; 75th percentile), based on the sample distribution. Qualitative variables were presented as numbers absolute/relative frequencies totals and percentages (n, %). The Kolmogorov-Smirnov test was applied to inform about the distribution of the patients sampled. Differences between observed and theoretical distributions were tested using the chi-square test for independence. Differences between proportions were examined using the z-test. A logistic regression was used to determine the effects of age group, gender, and vaccine type on the likelihood that patients experience adverse events – local or system – following the first and second doses. A 2-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics v. 26 software (IBM Corp. Released 2019. Armonk, NY: USA).

3. Results

In total, 253 people consented to participate in the study and responded to the questionnaire. They were split into two groups: those who received an mRNA-based vaccine (180 recipients of BNT162b2, commonly known as Pfizer-Biontech COVID-19 vaccine, and 12 recipients of mRNA-1273 commonly known as Moderna COVID-19 vaccine), and those who received a viral-vector based vaccine (52 recipients of ChAdOx1 nCoV-19 commonly known as AstraZeneca-Oxford COVID-19 vaccine, and 9 recipients of Ad26.COV2.S, commonly known as Janssen COVID-19 vaccine).

The mean age was 41.90±14.26 (20-75) years of age. Female participants composed 71.9% of the participants (Table 1). One-quarter of the participants reported at least one comorbidity. Thyroid-related diseases were the most common condition among the participants (27.4%), followed by arterial hypertension (25.8%), diabetes mellitus (8.1%), and respiratory diseases (6.5%).

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Table 1. Demographic characteristics and basic information of the respondents.

Variables	Results
Gender, n (%)	
Male	71 (28.1)
Female	182 (71.9)
Age, (median±SD)	41.9±14.3
Comorbidities, n (%)	
Yes	62 (24.5)
No	191 (75.5)
COVID-19 infection before vaccination, n (%)	
Yes	72 (28.5)
No	181 (71.5)
Adverse events following immunization in the past	
Yes	45 (17.8)
No	208 (82.2)

A total of 229 (90.5%) participants reported at least one local adverse event after the first dose of a vaccine, and the prevalence was higher (92.6%) in the mRNA-based vaccine group than in the adenoviral vector vaccine group (88.7%), but not statistically significant (Pearson $\chi 2$ test=0.965, p=0.326) (Table 2). Pain at the injection site was the most common local adverse event after vaccination with both vaccines: 92.1% for mRNA-based vaccines and 88.7% for adenoviral vector vaccines. The majority of respondents (72.3% for mRNA-based vaccines and 59.6 % for viral vector-based vaccines) rated the pain as mild. In terms of occurrence, high proportion of the participants (83.1% for mRNA-based vaccines and 78.8% for adenoviral vector vaccines) reported pain at the injection site around 24 hours after vaccine administration.

The prevalence of local adverse events after second dose of a vaccine was almost identical (82.6%), with mRNA-based vaccine recipients reporting more local reactions (85.8%) than adenoviral vector-based vaccine recipients (84.9%) but without statistical significance (Pearson χ 2 test=0.978, p=0.434). Pain at the injection site was the most common local reaction (87.0 for mRNA-based vaccines and 68.5% for adenoviral vector-based vaccines). The majority of respondents described the pain as mild (76.1% for mRNA-based vaccines, and 51% for viral vector-based vaccine) and stated that it started 24 hours after the second dose of the vaccine was administrated (82.2% for mRNA-based vaccine, and 64.1% for adenoviral vector-based vaccine).

Table 2. Local adverse events after the first and second dose of mRNA and viral-vector based vaccines.

Variables	1st dose		p-value	2nd dose		p-value
	mRNA n=191	Vector n=62		mRNA n=191	Vector n=53	
Pain, n (%)	**176 (92.1)**	55 (88.7)	0.404	163 (87.0)	43 (68.5)	0.455
Edema, n (%)	34 (17.8)	14 (22.6)	0.404	34 (22.0)	10 (11.3)	0.858
Redness, n (%)	36 (18.8)	8 (12.9)	0.283	30 (16.9)	7 (14.9)	0.654
Rash, n (%)	5 (5.4)	1 (2.8)	0.651	4 (3.5)	0 (0)	0.288
Nodule, n (%)	11 (12.0)	1 (97)	0.182	13 (8.8)	2 (5.9)	0.416
Local reactions, n (%)	177 (92.6)	55 (99.7)	0.326	164 (85.8)	45 (84.9)	0.434

A total of 187 participants (73.9%) reported at least one systemic adverse event (SAE). The prevalence of SAE was higher (83.8%) in the adenoviral vector-based vaccine group than in the mRNA-based vaccine group (70.6%), and the difference was statistically significant (Pearson $\chi 2$ test=4.223, p=0.040).

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The prevalence of SAEs after the first dose of a vaccine was statistically significant in recipients of adenoviral vector-based vaccines (83.8%) compared to mRNA-based vaccines (51.8%) (Pearson $\chi 2$ test=19.967, p=0.000).

The prevalence of SAE in the two groups did not reach statistical significance after the second dose of a vaccine (69.8% for adenoviral vector-based vaccine and 63.3% for mRNA-based vaccine, Pearson $\chi 2$ test=0.759, p=0.384). The most common systemic adverse events were listed in Table 3.

Table 3. Systemic adverse events after the first and second dose of mRNA and viral-vector based vaccines.

Variables	1st dose		p-value	2nd dose		p-value
	mRNA n=191	Vector n=62		mRNA n=191	Vector n=53	
Chills, n (%)	**41 (21.5)**	42 (67.7)	**0.000**	70 (36.6)	25 (47.2)	0.165
Fatigue, n (%)	76 (39.8)	44 (71.0)	**0.000**	93 (48.7)	32 (60.4)	0.132
Headache, n (%)	48 (25.1)	37 (59.7)	**0.000**	56 (29.3)	28 (52.8)	**0.001**
Muscle pains, n (%)	44 (23.0)	36 (58.1)	**0.000**	67 (35.1)	24 (45.3)	0.174
Joint pains, n (%)	31 (16.2)	24 (38.7)	**0.000**	47 (24.6)	18 (34.0)	0.173
Nausea/vomiting, n (%)	12 (6.3)	9 (14.5)	**0.041**	16 (8.4)	5 (9.4)	0.808
Diarrhea, n (%)	4 (2.1)	4 (6.5)	0.088	7 (3.7)	5 (9.4)	0.086
Reduced appetite, n (%)	8 (4.2)	24 (38.7)	**0.000**	19 (9.9)	14 (26.4)	**0.002**
Systemic reactions, n (%)	99 (51.8)	52 (83.8)	**0.000**	121 (63.3)	37 (69.8)	0.384

We discovered statistically significant differences when we examined the adverse events based on gender (Table 4). The prevalence of local adverse events following the first dose of a vaccine was higher in women than in men and it reached statistical significance (94.5% in women and 84.5% in men, Pearson $\chi 2$ test=6.708, p=0.010).

Table 4. Adverse events after 1st and 2nd dose of a vaccine depending on the age of the respondent.

Adverse event, n (%)	Respondents <30 y.o. n=71	Respondents > 30 y.o. n=182	p-value
Local AE after 1st dose of a vaccine	69 (97.1)	162 (89.6)	**0.048**
Systemic AE after 1st dose of a vaccine	56 (78.9)	95 (52.2)	**0.000**
Local AE after 2nd dose of a vaccine	62 (89.9)	145 (82.8)	0.170
Systemic AE after 2nd dose of a vaccine	53 (76.8)	105 (60.0)	**0.013**

A logistic regression was used to determine the effects of age group, gender, and vaccine type on the likelihood that patients experience adverse events – local or system – following first and second dose.

The logistic regression model for local adverse events following the first dose administration was statistically significant, $\chi 2(3)=15.84$, p=0.001. The model explained 13.9% (Nagelkerke R2) of the variance in vaccine local adverse events and correctly classified 91.7% of cases. Respondents under the age of 30 were associated with an increased likelihood of exhibiting local side effects ($\beta=8.36$) and especially if they were female. The participants who received the mRNA vaccine were 3.07 times more likely to experience local side effects after the first dose than those who preferred the adenoviral vector vaccine (Table 5).

The logistic regression model for local adverse events following the second dose administration was not statistically significant, $\chi 2(3)=5.84$, p=0.120. The model explained only 4.1% (Nagelkerke R2) of the variance in vaccine local adverse events (Table 5).

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Table 5. Multiple linear regression model for the onset of local AEs following the 1st and 2nd dose of a vaccine.

Model	Unstandardized Coefficients		Wald	df	Sig.	Exp(B)	95% Confidence Interval for B	
	B	Std. Error					Lower Bound	Upper Bound
Following the first dose administration								
(Constant)	1.696	0.530	10.224	1	0.001	5.451		
Age groups	2.124	0.830	6.547	1	**0.011**	8.364	1.644	42.562
Gender	-1.277	0.478	7.132	1	**0.008**	0.279	0.109	0.712
Vaccine platform	1.122	0.554	4.106	1	**0.043**	3.071	1.037	9.092
Following the second dose administration								
(Constant)	0.982	0.480	4.177	1	0.041	2.669		
Age groups	1.034	0.519	3.963	1	**0.047**	2.811	1.016	7.779
Gender	-0.369	0.386	0.910	1	0.340	0.692	0.324	1.475
Vaccine platform	0.795	0.480	2.747	1	0.097	2.214	0.865	5.667

The logistic regression model for adverse events following the first dose administration was statistically significant, $\chi 2(3)= 22.04$, $p=0.000$. The model explained 14.2% (Nagelkerke R2) of the variance in vaccine SAEs and correctly classified 59.7% of cases. Respondents under the age of 30 were associated with an increased likelihood of exhibiting SAEs ($\beta=2.30$) and gender was not significant for the model. The participants who received viral-vector based vaccine were 0.28 times more likely to experience SAE after the first dose than those who preferred the mRNA vaccine (Table 6).

The logistic regression model for SAEs following the second dose administration was statistically significant, $\chi 2(3)=11.12$, $p=0.01$, although explaining only 6.1% (Nagelkerke R2) of the variance in SAEs and correctly classified 66.0% of cases. Respondents under the age of 30 were associated with an increased likelihood of exhibiting systemic adverse events ($\beta=2.47$) and especially if they were female. The vaccine platform type was not significant for the model (Table 6).

Table 6. Multiple linear regression model for the onset of systemic AEs following the 1st and 2nd dose of a vaccine.

Model	Unstandardized Coefficients		Wald	df	Sig.	Exp(B)	95% Confidence Interval for B	
	B	Std. Error					Lower Bound	Upper Bound
Following the first dose administration								
(Constant)	1.271	0.401	10.040	1	0.002	3.566		
Age groups	0.834	0.352	5.606	1	**0.018**	2.303	1.154	4.595
Gender	-0.217	0.305	0.505	1	0.478	0.805	0.442	1.465
Vaccine platform	-1.280	0.397	10.404	1	**0.001**	0.278	0.128	0.605
Following the second dose administration								
(Constant)	0.528	0.399	1.757	1	0.185	1.696		
Age groups	0.904	0.371	5.934	1	**0.015**	2.468	1.193	5.107
Gender	-0.646	0.301	4.616	1	**0.032**	0.524	0.291	0.945
Vaccine platform	0.055	0.389	0.020	1	0.888	1.056	0.493	2.264

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4. Discussion

The adverse events following COVID-19 vaccination among Bulgarian healthcare workers were investigated in this cross-sectional online-based study. Overall, our findings are consistent with those of other survey-based studies from Central Europe, including Germany [14], the Czech Republic [15], and Slovakia [17].

After being vaccinated with any of the mRNA-based and viral vector-based vaccines, a high proportion of the HCW reported at least one local adverse event (92.6% for mRNA-based vaccines vs 88.7% for viral-vector based vaccines for the first dose of a COVID-19 vaccine and 85.8% for mRNA-based vaccine and 84.9% for viral-vector based for the second dose of a vaccine). Similar to other studies, there were more reports of local adverse events after the first dose of the vaccine than after the second dose [18,19].

In our study, the most common local adverse events reported by participants were pain and redness at the injection site. These cutaneous reactions are common not only after COVID-19 vaccination but after any other vaccines [20], and our results concurs with other studies on adverse events following COVID-19 vaccination [19,21,22]. Pain at the injection site was reported by 91.3% of the respondents that is higher than the results of other similar studies [18]. These variation discrepancies can be attributed to differences in study design [23], study population (demographic data such as age), psychological differences in symptom reporting, and pain threshold [24]. Consistent with other studies, only a minority of the respondents (8/253, 3.2%) rated the pain as severe [25,26]. In accordance with other similar surveys, redness and swelling were reported with much lower frequency after both doses [18,27].

Among participants in total 73.9% of them reported at least one post-vaccination systemic adverse event. Fatigue, headache and chills were the most commonly reported systemic reactions after vaccination. Fever can occur in about 10% or more of vaccines [28]. Other systemic reactions (e.g. headache) are also common occurrences after vaccination. After vaccination with the bivalent HPV vaccine for an instance fatigue and headache can be up reported by up to 33.0% and 30.0% of the vaccines respectively [28].

The incidence of systemic reactions among the recipients of mRNA-vaccine increased after the second dose, which is consistent with previous research [27,29,30]. Our findings demonstrated that systemic adverse events after both doses of COVID-19 vaccine were less common in the mRNA-based vaccine recipients compared to the viral-vector vaccine recipients, and these results are in line with other studies published in the literature [18,31]. The SAEs with highest reported frequency were fatigue, chills, headache, and muscle pains that were also discussed in other articles on the topic [15,18,26,32]. Our analysis points to COVID-19 vaccines as the cause of mostly minor and self-resolving systemic adverse reactions.

Gender-related comparison revealed that females had a higher prevalence of local adverse events after the first dose of a COVID-19 vaccine, which corresponds with a similar study [15]. Female HCWs in Italy were reported to have more potent immune response to the vaccine and serological parameters following the COVID-19 vaccination, implying a link with more frequent post-vaccination SAEs [33].

Local and systemic adverse events were more common in HCW under 30 years of age in both mRNA-recipients and viral-vector-based recipients, which is consistent with other similar studies [18,27,34]. Lower immune response is significantly associated with lower incidence of adverse events in older adults [35]. According to Dziedzic et al. [36], the most important factors predisposing to adverse events after both mRNA-based and viral-vector based vaccines were female gender, young age, presence of comorbidities and systemic medications use.

5. Conclusions

The reported adverse events in our study were mild, although they occurred in a high share of the respondents after both doses of the mRNA-based and the viral vector-based COVID-19 vaccines. Adverse events were reported more frequently in females and the age group of under 30 years of age.

No serious AEs attributable to the vaccines were reported. The results from our study added more evidence that mRNA-based and viral-vector based vaccines are generally safe.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: title; Table S1: title; Video S1: title.

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