

ADVERSE EVENTS FOLLOWING VACCINATION WITH A VIRAL VECTOR-BASED VACCINE - A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: The effectiveness and safety of recently implemented COVID-19 vaccine platforms are often compared since the launch of the mass vaccination campaign worldwide. The aim of the present study is to assess the prevalence of adverse events (AEs) occurring after vaccination with the two viral vector-based vaccines authorized in the European Union to prevent COVID-19.

Materials and methods: A survey was carried out among adults who have completed vaccination with either of the viral vector-based vaccine approved for use in Bulgaria ChAdOx1-S nCoV-19 vaccine (commonly known as Astra Zeneca or Vaxzevria) or Ad26.COV2S vaccine (commonly known as Janssen or JCOVDEN). For the data analysis, standard descriptive statistics was used. Quantitative variables are presented by the mean and standard deviation (mean \pm SD) or median (25th percentile; 75th percentile). Qualitative variables are presented as numbers absolute/relative frequencies totals and percentages. The Kolmogorov-Smirnov test was used to obtain information regarding the distribution of the sampled patients. The chi-square test for independence was used to determine whether differences between observed and theoretical distributions existed.

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Results: In total 314 respondents took part in the study. Of them, 273 (86.9%) reported at least one local AE after the first dose of a vaccine, and the prevalence among the ChAdOx1-S vaccine group was significantly higher (88.5%) than in the Ad26.COV2.S vaccine group (59.2%) (Pearson χ^2 test=19.942, $p=0.000$). The most common systemic AEs after administration of a viral vector-based vaccine were chills (77.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.), fatigue (76.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.), and headache (62.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.). Those adverse events appeared significantly more often in participants vaccinated with the ChAdOx1-S vaccine.

Conclusion: The analysis of the collected data proves that although common, AEs following vaccination with vector-based products are classified as mild and usually resolve within 48 hours of dose administration.

INTRODUCTION

The Effectiveness and safety of recently implemented COVID-19 vaccine platforms are often compared since the launch of the mass vaccination campaign worldwide. mRNA and viral vector-based vaccines were the first type of pharmaceutical prophylactic products to obtain authorization in the EU for protection against COVID-19. However, due to various reasons, concerns regarding their safety are often expressed in the public. Cases of thrombotic thrombocytopenia reported following the administration of viral vector-based vaccines prompted different countries to pause or suspend immunization with those pharmaceutical products [1], further eroding trust in immunization [2]. On the other hand, providing a choice of a vaccine to be administered was observed to have the potential to increase immunization acceptance levels [3].

According to immunization records in Bulgaria, 21.88% of the COVID-19 vaccine doses administered in the country pto viral vector-based vaccines. Vaccination with viral vector-based vaccines in Bulgaria started in week 5 of 2021 with the administration of the first 10 doses of the ChAdOx1-S nCoV-19 vaccine (commonly known as Astra Zeneca or Vaxzevria). In week 19 of 2021 first 398 doses of Ad26.COV2.S vaccine (commonly known as Janssen or JCOVDEN) were administered in the country. The total doses

administered until 26 January 2023 of Vaxzevria and JCOVDEN in Bulgaria are 478 524 and 514 492, respectively. The total number of doses administered of the two viral vector-based vaccines within the EU/EEA zone until the end of January 2023 is respectively 84 904 755 and 31 040 330 [4].

Although differences in immunization schemes were observed across countries, in Bulgaria the Vaxzevria vaccine was authorized for application in a 2-dose regime, while the JCOVDEN product was licensed to be administered as a single-dose vaccine, in line with the recommendations issued by the European Medicines Agency (EMA) [5, 6].

Both initial and post-roll-out safety assessment studies on available vaccines showed that in general no severe adverse events (AEs) have been observed after the administration of COVID-19 vaccines [7, 8, 9]. However, both local and systemic AEs appear to be more common and with a stronger presentation of systemic side effects in groups that received viral vector-based vaccines [7, 9, 10]. While adverse events following vaccination have been recorded more often after the second dose administration of mRNA products, AEs following vector-based vaccines are associated predominantly with first doses [7, 9]. Furthermore, the risk following administrations of the JCOVDEN product has been evaluated as greater than the one from mRNA vaccines for all events but anaphylaxis [12]. Similar observations were reported regarding the risk of systemic AEs after administration of Vaxzevria in comparison with the mRNA product Pfizer-BioNTech [13]. Females have been reported to be more commonly affected by AEs following vector-based vaccine administration [8, 10] while the risk of severe AEs was significantly higher for males [12].

Given the reported results that show a stronger association between the administration of viral vector-based vaccines and the presentation of AEs, we consider it important to understand the prevalence of vaccine reactions per category. The aim of the present study is to assess the prevalence of AEs occurring after vaccination among adults vaccinated with one of the possible vector-based vaccines. The study will help to improve pharmacovigilance efforts and thus it is intended to increase trust in vaccine safety.

MATERIALS AND METHODS

The survey is designed as a cross-sectional study among adults above 18 years of age, residing in one of the regions in Bulgaria – Plovdiv, vaccinated with one of the available viral vector-based vaccines and who have completed the vaccination regime. Before receiving a COVID-19 vaccine, prospective respondents were asked if they would be willing to participate as well as for their email addresses. Those willing to participate in the study received an online questionnaire in which they had the opportunity to report the AEs occurring after vaccination.

The questionnaire was created using the Microsoft Forms Platform and it consisted of four sections. The respondents filled out an informed consent on the first page of the questionnaire. An opt-out option was included. The first section of the form consisted of questions regarding the demographics of the participants, comorbidities, AEs following previous vaccinations and information about prior COVID-19 infection.

The second and third sections of the questionnaire collected information about the type of vaccine administered and the local and systemic AEs following the administration of the first and second dose of a vaccine, respectively. In those sections the participants had the possibility to report information about the type of AE, the time of occurrence (24 hours after vaccination, 24–48 hours after vaccination, and more than 72 hours after vaccination), and the severity of the reaction (mild, moderate, or severe). In the fourth section of the questionnaire the participants had the option to report other AEs that might have occurred or other details they considered important regarding vaccination.

For the analysis of the data standard descriptive statistics was used. Quantitative variables are presented by the mean and standard deviation (mean \pm SD) or median (25th percentile; 75th percentile). Qualitative variables are presented as numbers absolute/relative frequencies totals and percentages. The Kolmogorov-Smirnov test was used to obtain information regarding the distribution of the sampled patients. The chi-square test for independence was used to determine whether differences between observed and theoretical distributions existed.

RESULTS

In total 314 respondents filled out the questionnaire and took part in the study. The median age of the respondents was 44 years (35 y.o.; 54 y.o.) and they were predominantly females (67.2%). Looking further in the distribution of the age among the participants depending on the gender the median age of the female respondents was 43 years (32 y.o.; 51 y.o.) vs. 31 years (22 y.o.; 47 y.o.). Almost one-quarter of the participants in the study (23.2%) reported having at least one comorbidity. The most commonly reported comorbidities were arterial hypertension (n=23, 31.5%) and diabetes (n=21, 28.7%). A relatively small number of the respondents had been infected with COVID-19 before the administration of the vaccine (n=35, 11.1%).

The majority of the study participants have decided to receive the ChAdOx1-S nCoV-19 commonly known as Vaxzevria (n=287, 91.4%) and the rest have been vaccinated with the Ad26.COVS2.S, commonly known as JCOVDEN vaccine (n=27, 8.6%). The local adverse

AEs following the administration of 1st and 2nd doses of viral vector-based vaccines are presented in Table 2.

A total of 273 (86.9%) of participants reported at least one local AE after the first dose of a vaccine, and the prevalence among the ChAdOx1-S vaccine group was significantly higher (88.5%) than in the Ad26.COVS2.S vaccine group (59.2%) (Pearson χ^2 test=19.942, p=0.000). The most common local AEs after vaccination with both vaccines was pain at the injection spot (88.5% ChAdOx1-S and 59.2 % for the Ad26.COVS2.S vaccine respectively). The majority of respondents graded the pain as mild (63.4% for the ChAdOx1-S vaccine and 68.7 % for the Ad26.COVS2.S vaccine). Regarding the time of occurrence, most of the participants reported that they experienced pain at the injection spot around 24 hours after administration of the vaccine (78.7% for ChAdOx1-S and 62.5% for Ad26.COVS2.S vaccine).

The local reactions after the second dose of a viral vector-based vaccine were studied for the ChAdOx1-S

Table 1. Demographic characteristics of the respondents (n=314).

Variable	Results
Gender, n (%)	
Male	103 (32.4)
Female	211 (62.7)
Age, median (25th percentile; 75th percentile)	44 (35 y.o.; 54 y.o.)
Comorbidities, n (%)	
Yes	73 (23.2)
No	241 (76.8)
Have you been infected with COVID-19, n (%)?	
Yes	35 (11.1)
No	279 (89.9)

Table 2. Local AEs following the administration of the 1st and 2nd dose of a viral vector-based vaccine

Variables	1 st dose		p-value	2 nd dose
	ChAdOx1-S n=287	Ad26.COVS2.S n=27		ChAdOx1-S n=287
Pain n (%)	254 (88.5)	16 (59.2)	0.000	151 (48.1)
Edema, n (%)	69 (24.0)	2 (7.4)	0.000	22 (7.0)
Redness, n (%)	64 (22.3)	2 (7.4)	0.000	30 (9.6)
Rash, n (%)	8 (2.8)	0 (0)	0.000	3 (1.0)
Local reactions, n (%)	257 (89.5)	16 (59.2)	0.000	154 (49.0)

vaccine only as the vaccination scheme is a two-dose regime. The share of respondents reporting local AEs was lower (n=154, 49%). Again, the most common AE was pain at the injection site (n=151, 48.1%). The majority of respondents graded the pain as mild (n=131, 85.1%) and occurring predominantly 24 hours after administration of the second dose of the vaccine (n=130, 84.4%). The occurrence of local AEs after the first dose of a ChAdOx1-S vaccine was significantly higher compared to the second dose administration (1st dose- 89.5% vs 49 %, p<0.000).

SYSTEMIC REACTIONS AFTER VACCINATION

The most common systemic AEs after administration of a viral vector-based vaccine were chills (77.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.) fatigue (76.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.), and headache (62.3% for ChAdOx1-S and 25.9% for Ad26.COV2.S.). Those AEs appear significantly more often in participants vaccinated with the ChAdOx1-S vaccine. The same as with the local AEs, those adverse events were graded by most of the respondents as mild and occurring in the first 24 hours after administration of the vaccine. We can also note that the systemic AEs after the second dose of ChAdOx1-S vaccine were more common but were not statistically significantly higher compared with the systemic reactions after the first dose.

Looking into the distribution of AEs in terms of gender females were predominantly more often reporting local AEs compared to males (90.0% vs

80.2%, Pearson χ^2 test=6.139, p=0.046). Regarding the systemic reactions following immunization there wasn't a statistically significant difference in their occurrence between females and males (Pearson χ^2 test=0.703, p=0.704).

Regarding the distribution of AEs depending on the age, we established that local AEs were being reported significantly more frequently by respondents under 50 years of age (91.4% for <50 y.o. vs. 74.1% for >50 y.o., Pearson χ^2 test=15 923, p=0.000). For the systemic AEs, we also observed higher prevalence in the under 50 years of age group compared to the older participants (92.2% for <50 y.o. vs. 67.9 % for >50 y.o., Pearson χ^2 test=29 634, p=0.000). Regarding the possibility of a higher share of AEs in participants with comorbidities we were unable to find a statistically significant higher prevalence of local and systemic AEs in this group. When further analyzing the data we couldn't find a higher prevalence of AEs after the first or second dose of the vaccine among participants who reported having a previous COVID-19 infection compared to respondents who have not contracted COVID-19 yet (p=0.556).

DISCUSSION

This study was designed to evaluate the prevalence of local and systemic AEs after the administration of viral vector-based vaccines through self-reporting of experienced AEs. Within the limitations of our survey, the results obtained suggest that age, gender and type of vaccine received were the main

Table 3. Systemic AEs following the administration of the 1st and 2nd dose of a viral vector-based vaccine

Variables	1st dose		p-value	2nd dose
	ChAdOx1 –S n=287	Ad26.COV2.S. n=27		ChAdOx1 nCoV-19 n=287
Chills n (%)	222 (77.3)	7 (25.9)	0.000	229 (79.8)
Fatigue, n (%)	219 (76.3)	7 (25.9)	0.000	226 (78.7)
Headache, n (%)	179 (62.3)	7 (25.9)	0.000	186 (64.8)
Muscle pains, n (%)	183 (63.7)	2 (7.4)	0.000	185 (64.4)
Joint pains, n (%)	126 (43.9)	2 (7.4)	0.000	128 (44.5)
Nausea/vomiting, n (%)	42 (14.6)	2 (7.4)	0.301	44 (15.3)
Diarrhea, n (%)	14 (4.8)	0 (0)	0.240	14 (4.8)
Systemic reactions, n (%)	258 (89.9)	12 (44.4)	0.000	270 (94.0)

predictors and confounders affecting the prevalence of AEs.

Considering the study, a substantial proportion of our participants reported at least one local AE and this type of events were significantly more common in the group of ChAdOx-1 nCoV-19 vaccine recipients than the Ad26.COVS.2.S. recipients (88.5% vs 59.2 % respectively $p < 0.000$). The main local AEs experienced by most of the respondents was pain at the injection spot which correlates with similar studies [14]. The most frequently reported AEs in an interim review of four clinical studies for the ChAdOx1 nCoV-19 vaccine were tenderness at the injection site (63.7%), pain at the injection site (54.2%), headache (52.6%), and fatigue (53.1%) [15]. Most of the local AEs were mild to moderate in severity and subsided quickly after vaccination [15, 16]. Among the recipients of the JCOVDEN vaccine, the prevalence of local AEs was lower compared to the Vaxzevria group but it was comparable to the data of the report of the Centres for Disease Control and Prevention regarding the local and systemic reactions following vaccination with Ad26.COVS.2.S. vaccine [17]. The findings from the ENSEMBLE research and the Summary of Product Characteristics of JCOVDEN vaccine indicate that the most frequent side effects include discomfort, erythema, and edema at the injection site. Headache, exhaustion, myalgia, nausea, fever, and contraindication in individuals with severe anaphylactic reactions are additional systemic adverse effects. Most of these side effects appeared within seven days of vaccination. The common AEs following vaccination with the JCOVDEN vaccine include pain at the injection site, headaches, exhaustion, muscular aches, and nausea. These reactions usually subside on their own after a day or two [18, 19].

In our study, the most common systemic AEs were chills, fatigue and headache. A Similar study in South Korea reported that chills were registered in 63.5% of the respondents whereas headache was reported in 67.4% of the cases [10]. Another study also reports chills, fatigue and headache in a high share of the respondents [20]. ChAdOx1 nCoV-19 vaccine's safety report from the European Medicines Agency (EMA) listed headache (52.7%), fatigue (53%), malaise (44.4%), muscular discomfort (43.9%), fever (41.1%),

chills (32.2%), and joint pain (26.6%) as common systemic AEs [5].

Female gender was associated with a higher prevalence of local and systemic adverse events in our study. Similar results were reported by Riad et al. [21] and Alghamdie et al. [22]. The suggested explanations for the gender disparities in self-reported COVID-19 vaccination side effects are that women have a stronger immunological response and a lower pain threshold. The adverse events following COVID-19 vaccination on different genders should be the subject of future study [23, 24].

Both local and systemic post-vaccination AEs were considerably more prevalent among recipients aged < 50 years. According to Menni et al. research, adverse events following the administration of both mRNA-based and viral vector-based vaccines were much more common in British people aged 55 or younger [25]. The fact that AEs are a by-product of the excessive synthesis of type I interferon (IFN-I), which takes place to start an efficient immune response to the invading virus, can explain why AEs are more likely to develop in young adults [26]. Females and younger adults were shown to have more potent IFN-I production [26, 27].

In our study, we found that the presence of comorbidities was not associated with higher incidence and severity of AEs following vaccination with a viral vector-based vaccine. In a similar study, Beg et al. [28] in Pakistan reported that participants with comorbidities did not experience more AEs compared to participants with no history of such diseases.

Several studies have found that persons with prior SARS-CoV-2 infection experience more severe post-vaccination AEs after receiving the first dose of the COVID-19 vaccine and less severe but more frequent reactions after receiving the second dose [29-31]. In our study, we were unable to find such association.

CONCLUSION:

The results of the study confirm the findings described in the literature reviewed. The prevalence of AEs appears comparable to the values reported from other vaccinated populations with viral vector-based vaccine. The analysis of the collected

data proves that although common, AEs following vaccination with vector-based products are classified as mild and usually resolve within 48 hours of dose administration.

COMPLIANCE WITH ETHICS REQUIREMENTS:

“The authors declare no conflict of interest regarding this article “.

“The authors declare that all the procedures and experiments of this study were in accordance with the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study”.

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