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Safety and Reactogenicity of the ChAdOx1 (AZD1222) COVID-19 Vaccine in Saudi Arabia

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ABSTRACT

Introduction: The Kingdom of Saudi Arabia was one of the first countries to implement a COVID-19 vaccination program. This study estimated the safety and reactogenicity of the ChAdOx1-S vaccine after the first dose administered to adults.

Methods: This cross-sectional study included 1592 randomly selected vaccinees from April to May 2021. A questionnaire was delivered to the vaccinees via phone calls 7 and 21 days after the first vaccine dose.

Results: Of the 1592 vaccinees who had the first dose, the mean age was 37.4 (± 9.6) years and 81% were males. Of all the vaccinees, 553 (34.7%) reported an adverse reaction on the first telephone call. The most common symptoms were: pain at the site of injection (485, 30.5%), musculoskeletal symptoms (438, 27.5%), skin rash (307, 19.2%), gastrointestinal symptoms (379, 23.8%) and fever (498, 31.3%). Men were more likely to report fever (76.9% vs. 23.1%; P = 0.005), skin rash (81.1% vs. 18.9%, P = 0.005) and pain at the injection site (77.3% vs. 22.7%, P < 0.0001). Post-vaccine COVID-19 infection was 0.5% and there were no hospitalizations.

Conclusion: This study observed no major side effects of the ChAdOx1-S vaccine and no reported breakthrough infection during the observation period.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) caused the current Coronavirus Disease 2019 (COVID-19) pandemic. The pandemic has resulted in a significant disruption in social lives and has had a major economic impact. Countries around the globe have taken extraordinary measures to combat the disease. The results from phase III clinical trials have shown that both the Pfizer-BioNTech messenger RNA (mRNA) vaccine (BNT162b2) and the Oxford-AstraZeneca adenovirus vector vaccine ChAdOx1-S, also known as Ad26.COV2.S, are very effective in decreasing disease and mortality with a planned two-dose schedule (Polack et al., 2020). In addition, the ChAdOx1-S trial proposed that increasing the dosing interval between the first and the second dose provides increased protection (Voysey et al., 2021). The efficacy of a single dose of the BNT162b2 trial data suggests that a single dose of this vaccine has an efficacy of 92.6% in the early post-vaccination period (Vergnes, 2021). It had been also shown that extending the interval between the first and the second dose results in an enhanced immune response (Ledgerwood et al., 2013). The emergence of SARS-CoV-2 variants of concerns such as the alpha, beta and delta variants has caused significant attention, as a few of

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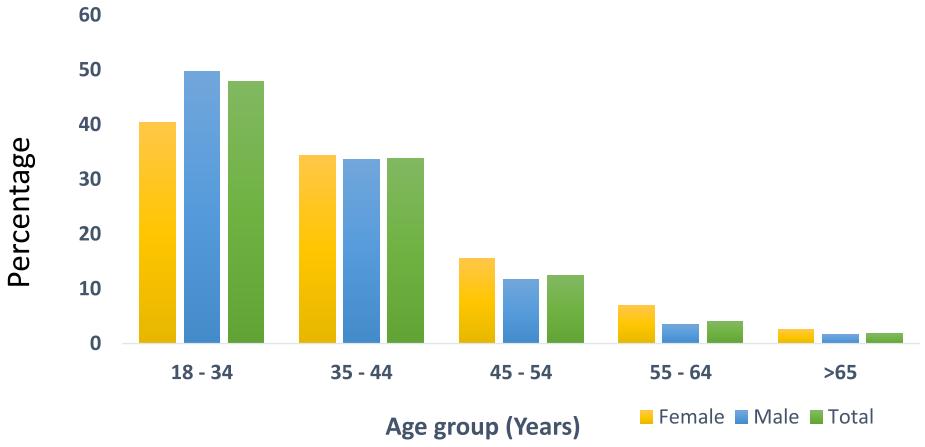

Figure 1. Age distribution percentages of the total, female and male vaccinees.

these variants such as the alpha variant are 50% more infectious (Davies et al., 2020). This variant within the B.1.1.7 lineage has several mutations; the most significant is N501Y within the S protein. The BNT162b2 vaccine has been shown to neutralize the N501 and Y501 viruses in vitro (Xie et al., 2021).

The Kingdom of Saudi Arabia (KSA) was one of the first countries to implement several preventive measures to halt the spread of the disease (Al-Tawfiq et al., 2020; Al-Tawfiq and Memish, 2020). In addition, the KSA was one of the first countries to introduce COVID-19 vaccination programs following approval of the BNT162b2 vaccine (Assiri et al., 2021). The program then encompassed the ChAdOx1-S vaccine with scale-up of activities over time (Assiri et al., 2021). As part of the vaccine rollout, the KSA planned a phased approach to initially target the most vulnerable populations, including first responders, healthcare workers, individuals with comorbid illnesses, and the elderly. A second and third phase will follow, with the goal of vaccinating at least 70% of the whole population. The Ministry of Health requested that the population register to receive the vaccine via online platforms and smartphone applications, and provided a supportive digital infrastructure for doing so. Vaccines were distributed within major cities. Mass vaccination centers were erected across the country to meet the storage conditions of the vaccines (Assiri et al., 2021).

The vaccination campaign in the KSA was started on 17 December 2020 with the Pfizer- BioNTech vaccine and in February 2021 with the introduction of the ChAdOx1-S vaccine (Assiri et al., 2021). The KSA opened additional centers to accommodate and speed up the vaccination program (Assiri et al., 2021). The vaccination activity at the King Fahd Military complex started on 22 February 2021, and consisted of five clinics with an initial number of 1000 vaccinees per day. A total of > 50,000 vaccine doses were given by the end of April 2021. Later on, the clinics were also opened for all Saudi Arabian residents. This study presents the initial experience of vaccination and reports the reactogenicity among vaccinated individuals as well as the efficacy within 30 days of vaccination.

Materials and Methods

This was a phone call-based questionnaire and members of the study group called individuals who received the first dose of the ChAdOx1 (AZD1222) COVID-19 vaccine at the King Fahd Military complex between 10 April and 20 May 2021 when a total of 29,355 first dose vaccines were administered. The respondents who agreed to participate gave verbal consent and their responses were included anonymously. The study included a population who received their vaccine at King Fahad Military Medical complex, Dhahran. The questionnaire was designed and delivered to the candidates via phone calls (hospital Avaya System). One part of the survey covered demographics of the vaccinees, including: nationality, sex, age, and earlier infection with SARS-CoV-2. The second part of the study inquired about any reactions to the COVID-19 vaccine, and timing of these side-effects. The phone calls were performed twice: the first was 7 days and the second was 21 days after receiving the vaccine.

Table 1
Overall rate of reactogenicity to the ChAdOx1 (AZD1222) COVID-19 vaccine.

	Frequency	Percentage
Any adverse event	553	34.7
Pain at the site of injection	485	30.5
Musculoskeletal (joint pain, myalgia)	438	27.5
Skin rash	307	19.3
Gastrointestinal (abdominal pain, diarrhea, vomiting)	379	23.8
Fever	498	31.3
Cardiac disorder (palpitation, chest pain)	7	0.4
Central nervous system	3	0.2
Blood disorder (anemia, bleeding, thrombosis)	1	0.1
Respiratory (shortness of breath)	2	0.1
Hemodynamic vasovagal attack	2	0.1
Lymphadenopathy	0	0
Admission to hospital	0	0

Results

This study included 1592 vaccinees who received a first dose of the ChAdOx1-S vaccine; the mean age (± SD) was 37.4 (± 9.6) (range 19-83) years (Figure 1) and 81% were males. Of all the vaccinees, 553 (34.7%) reported a reaction on the first call and none reported any reaction on the second call (Table 1). The most common symptoms were: pain at the site of injection (485, 30.5%), musculoskeletal symptoms (438, 27.5%), skin rash (307, 19.2%), gastrointestinal symptoms (379, 23.8%) and fever (498, 31.3%).

Males were more likely to report fever (76.9% vs. 23.1%; P = 0.005), skin rash (81.1% vs. 18.9%, P = 0.005) and pain at the injection site (77.3% vs. 22.7%, P = 0.01). The rate of post-vaccine COVID-19 infection was 0.5% and there were no hospitalizations. Males had more reactions than females overall (76.7% vs. 23.3%; P = 0.001). In addition, there was a substantial difference in the rate of pain at the site of injection, skin rash and fever between males and females (Table 2). Males were more likely to report fever (76.9% vs. 23.1%; P = 0.005), skin rash (81.1% vs. 18.9%; P = 0.005) and pain at the injection site (77.3% vs. 22.7%; P < 0.0001).

Table 2
Univariate analysis of the local and systemic reactogenicity to ChAdOx1 (AZD1222) COVID-19 vaccine in relation to gender.

	Male		Female		Chi square	P-value	Confidence interval
	Frequency	Percentage	Frequency	Percentage			
Fever	383	76.9	115	23.1	111.54	< 0.0001	44.20 – 61.62
CNS	2	66.7	1	33.3	0.20	0.65	-43.12 – 75.53
GI (abdominal pain, diarrhea, vomiting)	314	82.8	65	17.2	113.54	< 0.0001	53.75 – 73.79
Blood disorder (anemia, bleeding, thrombosis)	0	0	1	100	-	-	-
Cardiac disorder (palpitation, chest pain)	3	42.9	4	57.1	0.12	0.73	-42.11 – 59.94
Musculoskeletal (joint pain, myalgia)	342	78.1	96	21.9	104.94	< 0.0001	45.82 – 64.38
Lymphadenopathy	-	-	-	-			
Respiratory (shortness of breath)	1	50	1	50	0.00	1.00	-62.99 – 62.99
Skin rash	249	81.1	58	18.9	85.34	< 0.0001	49.18 – 71.33
Hemodynamic vasovagal attack	0	0	2	100	-	-	-
Pain at the site of injection	375	77.3	110	22.7	111.10	< 0.0001	44.83 – 62.49
Any AEs	424	76.7	129	23.3	122.56	< 0.0001	44.34 – 60.88

CNS, central nervous system; AE, adverse event

Table 3
Reactogenicity to ChAdOx1 (AZD1222) COVID-19 vaccine in relation to age group (based on age group 18-34 years as the comparison group).

	Adverse events		95% CI		
	n/N (%)	OR	Lower	Upper	P-value
18 - 34	288/759 (38)	___	___	___	___
35 - 44	158/536 (29.5)	0.655	0.312	1.377	0.265
45 - 54	60/196 (31)	0.448	0.211	0.95	0.036*
55 - 64	33/65 (51)	0.473	0.215	1.041	0.063
≥ 65	14/29 (48)	1.105	0.46	2.653	0.823

Older individuals were more likely to report symptoms compared with the younger population (Table 3). However, based on the rate of reactogenicity in those aged 18-34 years as the comparison group, vaccinees aged => 65 years had an Odds Ratio of 1.105 (95% CI: 0.46-2.653; P = 0.823) and only those aged 45-54 years had an OR of 0.448 (95% CI: 0.211-0.95; P = 0.036), indicating fewer events. The overall rate of post-vaccine COVID-19 infection was 0.5% with no hospitalization during the study period.

Discussion

This study evaluated local and systemic responses to the first dose of the ChAdOx1 nCoV-19 (AZD1222) vaccine. The data showed that the vaccine was well tolerated, with differences in the reactogenicity between males and females. There were no reported COVID-19 infections, hospital admissions or deaths in the follow-up period. However, prevalence of the different variants in the KSA was not reported. In an international randomized, double-blind, placebo-controlled, phase 3 clinical trial a single dose of the Ad26.COV2.S vaccine showed 67% efficacy in preventing moderate to severe–critical COVID-19, as evaluated 14-28 days after dose administration. The efficacy against severe–critical COVID-19 was 77-85%, as evaluated 14-28 days after administration (Sadoff et al., 2021b).

The reactogenicity of the Ad26.COV2.S vaccine was short-lived, acceptable, transient, and lower in those who were relatively old (Sadoff et al., 2021a). In the current study, the first AstraZeneca-Oxford vaccine dose was associated with 34.7% of any type of reactogenicity symtoms and the incidence of pain at the local site of injection was 30.5%. In a phase 3 clinical trial, injection site pain was observed in 48.6% of the participants (Sadoff et al., 2021b). Pain at the injection site was commonly reported as the local reaction in the different COVID-19 vaccines (McDonald et al., 2021).

The most prevalent systemic symptoms included: fever, chills, headache, myalgia, and fatigue, as documented in a meta-analysis of all COVID-19 vaccines (McDonald et al., 2021). The administration of COVID-19 vaccination could be homologous (the first and second doses are of the same vaccine) or heterologous (different vaccines for the first and the second doses). The occurrence of post-COVID-19 symptoms was more pronounced if AstraZeneca and Pfizer vaccines were used sequentially, with a report of 41% having symptoms in those having Pfizer-BioNTech followed by the AstraZeneca-Oxford vaccines as compared with the 21% rate in the Pfizer-BioNTech for both doses (Shaw et al., 2021). However, the current study also observed that side effects were more common among males than females. The reactions and immunogenicity towards vaccinations are probably related to the immune response among the gender differences (Flanagan et al., 2017). The current study observed lower reactogenicity among those aged 45-54 years, with an OR of 0.448 (95% CI: 0.211-0.95; P = 0.036) indicating lower events compared to younger people. In a clinical trial, reactogenic symptoms were less common in those aged ≥ 56 years (Ramasamy et al., 2020). The variances might be secondary to the differences between the included population in the two reports. Severe reactogenicity (grade ≥ 3) and the need for hospitalization were not reported by the included vaccinees in this study. There were no reported anaphylactic reactions among AstraZeneca Oxford COVID-19 vaccine recipients (Moghimi, 2021). Previous studies have shown occurrence of anaphylactic reactions after the AstraZeneca COVID-19 vaccine and one study reported 28 thrombotic events at the time when 17 million people were vaccinated (Tobaiqy et al., 2021).

There were several limitations of the current study. The study was based on phone calls to vaccinees. The follow-up period was short and a longer duration is required to verify the prevention of SARS-CoV-2 infections. The study had a relatively small sample size and thus further studies with larger sample sizes are required to ascertain the safety profile. In addition, a multi-center evaluation of the vaccine from the KSA is needed to examine the reactogenicity profile of the introduced SARS-CoV-2 vaccines. The study was also predominated by males and a better male to female ratio is needed to confirm gender predominance.

In conclusion, this study observed no major side effects of the ChAdOx1-S vaccine and no reported breakthrough infection during the observation period. There was a difference in the reported symptoms between males and females and across the age groups.

Conflict of Interest

All authors have no conflict of interest to declare.

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None.

Ethical Approval

The IRB of the King Fahad Military Medical Complex approved the study (AFHER-IRB-2021-011).

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