Adverse effect profile of COVID-19 vaccine in Northern Nigeria: a prospective observational study

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Informed consent: informed consent was obtained from each participant before the commencement of the interview. The process included an explanation of the purpose of the study, the risks and benefits of participation, and the right to stop and withdraw at any time during the interview without any penalty or loss of privileges due to them.

Patient's consent for publication: the patients gave their written consent to use their personal data for the publication of this paper and any accompanying images.

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Abstract

In March 2021, the Nigerian Government approved Coronavirus 2019 (COVID-19) vaccines, including CHAd0x1 nCov-19, Ad26.Cov2.S, mRNA-1273 and BNT162b2. Many, including healthcare workers, expressed hesitancy due to potential adverse effects. We conducted an observational study to assess the adverse effects of post-vaccination. We followed vaccinated and unvaccinated cohorts daily for 7 days and then weekly for 3 weeks. We compared adverse effects between groups. Vaccinated participants were 21 times more likely to experience an adverse effect (Relative Risk, RR=21.30; 95% Confidence Interval, 95%CI=8.107-56.012) and 4 times more likely to experience systemic adverse effects (RR=3.97; 95%CI=1.70-9.27) when compared to unvaccinated participants. Female participants were significantly associated with the development of both local and systemic adverse effects, X^2=77.9% ($p \leq 0.001$) and X^2=47.1% (p=0.0037), respectively. Up to 81.6% of second-dose vaccine recipients compared to 68.4% of first-dose vaccine recipients developed at least one adverse effect, X^2=5.25 (p=0.071). None of the vaccinated participants developed severe adverse effects during the study period. Adverse effects from COVID-19 vaccination are common, but generally safe and tolerable. Females play a significant role in reporting adverse effects. Both systemic and local adverse effects are expected to resolve within a few days post-vaccination.

Introduction

As of the end of the first quarter of 2021, over 120 million people globally were infected with SARS-Cov-2, and nearly 3 million people died from Coronavirus 2019 (COVID-19).[1] Most vulnerable people included the elderly, male gender, and those with comorbidities.[2,3] As the pandemic continued to unfold, there was a notable negative impact on healthcare delivery and economies around the globe. Therefore, an effective and safe vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) would help the nations of the world to achieve herd immunity, prevent severe disease, and reduce health and economic crises.

Since the sequencing of the SARS-COV-2 virus,[4] researchers have rushed into the development of its vaccine. As of May 2021, six candidate vaccines (Pfizer/BioNTech, Moderna, Oxford-AstraZeneca AZD1222, J&J Ad26.COV2.S, Serum Institute of India, and Sinopharm) had received approval for emergency use,[5] and a couple of dozen were at various stages of trials.

Many safety concerns were raised during phase three and mass public administration of the vaccines. Most of these adverse effects are tolerable, however, a temporal stoppage of the vaccine administration order was made in certain countries to give room

for further studies.[6] Likewise, due to the effect of viral mutation, there were also issues regarding the effectiveness of certain vaccines against certain strains of the viruses, e.g., the Oxford-AstraZeneca vaccine against the South African variant.[7,8]

In phase three trials, SARS-CoV-2 vaccines were shown to be safe and efficacious against virus transmission. Results from the early deployment of Pfizer-BioNTech and Oxford-AstraZeneca had further shown a better safety profile compared to the report from the phase 3 trial.[9] However, the development of SARS-CoV-2 vaccines, just like many previous vaccines, came with many controversies concerning efficacy and adverse effects. In addition, findings of a rare blood clot formation in some recipients of Oxford-AstraZeneca and J&J Ad26.COV2.S added to the fears.[6,10] As a result, many people expressed hesitancy towards taking the vaccine. Therefore, this study sought to determine the local and systemic adverse effects of the SARS-CoV-2 vaccine among recipients in Northern states of Nigeria

Materials and Methods

This observational cohort study was carried out between January 19, 2022 and May 19, 2022 in two States of Northern Nigeria, Adamawa and Plateau. Data was collected from persons 18 years and above; cohorts of vaccinated and unvaccinated participants. The data collected from the vaccinated cohort included documentation of local and systemic adverse events after the initial dose and subsequent buster doses. A structured questionnaire was administered to both cohorts of vaccinated and unvaccinated participants. Vaccinated individuals were either recipients of the first dose or recipients of booster doses. Trained healthcare workers administered the questionnaire in person or through phone calls. The questionnaire was completed daily for the first week and then weekly during the following 4 weeks. Severe adverse effect was defined as an adverse event that results in any of the following conditions: death; life-threatening condition at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity. Information collected included biodata, contact information, comorbidity, previous diagnosis of COVID-19, name of vaccine administered, dose of vaccine received, and local and systemic adverse effects. Data was stored in Microsoft Excel and then transferred to the Statistical Package for Social Sciences (SPSS) (IBM Corp., Armonk, USA) for analysis.

Statistical analysis

Data analysis was done by IBM SPSS Statistics 21. The sociodemographic characteristics were expressed in frequencies and percentages. Chi-square test analysis was computed to assess the difference in occurrence of adverse effects among groups, including sex, age groups, vaccine platform received, and vaccine dose received. A p-value of <0.05 was taken to be statistically significant. The relative risk for the development of adverse effects between the cohort of vaccinated and unvaccinated participants was calculated.

Results

Sociodemographic characteristics

During the study period, we enrolled 315 participants, including 60 of the unvaccinated cohort (non-exposed) and 255 of the vaccinated cohort (exposed) from two northern states of Adamawa and Plateau. Of the 60 non-exposed, 5 were lost to follow-up 5 opted out. Of the 255 exposed, 26 were excluded from the final analysis due to loss to follow-up. The demographic characteristics details among participants are summarised in Table 1. Of the 229 vaccinated participants, 181 (79.0%) had an mRNA vaccine platform, and 48 (21.0%) had an adenoviral-vectored vaccine platform. Two adenoviral vaccines, CHAd0x1 nCov-19 (Oxford-AstraZeneca) and Ad26.Cov2.S (J&J), were used, and 2 mRNA vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer-Biotech), were used. Most vaccinated participants had Modana (46.3%), others included Pfizer (32.8%), AstraZeneca (14.3%), and J&J (2.9%).

Aggregate events (local and systemic) among all participants (vaccinated and unvaccinated)

On aggregate, the risk of developing adverse effects among vaccinated participants is more than 21 times among the vaccinated participants, 161 (70.3%) compared to unvaccinated participants 5 (10%), Relative Risk, RR (Confidence Interval, CI) =21.309 (8.107-56.012). Of the 229 vaccinated participants, 149 (65.1%) reported at least one local adverse effect. In comparison, none (0.00%) of the 50 unvaccinated participants developed local adverse effects, (p=0.0001). The risk of developing systemic clinical features is almost four times higher among vaccinated participants 91 (39.7%) than among unvaccinated participants 5 (10.0%), RR(CI)=3.97 (1.704-9.267).

Incidence of reported adverse events among the first-dose compared to the second-dose vaccine recipients

The incidence of adverse events among second and first-dose vaccine recipients was 81.6% and 68.4% respectively. The observed difference is not statistically significant, $X^2(1, N=229) =5.253$, p=0.071.

Vaccine-type related local and systemic clinical features among vaccinated participants

There was no significant relationship between the development of local adverse effects and the vaccine platform received. Adverse

Table 1. Sociodemographic characteristics of vaccinated participants (n=229).

Variable	Frequency (%)
Sex	
Male	122 (54.7)
Female	101 (45.3)
Age group in years	
<20	10 (4.4)
20-29	53 (23.3)
30-39	51 (22.5)
40-49	30 (13.2)
50-59	34 (14.0)
≥60	49 (21.6)
Healthcare worker	
No	193 (84.4)
Yes	33 (14.6)
Comorbidities	
No	178 (79.8)
Yes	45 (20.2)
Previous COVID-19 infection	
No	198 (93.8)
Yes	13 (6.2)
	211 (92.1)

effect among recipients of mRNA vaccines was 120 (66.3%), and among recipients of adenoviral-vector vaccines was 29 (60.4%), $X^2(1, N=229) = 0.557$, p=0.447. Over 70% of participants that had the Pfizer vaccine developed at least 1 local adverse effect compared to less than 40% of J & J, 65% of AstraZeneca, and 63.2% of Moderna vaccines, although did not differ significantly when compared, $X^2(1, N=229) =3.87$, p=0.276. Seventy-nine point six percent and 62.6% of the second and first-dose vaccine recipients respectively had at least one adverse effect and this differed significantly between the groups when compared, $X^2(1, N=220) =4.942$, p=0.027. Seventy-seven (42.5%) recipients of mRNA vaccines developed systemic clinical features compared to 14 (29.2%) recipients of adenoviral-vectored vaccines, but this observed difference was not statistically significant $X^2(1, N=229) =2.834$, p=0.092. Likewise, there was no significant relation between the type of vaccine and post-vaccination systemic adverse effect, $X^2(3, N=229) =3.232$, p=0.357. Pfizer 32 (42.7%), Moderna 45 (42.5%), J&J 3 (37.5%), and AstraZeneca 11 (27.5%). A statistically significant proportion of recipients of the first dose vaccine, 76 (44.4%), reported systemic post-vaccination clinical features compared to recipients of the second dose vaccine 13 (26.5%), $X^2(1, N=220) =5.074$, p=0.024.

Sociodemographic-related local and systemic adverse effects

In Table 2, a significantly higher proportion of vaccinated females (77.9%) reported at least one local adverse effect compared to vaccinated males (54.4%), $X^2(1, N=229) =13.77$, p=<0.001. Similarly, vaccinated female (47.1%) than male (33.6%) developed systemic adverse effects, $X^2(3, N=229) =4.330$, p=0.037.

Local and systemic adverse effects in the first four weeks

Figure 1 demonstrates the frequencies of systemic adverse effects among vaccinated participants in the first month, the first week, and the first day post-vaccination. Of the 151 person-week who developed local adverse effects, up to 48 (98%) were reported in the first week. Of the 279 person-days that developed local adverse effects, the majority, 140 (50.2%), were reported on day 1 compared to other days post-vaccination. Pain at the injection site

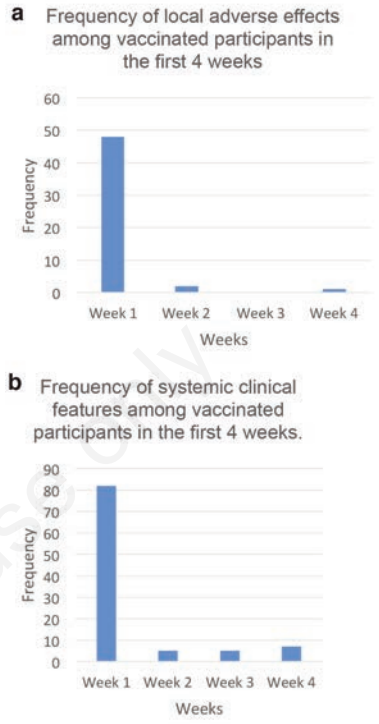

Figure 1. Frequencies of **a**) local and **b**) systemic adverse effects among vaccinated participants in the first 4 weeks.

Table 2. Sociodemographic-related local and systemic adverse effects among vaccinated participants during the study period.

Variable	Local adverse effects				Systemic adverse effects			
	Vaccinated participants (%)	Local adverse effects during the study period		X^2 (p-value)	Vaccinated participants (%)	Systemic adverse effects during the study period		X^2 (p-value)
		Yes	No			Yes	No	
Sex at birth								
Male	125 (54.6)	68 (54.4)	57 (45.6)	13.774 (<0.001)	125 (54.6)	42 (33.6)	83 (66.4)	4.330 (0.037)
Female	104 (45.4)	81 (77.9)	23 (22.1)		104 (45.4)	49 (47.1)	55 (52.9)	
Age group in years								
<20	10 (4.4)	8 (80.0)	2(20.0)	5.922 (0.314)	10 (4.4)	2 (20.0)	8 (80.0)	3.409 (0.637)
20-29	53 (23.3)	37 (69.8)	16 (30.2)		53 (23.3)	25 (47.2)	28 (52.8)	
30-39	51 (22.5)	36 (70.6)	15 (29.4)		51 (22.5)	22 (43.1)	29 (56.9)	
40-49	30 (13.2)	21 (70.0)	9 (30.0)		30 (13.2)	11 (36.7)	19 (63.3)	
50-59	34 (15.0)	15 (44.1)	19 (55.9)		34 (15.0)	13 (38.2)	21 (61.8)	
≥60	49 (21.6)	27 (55.1)	22 44.9)		49 (21.6)	18 (36.7)	31 (63.3)	
Healthcare worker								
Yes	33 (14.6)	24 (72.7)	9 (27.3)	1.116 (0.294)	33 (14.6)	11 (33.3)	22 (66.7)	0.579 (0.410)
No	93 (85.4)	122 (63.2)	71 (36.8)		193 (85.4)	79 (40.0)	114 (59.1)	
Comorbidity								
Yes	25 (79.8)	28 (62.2)	17 (37.8)	0.194 (0.659)	45 (20.2)	18 (40.0)	27 (60.0)	0.0001 (0.989)
No	45 (20.2)	117 (65.7)	61 (34.3)		178 (79.8)	71 (39.9)	107 (60.1)	
Previous COVID-19 infection								
Yes	13 (6.2)	7 (53.8)	6 (46.2)	1.139 (0.286)	13 (6.2)	4 (30.8)	9 (69.2)	0.382 (0.536)
No	198 (93.8)	135 (68.2)	63 (31.8)		198 (93.8)	78 (39.4)	120 (60.6)	

132 (59.7%) was the commonest local adverse effect and swelling at the injection site 29 (13.1%) was the second, others were redness 15 (6.8%), feeling of warm 19 (8.6%), bruise 4 (1.8%), swelling of regional lymph nodes 2 (0.9%), itching 2 (0.8%), and other local side effects 18 (8.1%), Figures 2 and 3. A similar trend was observed with systemic adverse effects. Of the 99 person-weeks that developed systemic clinical features, 82.8% did so in the first week. Up to 44% of the 175 person-days adverse effects were reported on the first day. Chills, 42 (28.2%), and low energy, 40 (26.8%), were the predominant adverse effects.

Discussion

In this prospective cohort study, conducted in two northern Nigerian States, we investigated the adverse effects following the administration of four different COVID-19 vaccines, CHAd0x1 nCov-19 (Oxford-AstraZeneca), Ad26.Cov2.S (J&J), mRNA-1273 (Moderna) and BNT162b2 (Pfizer-Biotech). The majority of the participants were less than 40 years old, lower than those of the study app in the UK study,[9] and this may be a reflection of the relatively younger population in the country. The prevalence of comorbidities among participants was 19%, similar to a study from Greece.[11] However, only 5.7% of vaccinated participants in our study were previously diagnosed with COVID-19 compared to 69.3% in the Greece study. This observed difference may be due to a high prevalence of COVID-19 among the general population in Greece at the time its study was conducted.

Many had concerns about possible severe adverse effects when COVID-19 vaccines were introduced for emergency use, and as a result, wide application was threatened by vaccine hesitancy. In our study, there was no recordable serious adverse event during the study period. This finding is consistent with other studies that found few or no cases of serious adverse events.[12-16] However, in phase III randomized clinical trials of Pfizer and Moderna mRNA vaccines in adults, both individual vaccines and when combined demonstrated that exposure increased the chance of serious adverse events.[17] The risk of developing at least one adverse event was 21 times among vaccinated participants (70%). This finding suggests a causal relationship between the development of adverse effects and the administration of the COVID-19 vaccine. This value is higher than the 54.6% recorded in a cross-sectional study in Mexico.[18] We also assessed the difference in the incidence of adverse effects among recipients of first dose and recipients of second dose vaccines. Though not statistically significant, the incidents of adverse events were higher among recipients of second dose vaccine compared to recipients of first dose vaccine, p=0.07. This finding suggests a higher reactogenicity of the vaccine following the booster dose. The majority of our participants had the Moderna vaccine, and our finding mirrors the Moderna COVID-19 Vaccine VRBPAC Briefing Document, a phase 3 randomised, stratified, observer-blind, placebo-controlled study that evaluated the efficacy, safety, and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. Local as well as systemic adverse effects were higher among recipients of the booster dose compared to first-dose recipients.[19] Wi Y. *et al.* also reported a higher incidence of adverse effects among recipients of booster doses of BNT162b2 (Pfizer-BioNTech), an mRNA vaccine.[20] Contrary to our findings, another phase 3 trial that studied the safety and efficacy of the ChAdOx1 nCoV-19 vac-

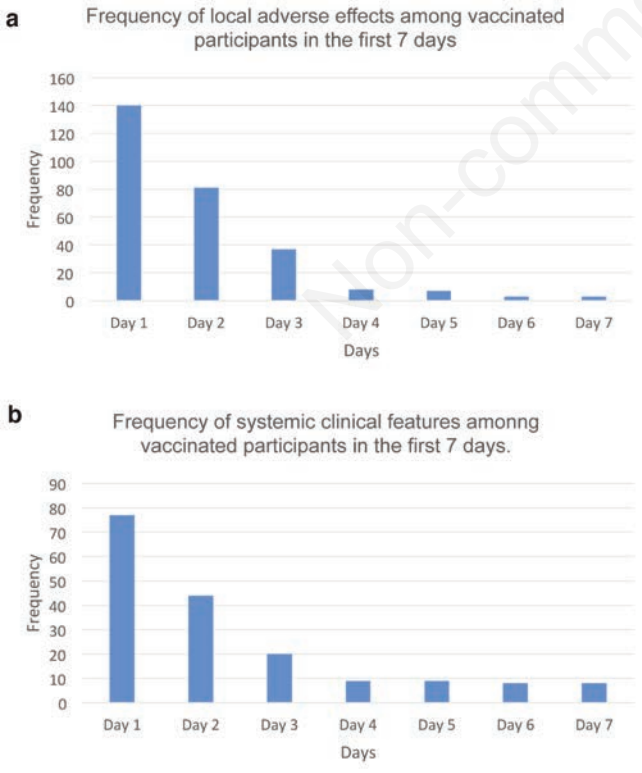

Figure 2. Frequencies of **a**) local and **b**) systemic adverse effects among vaccinated participants in the first 7 days..

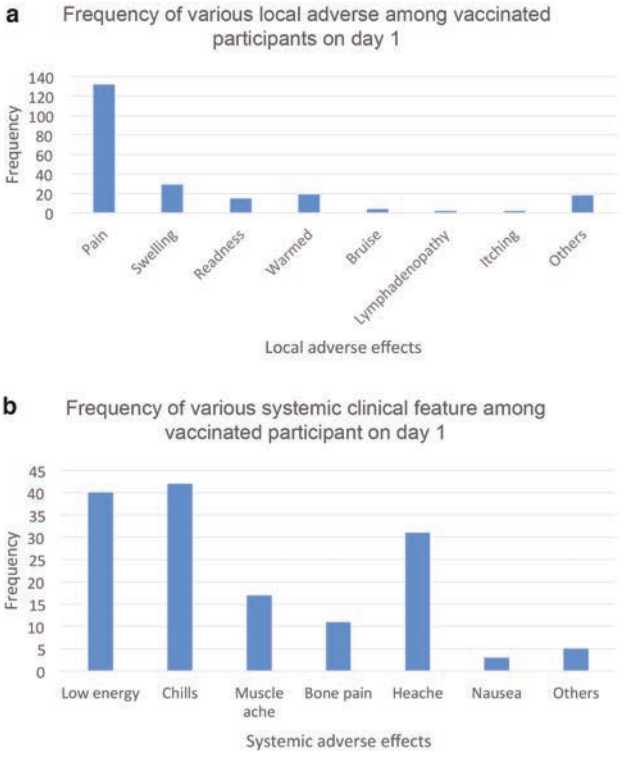

Figure 3. Frequencies of **a**) local and **b**) systemic adverse effects among vaccinated participants on day 1.

cine found fewer adverse events following the administration of a second dose of the vaccine.[21] ChAdOx1 nCoV-19 (Oxford-AstraZeneca) is an adenoviral-vectored vaccine, a plausible reason for the observed difference. When stratified into local and systemic adverse events, a statistically significant proportion of recipients of second dose vaccine reported local adverse events, p=0.027, whereas statistically significant recipients of first-dose vaccine recipients developed systemic adverse events, p=0.024. With regards to local and systemic advert events, the risk of developing systemic events during the study period was more than 3 times among vaccinated participants, 39.7% *vs* 10%. Though we were not surprised by this outcome, but also believed that some of the systemic events might have been confounded by other prevailing causes of febrile illnesses, like malaria fever and typhoid fever, among the participants. As expected, none of the unvaccinated participants developed a local side effect, but over 65% of the vaccinated participants reported at least one local side effect. A general concept of all vaccines is the capacity to trigger inflammation[19,22] and is consistent with COVID-19 vaccine phase III trials.[9]

We found no statistically significant relationship between administering mRNA-based vaccines versus adenoviral-vectored-based vaccines and the development of both local and systemic advert events, p=0.447 and 0.092, respectively. We found no immediate explanation for the lack of difference despite previous documentation that mRNA vaccines are more likely to cause adverse events in comparison to viral vector ones.[16,23,24] Our findings and the aforementioned are in variant with a study from South Korea where a significantly higher proportion of recipients of adenoviral-vectored vaccine developed adverse effects as compared to recipients of mRNA vaccine.[20]

The vaccinated female participants were more likely to report local adverse events ($p \leq 0.001$); a similar observation was made with systemic adverse events (p=0.037). This finding mirrors the differences in sex variation concerning reactogenicity, tolerance to discomfort, health-seeking behaviour, hormones, genes, and immune system activation as possible explanation.[22] Other studies also reported higher cases of vaccine-related adverse events among female participants.[9,11,18] Interestingly, while most studies reported a higher incidence of adverse effects among females, a review article that sought to study the risk of post-COVID-19 vaccine-induced myocarditis by sex, age, dose number, and manufacturer, found myocarditis to disproportionately affect males under the age of 40 years who receive a second dose of mRNA vaccine.[25] Age group, being a healthcare worker, having at least one comorbidity, or history of previous COVID-19 diagnosis did not significantly contribute to local or systemic adverse events (Tables 2). This is similar to a study among healthcare workers in Indonesia who were studied after receiving the Moderna vaccine.[26] Other studies found the contrary.[27,28]

Our study also demonstrated the frequencies of local and systemic adverse events in the first 4 weeks post-vaccination and the frequencies of various adverse events. Most of the systemic and local adverse events were reported in the first week, especially on the first-day post-vaccination (Figures 1-3). Pain at the injection site and injection site swelling constituted more than half of the local adverse events, while chills and low energy predominated the systemic adverse events. This finding typified activities of innate immune response that are known to be mobilised a few hours after vaccine injection. The mediators and products of inflation at the localised site may spill into the circulation causing a systemic adverse effect. Immune regulation ensures the innate immune cells and mediators return to steady-state levels after 5 to 7 days[22]. Previous researchers corroborate our findings.[9,15,29]

Conclusions

Vaccine hesitancy characterised the introduction of the COVID-19 vaccine due to fear of unintended adverse effects. Our study found that adverse effects are common, and most local events included pain and swelling at the injection site. For systemic events, low energy, chills, and headache predominated. The adverse effects are mild and tolerable and resolve within a few days. Women are more likely to report adverse effects. While the first-dose recipients are more likely to report local events, second-dose recipients are more likely to report systemic events. The COVID-19 vaccine's short-term safety profile is good. Long-term follow-up is required to determine the outcome of its long-term safety profile.

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Online supplementary material.
Appendix 1. COVID-19 adverse effects proforma.