Original Article

Cohort Event Monitoring for Safety Signal Detection in Adult Individuals 18 Years and Above after Immunisation with Coronavirus Disease 2019 Vaccines in Nigeria

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Abstract

Introduction: In Nigeria, immunisation with coronavirus disease 2019 (COVID-19) vaccines commenced in March 2021. COVISHIELD from AstraZeneca (AZ), a viral vector vaccine, was the brand administered in the first phase of vaccinations for pre-determined eligible adults 18 years and above. As more brands of COVID-19 vaccines have been introduced in Nigeria, identifying effective and safe vaccine brands is essential to pharmacovigilance and public health. The current study assessed the safety of the AZ-AZD1222 (ChAdOx1) COVID-19 vaccine in adults during the first phase of the vaccination exercise in Nigeria. **Methodology:** We conducted a descriptive analysis of safety data from selected vaccination sites across six states in Nigeria between June 2021 and September 2021. Respondents were monitored over 3 months for local and systemic reactions, as well as hospitalisation and mortality. Measures obtained from respondents include age, sex, pre-existing comorbidity, local and systemic reactions to vaccines, timing onset of reactions, hospitalisation and mortality. Bivariate and multivariable regression models were used to assess factors associated with vaccine reactogenicity. **Results:** A total of 1284 individuals were enrolled in the cohort study from the six selected states (Anambra, Borno, Edo, Katsina, Lagos and Plateau) representing the geopolitical zones of Nigeria. A total of 675 individuals or 52.6% of enrolees reported non-serious adverse effects, and only one individual or 0.08% reported a serious adverse event following immunisation in the first 7 days after vaccination. None of the enrolled participants reported adverse events requiring hospitalisation. The most common self-reported symptoms amongst vaccine recipients were tenderness at the injection site 20.9% and fever 20.3%. A majority of symptoms (55.5%) occurred on or before the 3rd day after vaccination. Multivariable logistic regression model showed that age 60 years or above (vs. 18–24 years) was significantly associated with a lower likelihood of a vaccine-related symptomatic reaction (adjusted odds ratio: 0.35; 95% confidence interval: 0.20–0.61). There was no reported mortality amongst all the enrolled and followed-up vaccine recipients. **Conclusion:** Our findings suggest that the safety profile of the AZ vaccine is acceptable, and the observed symptoms were mild and mostly within the first 3 days following vaccination. Vaccine recipients will benefit from counselling about potential transient reactions, and improving public awareness can potentially encourage the uptake of vaccines and reduce the spread of the COVID-19 pandemic.

Keywords: Adverse events, coronavirus, reactogenicity, vaccines

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Introduction

The development of effective vaccines is important in the implementation of preventive measures to curb the SARS-CoV-2 pandemic. Furthermore, providing equitable access to vaccines in the population, especially amongst the most vulnerable, is a crucial strategy to prevent the public health and economic impact of the pandemic.[1] Current vaccines for the coronavirus disease 2019 (COVID-19) include novel forms such as nucleic acid and viral vector-based vaccines, as well as older forms which include the traditional virus- and protein-based vaccines.[2] The National Immunisation Programmes (NIPs) in several countries have approved the use of certain vaccines, which are considered safe and efficacious following randomised controlled clinical trials. However, despite rigorous safety and efficacy evaluations during clinical trials, current SARS-CoV-2 vaccines might carry some risks with occasional adverse events when implemented at the population level.

While vaccines are usually recommended for otherwise healthy individuals, vaccine hesitancy can pose a barrier, thus the success of NIPs depends on public trust in vaccine safety.[3] Therefore, deliberate and rigorous vaccine safety surveillance is important for promoting public trust,[4] in countries with pharmacovigilance capacities. Furthermore, because of the scale of the COVID-19 disease, routine passive reporting systems might be insufficient for a thorough assessment during the COVID-19 vaccine introduction. Thus, active safety surveillance is recommended for a thorough and rigorous approach.[5]

In Nigeria, the administration of the COVID-19 vaccine started on 15 March 2021.[6] The vaccination took place with COVISHIELD from AstraZeneca (AZ)-AZD1222 (ChAdOx1), a viral vector vaccine manufactured by the Serum Institute of India.[7] As a result, the National Primary Health Care Development Agency instituted an active surveillance process to determine the safety of the AstraZeneca vaccine by commissioning a research-oriented monitoring programme to collect, collate, analyse and interpret data on the occurrence of adverse events following immunization (AEFI) with the AZ vaccine. Data from this research were deemed valuable to inform national policies regarding further administration of COVID-19 vaccines in Nigeria. The aim of the study was to monitor the safety of COVID-19 vaccines in enrolled adult individuals 18 years and above who have received the AZ COVID-19 vaccine in Nigeria for safety signal detection.

Methodology

Study design and settings

The study was a prospective single-arm cohort study in selected vaccination facilities across six selected states in Nigeria between June 2021 and September 2021.

Ethics

The Health Research and Ethics Committee (HREC) of the Lagos University Teaching Hospital approved the study (ADM/DCST/HREC/APP/4335), while permission and social approval were sought from the respective State Ministries of Health and Primary Health Care Boards.

Sample size

For sample size selection to assess reactogenicity, we calculated the precision using the Clopper–Pearson exact method.[8] Based on a sample size estimate of 1000 participants, we anticipated a reactogenicity prevalence of 5%–10% with a 2% precision. For the current study, a minimum of 1200 participants were planned nationwide [Appendix 1].

Study procedure

Multistage sampling was used to select vaccine recipients for the study.

One state was randomly selected from each of the six geopolitical zones in the country. The six states selected were Borno State for the Northeast geopolitical zone, Plateau State for the North Central geopolitical zone, Katsina for the Northwest geopolitical zone, Anambra State for the South-East geopolitical zone, Edo State for the South-South geopolitical zone and Lagos State for the South-West geopolitical zone. In each of the states, four local government areas (LGAs) were randomly selected, and two COVID-19 vaccination sites were selected per LGA by ballot technique. Study sites were selected from facilities approved for the administration of the COVID-19 vaccine [Appendix 2]. A total of 25 consenting vaccine recipients, who were consecutively recruited, were enrolled from each selected vaccination site. Thus, a total of 1200 vaccine recipients were to be enrolled in the study nationally. Participants were recruited amongst eligible adult individuals 18 years and above in the first phase of the vaccination roll-out programme. Study participation was strictly voluntary, with no penalties whatsoever for refusal to participate.

Staff in all approved vaccination sites had previously been trained on the reporting of AEFIs as well as signs and symptoms of adverse events of special interests. The selection criteria for the vaccination sites include the availability of sufficient human resources, access to a general hospital or tertiary hospital and access to computer for data collection at the site level.

Study staff were trained to collect sociodemographic information and immunisation details. Participants were to complete questionnaires at weekly intervals for 3 months following each vaccine dose administration (d0 [day of immunisation], d7, d14,…, d91). Participants in the reactogenicity subset were additionally followed up daily from the day of immunisation (d0) till 7 days after (d0 [day of immunisation], d1,…, d7).

Study variables

Age was assessed in years using five categories 18–24, 25–34, 35–44, 45–60 and 60 and above. Biological sex was obtained. Furthermore, a list of local and systemic reactions to vaccines, as well as the time of onset of the reaction, was obtained from the paper diary completed weekly by participants for 3 months. At the end of 3 months, hospitalisation and mortality were also investigated for each of the participants by telephone calls to the participants or next of kin.

Data analysis

Participants' demographic characteristics were analysed descriptively using frequencies and percentages. To determine the association between reactogenicity (local and systemic) and demographic factors, bivariate and multivariable logistic regression models were used. For the analyses, the outcome variable was in a binary form, as 'no reactogenicity' – 0 and 'reactogenicity' – 1; the primary independent variables were age category, sex and pre-existing comorbid condition. In these models, we adjusted for sociodemographic factors (age, sex and pre-existing comorbid condition). Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated for the logistic regression models. *P* values were considered statistically significant at <0.05. Data analyses were conducted using STATA by Stata Corp, College Station, Texas, USA.

Results

The study comprised a total of 1284 consenting participants from six states in Nigeria. Enrolled participants ranged from 193 in Katsina State to 247 in Edo State [Table 1]. A majority of the participants were aged 45–60 years (34%), with a mean age of 44.5 years (± 13.8). There were more males (60%) than females, with a male-to-female ratio of 1.5:1. About 6.2% (*n* = 79) of participants had underlying illnesses, and hypertension was the most common [*n* = 51, Table 1].

Table 2 demonstrates a total of 675 participants (52.6%) who reported non-serious adverse events, and only one participant (0.08%) reported a serious adverse event in the 1st week after vaccination. No study participants who reported an adverse event required hospitalisation.

Furthermore, Table 2 and Figure 1 show that the most common symptoms reported by participants were tenderness at injection site (20.9%) and fever (20.3%). A majority of the reported symptoms (55.5%) occurred on or before the 3rd day after vaccination, while 40.2% of the participants who indicated they had symptoms could not recall the time of onset of the reported symptoms [Table 2]. It is to be noted as shown in Table 2 that some participants reported multiple symptoms.

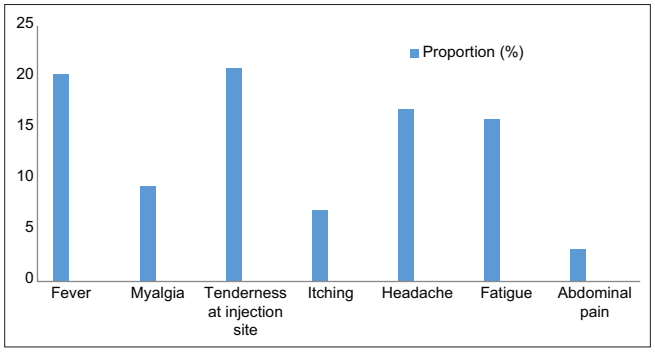

Figure 1: Distribution of reactogenicity symptoms. Local reactogenicity is here defined as the presence of pain, redness, warmth, swelling, hardening/induration, haematoma or itching at or near the injection site. Systemic reactogenicity is defined as the presence of fever, chills, headache, nausea, muscle ache, joint pain or malaise

The relative prevalence of local and systemic adverse events amongst participants who developed AEFIs is represented in percentages and proportions in Table 3 and Figure 2 to further demonstrate that tenderness at the injection site was the most common symptom, followed by fever and headache, respectively. AEFIs were mostly reported in younger age groups, with 65.1% of those aged 18–24 years reporting local and systemic adverse events compared to 38.5% of those aged above 60 years. There was also a decrease in the rate of local and systemic adverse events with increasing age.

In addition, Table 4 demonstrates that there was a reduced likelihood of reactogenicity with increasing age. On the binary regression model, participants aged 45–60 years had lower odds of reactogenicity compared to those aged 24 years or less (OR: 0.54; 95% CI: 0.33–0.89; *P*: 0.015). Furthermore, participants aged above 60 years had lower odds of reactogenicity compared to those aged 24 years or less (OR: 0.34; 95% CI: 0.20–0.58; *P*: < 0.001). Similarly, on the multivariate regression model, participants aged between 45 and 60 years had reduced odds of reactogenicity compared to those aged 24 years or less (OR: 0.56; 95% CI: 0.34–0.92; *P*: 0.021); and participants aged above 60 years

Table 1: General characteristics of study participants

Variables	*n* (%)
State of enrolment	
Lagos	240 (18.69)
Katsina	193 (15.03)
Plateau	205 (15.97)
Anambra	200 (15.58)
Borno	199 (15.50)
Edo	247 (19.24)
Age (years), mean±SD†	44.46±13.81
18-24	83 (6.46)
25-34	249 (19.39)
35-44	337 (26.25)
45-60	437 (34.03)
>60	174 (13.55)
Sex	
Male	781 (60.83)
Female	503 (39.17)
Pre-existing morbidities	
Present	79 (6.15)
Absent	1205 (93.85)
Type of pre-existing morbidities (*n*=79)	
Hypertension	51 (64.56)
Diabetes	7 (8.86)
Hypertension and diabetes	7 (8.86)
Others¶	14 (17.72)

†Four participants did not indicate their age, ¶Peptic ulcer disease, chronic liver disease, asthma, chronic obstructive pulmonary disease and prostatitis. SD: Standard deviation

Table 2: Distribution of adverse events

Symptom	*n* (%)
Adverse events	
No adverse event	608 (47.35)
Non-serious adverse event	675 (52.57)
Serious adverse event	1 (0.08)
Number of symptoms (*n*=676)	
1	337 (49.85)
2	167 (24.70)
≥3	172 (25.45)
Fever	
Present	260 (20.25)
Absent	1024 (79.75)
Muscle ache	
Present	120 (9.35)
Absent	1164 (90.65)
Tenderness at the injection site	
Present	268 (20.87)
Absent	1016 (79.13)
Itching at the injection site	
Present	90 (7.01)
Absent	1194 (92.99)
Headache	
Present	217 (16.90)
Absent	1067 (83.10)
Fatigue/general weakness	
Present	204 (15.89)
Absent	1080 (84.11)
Abdominal pains	
Present	41 (3.20)
Absent	1242 (96.80)
Median (range of symptoms)	1 (0-10)
Time to onset of symptoms (*n*=676)	
≤1 day	256 (37.87)
2-3 days	119 (17.60)
>3 days	29 (4.29)
Cannot recall time of symptom onset[t]	272 (40.23)

[t]Participants who could not recall time of onset, despite reporting symptoms after vaccination

Table 3: Relative proportion of symptoms by participants who presented with reactogenicity

Total AEFI	*n* (%) (*n*=676; 100%)
Fever	
Present	260 (38.46)
Absent	416 (61.54)
Muscle ache	
Present	120 (17.75)
Absent	556 (82.25)
Tenderness at injection site	
Present	268 (39.64)
Absent	408 (60.36)
Itching at injection site	
Present	90 (13.31)
Absent	586 (86.69)
Headache	
Present	217 (32.10)
Absent	459 (67.90)
Fatigue/general weakness	
Present	204 (30.18)
Absent	472 (69.82)
Abdominal pains	
Present	41 (6.07)
Absent	635 (93.93)

AEFI: Adverse event following immunisation

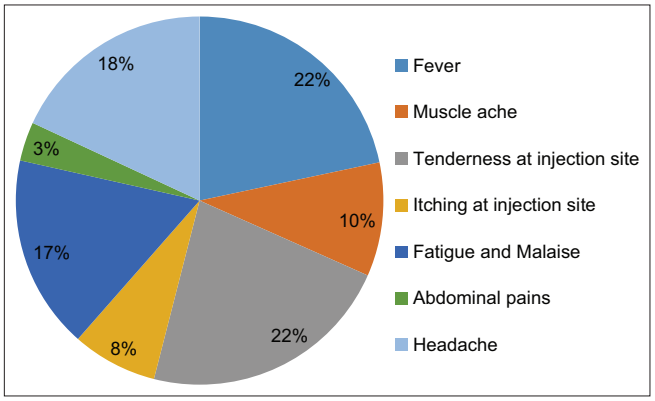

Figure 2: Relative proportion of symptoms by participants who presented with AEFI (*n* = 676). AEFI: Adverse events following immunization

had reduced odds of reactogenicity compared to those aged 24 years or less (OR: 0.35; 95% CI: 0.20–0.61; *P*: < 0.001), after adjusting for sex and pre-existing morbidities [Table 4]. There was no significant association between sex, pre-existing morbidities and reactogenicity on either the bivariate or multivariate regression model. Overall, there was no report of vaccine-related mortality during this study.

Discussion

The current study assessed the safety of the AZD1222 (ChAdOx1) vaccine in adults across six states in Nigeria. Our findings suggest that 52.6% of the participants developed local and systemic reactions to the AZD1222 vaccine within 7 days of administration. Amongst these, the majority presented with symptoms within 24 h, and the most common local and systemic events were tenderness at the injection site and fever, respectively. Other symptoms, such as headache and myalgia, were also reported, and these findings aligned with reports from prior safety trials of the AZD1222 vaccine and other mRNA vaccines.[9-15] Further, nine out of ten participants in the present study had non-serious (mild to moderate) adverse events. Thus, our results corroborate findings from the phase 3 clinical trial of the AZD1222 vaccine conducted in Chile, Peru and the United States.[9]

Concerning the severity of adverse events, in another randomised trial of the AZD1222 vaccine in the United Kingdom, South Africa and Brazil,[10,11] 0.7% of the vaccine group reported serious adverse events. This is higher than the current study's 0.08% incidence of serious adverse events. The disparity in the

Table 4: Association between demographic characteristics and vaccine reactogenicity

Variables	OR (95% CI)	*P*	aOR (95% CI)	*P*
Age				
18-24	1 (ref)		1 (ref)	
25-34	0.77 (0.46-1.30)	0.331	0.79 (0.47-1.33)	0.379
35-44	0.66 (0.40-1.09)	0.105	0.68 (0.41-1.13)	0.142
45-60	0.54 (0.33-0.89)	0.015*	0.56 (0.34-0.92)	0.021*
>60	0.34 (0.20-0.58)	<0.001*	0.35 (0.20-0.61)	<0.001*
Sex				
Female	1 (ref)		1 (ref)	
Male	1.22 (0.97-1.53)	0.082	1.17 (0.93-1.48)	0.171
Pre-existing morbidities				
No pre-existing morbidities	1 (ref)		1 (ref)	
Present	0.78 (0.49-1.23)	0.287	0.91 (0.57-1.45)	0.692

*P<0.05. OR: Odds ratio, aOR: Adjusted OR, CI: Confidence interval, Ref: Reference value

number of serious adverse events observed in the clinical trial compared to this study can be explained by the larger study population, possible genetic factors, as well as the very diverse demographic and ethnic background in the clinical trial.[10,11]

Previous reports from several countries have indicated the risk of vaccine-induced immune thrombotic thrombocytopenia following the administration of the ChAdOx1 AZD1222[16-19] and other candidate mRNA vaccines.[15,20,21] However, no such risk was observed in our study, and no thrombotic event with thrombocytopenia was identified. Therefore, we surmise that based on our current findings, the vaccine's benefits outweigh the risk.

We also found a reduced likelihood of reactogenicity with increasing age. This was demonstrated by the lower proportion of adverse events reported by participants between ages 45 and 60 years and those above 60 years, compared to those aged 24 years or less. Our findings are supported by prior studies using the AZD1222 (ChAdOx1) vaccine,[10] as well as other vaccine candidates.[13,22] This finding may be explained by the lower immune response generally found in older age groups compared to the younger. However, in the current study, there was no significant association between sex, the presence of a comorbidity and reactogenicity in the study population before and after adjusting for age. Nonetheless, participants with comorbidities had reduced odds of reactogenicity compared to those without.

The present study has several limitations. A randomly selected population from six states was enrolled for the study, and this population may not be generalisable to the entire national population that was vaccinated. In addition, we used a passive surveillance method, and recall bias may have contributed to underreporting amongst participants. However, this was reduced by daily contact with participants. Further, due to the absence of a centralised health record system in the country or across the study centres, participants who were lost to follow-up might have developed more severe symptoms or death outside the study time frame of 3 months. However, because of the centralised reporting surveillance system put in place by the National Primary Health Care Development Agency, these would have been reported if the participants presented at any tertiary, secondary or primary healthcare facility in the country. Finally, the current study does not address safety in vulnerable populations, such as minors (<18 years), and pregnant and lactating women who were ineligible at the time of the study. Future surveillance reports can improve our understanding of the AZD1222 vaccine safety by monitoring these vulnerable populations and including serological markers to determine antibody levels over time.

The ChAdOx1 AZD1222 vaccine was developed using a replication-deficient chimpanzee adenovirus vector ChAdOx1 which contained the SARS-COV-2, which has a structural surface glycoprotein antigen gene.[10] The safety profile has been corroborated by several trials,[9,12] which demonstrate the induction of neutralising and binding antibodies and the production of higher antibody titres after the second dose of the vaccine.[11,12] The vaccine has been administered to hundreds of million people in more than 100 countries, including Nigeria.[9]

Our findings suggest the safety of the AZD1222 (ChAdOx1) vaccine in adults above 18 years in Nigeria and validate prior results from clinical trials in other populations. An overwhelming majority of participants who developed solicited local and systemic reactions across the country presented with non-serious AEFIs. Only one case of a serious adverse event was reported, and no incident of death occurred throughout the follow-up. This study provides preliminary data on COVID-19 vaccination reactions from the African continent. Clearly, surveillance measures monitoring the response to COVID-19 vaccines at the population level are crucial for making risk–benefit assessments to support policies and provide early warning about safety concerns.

Conclusion

The findings from this study suggest that the safety profile of the AZ vaccine is good, and mild symptoms are expected on or before the 3rd day following vaccination. Vaccine recipients will benefit from counselling on symptoms to expect before vaccination, as this might encourage uptake in the population.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Sample size required to estimate reactogenicity prevalence with a specified level of precision with a 95% confidence interval using Clopper-Pearson exact calculation for the proportion

Sample size	Precision for different levels of reactogenicity prevalence						
	1%	2%	5%	10%	15%	25%	50%
200	0.03	0.03	0.04	0.05	0.06	0.07	0.07
500	0.01	0.02	0.02	0.03	0.03	0.04	0.04
1000	0.01	0.01	0.02	0.02	0.02	0.03	0.03

Appendix 2: Study sites

Site	LGAs	Immunisation sites
Katsina State	Katsina	
	Kankia	
	Kaita	
	Batagarawa	
Borno State	MMC	State Specialist Hospital
		Yerwa Maternal and Child Health Center
	Jere	University of Maiduguri Teaching Hospital
		Dalaram Clinic
	Konduga	Pompomari Clinic
		Maternal and Child Health Center Konduga
	Biu	Maternal and Child Health Center Biu
		Biu General Hospital
Plateau State	Jos North	JUTH, Jos North
		PSSH, Jos North
	Jos South	Bukuru Central, Jos South
		PHC Rayfield, Jos South
	Mangu	Gindiri, Mangu
		PHC Mangu, Mangu
	Shendam	PHC Yamini, Shendam
		Shendam A, Shendam
Edo State	Ovia North East	Okada PHC, Okada
		Oluku PHC, Oluku
	Orhionmwon	General Hospital, Abudu
		General Hospital, Igbanke
	Egor	Egua-Edaiken, Comprehensive Health Centre, Uselu Benin City
		University of Benin Teaching Hospital, Benin City
	Ikpoba-Okha	Evbomodu PHC, Aduwawa
		Ogbeson PHC, Old Agbor Road, Benin City
Anambra State	Anaocha	PHC Mgbudu, Ichida
		Model PHC Amatutu, Agulu
	Awka South	Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka
		Maternal and Child Health Clinic, Amawbia
	Nnewi North	Nnamdi Azikiwe University Teaching Hospital, Nnewi
		PHC Okponoegbu, Nnewi
	Onitsha North	General Hospital, Onitsha
		Inland Town Ogboye PHC, Onitsha
Lagos State	Ikeja (urban)	Lagos State University Teaching Hospital
		Oregun Primary Health Care Center
	Kosofe (urban)	Gbagada General Hosptial
		Ogudu PHC
	Ibeju Lekki (rural)	Ibeju Primary Healthcare Center
		Akodo Primary Healthcare Center
	Ikorodu (rural)	Ipakodo Primary Healthcare Center
		Igbogbo Primary Healthcare Center

PHC: Primary Health Centre, JUTH: Jos University Teaching Hospital, PSSH: Plateau State Specialist Hospital