International Journal of Dentistry, Diabetes, Endocrinology and Oral Hygiene
Vol. 4, No,1, pp, 15-24 2022
Print ISSN: ISSN 2631-567X
Online ISSN: ISSN 2631-5688

Neutralizing SARS-CoV-2 Antibody response to 1st dose of AstraZeneca-Oxford AZD1222 Vaccine Among Health Workers in North-Central, Nigeria

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Citation: Aisha F. Lawal, Mohammad A. Obeid , Chinedu Egejuru, Adeola Adefioye, Adedapo Adesokan, (2022) Neutralizing SARS-CoV-2 Antibody response to 1st dose of AstraZeneca-Oxford AZD1222 Vaccine Among Health Workers in North-Central, Nigeria, *International Journal of Dentistry, Diabetes, Endocrinology and Oral Hygiene*, Vol. 4, No,1, pp, 15-24

ABSTRACT: *Speed is an effective catalyst that can differentiate a time of war from other times. Thus, in a global record time of 11 months, the leading COVID-19 vaccine manufacturers completed the first COVID-19 vaccines. However, curbing the epidemic of anti-vaxxers has not been so easy globally. The world, particularly, in Africa has been largely influenced by the myths and conspiracy theories dissuading the public from accepting COVID-19 vaccination as the most effective response against the pandemic. Hesitancy remains the status quo of many Africans to the innovation.This study is centred on findings from a multi-centre study in Ilorin located in North Central, Nigeria among 92 Health Workers (HCWs). The primary objective of the study was to evaluate the efficacy of the first dose of the ChAdOx1 nCoV-19 vaccine. The blood samples of 92 health workers who received their first AstraZeneca-Oxford AZD1222 vaccination dose between March and April 2021 were taken to determine their antibody responses with the hope to ascertain vaccine effectiveness and also to serve as a means of encouragement to Africans in a hope to allay their fears. The overall goal of the study is to provide a scientific basis for advocacy of vaccination in Africa.This study is limited to single dose and owing to scare resources, blood samples were ran once using the cPass kit which is designed based wildtype S protein Receptor Binding Protein (RBD). As a secondary objective, the researchers evaluated but found no association between the level of neutralizing antibodies generated by this first dose and the demographics or the clinical characteristics of the participants. The demographics considered include age ($p > 0.05$), Gender ($p > 0.05$) and BMI ($p > 0.05$). Existing comorbidities of interest in the study were hypertension ($p > 0.05$), diabetes ($p > 0.05$) and drug misuse ($p > 0.05$).The study revealed that over 81.5% of the vaccinated study participants mounted a strong neutralizing antibody response to their first vaccine dose, while only about 11% of the study participants had a weak antibody response.*

KEY WORDS: Neutralizing Antibodies, SARS-CoV-2, AstraZeneca-Oxford AZD1222 Vaccine, Health Workers, Nigeria

INTRODUCTION

Coronavirus is a large family of viruses, pathogenic examples are MERS, SARS-CoV, SARS-COV-2, coronaviruses causing common cold. They are found in animals like camel, cattle, bats etc. [1] Coronaviruses have caused two large-scale pandemics in the past two decades, SARS and Middle East respiratory syndrome (MERS). [2,3] The current pandemic, COVID-19 was first reported in Wuhan China on December 30th 2019 [4] and soon became a global disease of immense significance due to global travels. SARS-CoV-2 virus transmits through 4 main ways: direct contact, via physical contact with a carrier; indirect contact, interactions with contaminated objects; droplet and airborne transmission, often through coughs, sneezes and breathing; and, aerosolization, atomised virus suspended in airflow. [5]

Vaccine development usually takes 10-15 years and involves several stages of development.[6-9] It involves Exploratory Stage which is basically initial laboratory research development phase which could last up to 2-4 years. Thereafter the Pre-Clinical Stage, this pre-clinical study utilises tissue-culture or cell-culture systems and animal testing to assess the immunogenicity and safety of the candidate vaccine. In case of this COVID AstraZeneca Chimpanzee Adenovirus was utilised to create the gene carrier in form of vaccine vector. These studies give clues of the cellular responses and ability of lead vaccine candidate to provoke an immune response. This stage of development also gives an indication of a safe starting dose and route of administration of the vaccine. This pre-clinical stage usually lasts 1-2 years, several vaccine candidates fail at this stage and the successful ones the proceed to the IND application phase.
A sponsor, usually giant Pharmaceutical companies applies for an Investigational New Drug (IND) to the regulatory authorities in US, EU and UK. This entails the sponsor submitting a synopsis detailing the manufacturing, testing processes, summarizes the laboratory reports etc. Once the IND application has been approved, the vaccine is subject to three phases of testing; namely Phase I, II, and III trials. Phase I Vaccine trials assesses the candidate vaccine in humans involves a small group of adults to determine the safety and immunogenicity. Thereafter Phase II Vaccine trials which involves a larger group of several hundred individuals of study participants. These trials are usually randomized and involve a placebo group. This phase of the trials determines the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery. Phase III Vaccine trials involves thousands to tens of thousands of people. These Phase III tests are randomized, double blinded and involve the experimental vaccine being tested against a placebo the overall aim of this phase is determine safety in a large group of people as certain rare side effects might not occur in the earlier Phase I and II. It is after this usually multi-continent phase 3 study that the manufacturer applies for approval and License. In total, the process can take 10-15 years, however due to pandemic nature of COVID-19, In global record time of 11 months, the leading COVID-19 vaccine manufacturers made the vaccines available worldwide following the regulatory authorities around the world granting the emergency authorisation. [10]

Development of vaccines to prevent coronavirus disease 2019 (Covid-19) has occurred with unprecedented speed.[11] ChAdOx1 nCoV-19, a replication-deficient chimpanzee adenoviral vector containing the sequence for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structural surface glycoprotein antigen. [12], is one of four COVID-19 vaccines based on that have been authorized for emergency use by FDA and MHRA. [13-16]

A pooled analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine in the United Kingdom, Brazil, and South Africa, performed before the emergence of the B.1.351 and P.1 variants, reported an overall vaccine efficacy of 66.7% (95.8% confidence interval [CI], 57.4 to 74.0).[17] Recent analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine against the B.1.1.7 variant in the United Kingdom was 74.6% (95% CI, 41.6 to 88.9.[18]

We conducted this study on 92 health workers who received their first AstraZeneca-Oxford AZD1222 vaccination dose between to determine the antibody response in to provide a scientific basis for advocacy vaccination in Nigeria and rest of Africa.

For the study we use the cPass kit (GenScript BV Biotech, Netherlands) is a first-in-the world "rapid smart test kit". It is a SARS-CoV-2 surrogate virus neutralization test (snit).[19] It was our choice test kit considering we were performing the test in a developing country and such tests can be conducted in most clinical laboratories within an hour. Compared to either pVNT (pseudovirus-based Virus Neutralization Test) which requires use of live SARS-CoV-2 viruses and cells in a biosafety level 2(BSL2) facility or cVNT (conventional virus neutralization test which is time consuming, laborious and requires handling live SARS-CoV-2 in a specialized biosafety level 3(BSL3) laboratory. cVNT such as the cPass is a robust, fast means to conduct serological test without use of live biologic materials or biosafety containment that allows for the rapid detection of total neutralizing antibodies (NAbs) in blood samples by mimicking the interaction between the virus and the host cell hence able to predict humoral protection in vaccinated humans. To initiate the process of a virus to attach and infect a host cell, a viral receptor binding protein (RBD) first needs to interact with the host cell's membrane receptor protein (ACE2). The virus-host interaction and subsequent viral infection of the host cell leads to the activation of an individual's immune response after antigen presentation to result in production of antibodies against the virus. Some of these antibodies can bind to the virus, but not necessarily block viral infection. Other antibodies can bind to the RBD in a way that blocks the interaction with the ACE2 receptor. The cPass kit detects total immunodominant neutralizing antibodies targeting the viral spike (S) protein receptor-binding domain (RBD) in an isotope and species independent manner.[19] This implies that this kit is designed based on antibody-mediated blockage of the interaction between ACE2 receptor protein and the purified receptor binding domain from the S protein. The kit has been validated in tests on two cohorts of patients with COVID-19 in two different countries achieving 99.93% specificity and 95-100% sensitivity. [(20)] It is well documented that ACE2 is the main functional receptor for SARS-CoV-2 viral entry in humans.[20] In developing the cPass kit a cut-off of 30% inhibition was chosen from testing over 500 negative human sera.[19] The NAbs percentage inhibition levels (in %) is a good indicator of protective immunity. [19] To calculate this Inhibition (%) = (1-sample optical density value/negative control optical density value X 100)

METHODS

An immunogenicity evaluation was carried out among HCWs vaccinated at the in Ilorin, North Central Nigeria. All HCWs were vaccinated by the national vaccine campaign at the between March and April 2021. 92 vaccinated HCWs were enrolled in the study. All eligible participants were assigned after receiving the priming dose, 50-60 days later blood samples were collected.

Efficacy Objectives
The primary end point was efficacy in terms of neutralizing antibody inhibition activity expressed by on subjects who have been vaccinated with the ChAdOx1 nCoV-19 vaccine 50-60 days previously. Secondary efficacy objectives included efficacy neutralizing antibody inhibition activity expressed by on subjects on 92 subjects who have been vaccinated with the ChAdOx1 nCoV-19 vaccine 50-60 days previously correlating this to their ages, sex, BMI and presence of co-morbidities like hypertension, diabetes etc

Study Site and Enrolment of Participants.
We collected blood samples from 92 health workers s across four sites: General Hospital Ilorin, Children Specialist Hospital Ilorin, Sobi Specialist Hospital Ilorin and Okelele Healthcare Center between 18th and 25th of May 2021. All participants had received the vaccine, gave consent and had blood sampling were included in the analysis. Inclusion criteria were I) Age >16 years;

ii) Health worker in Kwara State iii) Consent to partake in study granted
Health workers were first given informed consent to fill to be eligible to participate to in the study. An information document that clearly indicates the risks and the benefits associated with the participation to in the study. After consenting to participate, patient identification, a study number were assigned sequentially to participants for identification, blood assayed for the study and the study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines of good clinical practice, the Helsinki Declaration, and applicable standard operating procedures.

The clinical data will be obtained using a completed COVID-19 Proforma on an excel sheet comprising of 92 health workers
1) Patients BMI (underweight (<18.5), normal (18.5-24.9), overweight 25-29.9, Obese>30-39.9, Morbidly Obese >40
2) Demographics: Age, Sex, (Weight, Height interpreted as BMI), Blood Group
3) Co-Morbidities (Diabetes, Hypertension, opioid drugs misuse,)
4) Previous COVID-19 infection i.e. Convalescent subject
Non- Convalescent subject (no previous COVID infection)

We measured the neutralizing activity of serum specimens obtained from 1 vaccinated convalescent persons and from 91 vaccinated non- convalescent recipients of the AstraZeneca-Oxford AZD1222 vaccine.In this multi-site study conducted in Ilorin Kwara State Nigeria, we assessed the efficacy of one single doses of the ChAdOx1 nCoV-19 vaccine after 50-60 days of administration in terms of immune response. Adults 18 and above were eligible for participation. Key exclusion criteria were human immunodeficiency virus (HIV) positivity at screening (for the efficacy cohort), a history of anaphylaxis in relation to vaccination.
The authors had full access to the study data, confirmed the accuracy and completeness of the data reported, and vouch for the fidelity of the study to the protocol.

The study protocol was reviewed and approved by the Kwara State Ethics Committee before study initiation with Ethics approval number MOH/KS/EU/777/491 granted. All participants

were fully informed about the study procedures and the possible minimal blood sampling risks, and all signed written informed consent documents before enrolment in the trial.

Study Procedures

Study participants who received 0.5ml dose of the ChAdOx1 nCoV-19 vaccine by intramuscular injection on the 50-60 days later has 4ml of blood sampled from them into a plain non-coagulant containing blood bottle. Their bloods were taken from the antecubital fossa branchial vein of the nondominant arm, and participants were observed for 15 minutes afterwards. Samples were taken by phlebotomist staff who were aware of participants' study goal but were not involved in any other study procedures.

Neutralization Assays

SARS-CoV-2 serostatus were evaluated with the use of a questionnaire as described in the appendix. For antibody-neutralization studies, cPass neutralization assay was used on serum samples obtained 50-60 days after receiving the first dose of vaccine in 92 randomly selected ChAdOx1 nCoV-19 vaccine recipientsTo assess neutralization activity of vaccine-elicited antibodies against wildtype S protein, serum samples from 92 participants who were either vaccinated convalescent (had previous COVID infection) or vaccinated non-convalescent negative SARS-CoV-2 PCR (never experienced SARS-CoV-2 symptoms and never had positive PCR SARS-CoV-2 result)

Testing of neutralizing antibody activity against the wildtype S protein was undertaken using the cPass kit.

Statistical analysis

One-way analysis of variance (ANOVA) was used to assess statistical significance. Tukey's multiple comparison test and t-test were performed for paired comparisons. The statistical analysis was performed using SPSS software. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

92 vaccinated HWCs sera were analysed using the cPass kit, 25 women (27.2%) and 67 men (72.8%). After the first dose of vaccine, 81.5% of study participants developed a strong humoral immune response with neutralization inhibition activity as percentage inhibition revealed strong antibody response (greater than 80%,). Intermediate antibody response (50-80% inhibition) in 4.3% of the study participants. While mild antibody response (30-50% inhibition) was experienced in 3.3% and 10.9 % of them had low antibody response (less than 30% inhibition), summary is shown in Table 1 below.

Interpretation of results

Participants who received one dose of the ChAdOx1 nCoV-19 vaccine within 50-60 days prior to blood sampling with were classified neutralization inhibition activity as;

A. Strong antibody response (greater than 80%,)
B. Intermediate antibody response (50-80%)
C. Mild antibody response (30-50%)
D. Low antibody response (less than 30%)

The primary efficacy analysis was end-point–driven for the composite of high, intermediate, mild or low antibody response (with a lower bound of 0% for the 95% confidence interval), with 30% inhibition as cut-off. Only participants in the per-protocol population (subjects who have been vaccinated with the ChAdOx1 nCoV-19 vaccine 50-60 days previously who had never had COVID-19 through positive PCR result) were included in the primary and secondary efficacy analysis. While participants in the per-protocol population (subjects who have been vaccinated with the ChAdOx1 nCoV-19 vaccine 50-60 days previously who had Positive PCR COVID-19 result) were included in the secondary efficacy analysis for correlation between extent of immune response and variables like age, sex, BMI, co-morbidities like hypertension, diabetes etc. Percentage inhibition extrapolated from the optical density of the ELISA plates of the controls and 92 study participants is (as shown in Table 1 below)

3.2 Baseline Characteristics of the Overall Population Contributing to the Primary Efficacy End Point Analysis.

Table 1 Demographic and clinical characteristics of study participants, stratified by immune response to the first dose of AstraZeneca-Oxford AZD1222 vaccine
Overall neutralizing antibody response: 92: n (%): Strong response (>80% inhibition) 75 (81.5) Intermediate response (50-80% inhibition 4(4.3), Mild response (30-50% Inhibition) 3 (3.3), Low response (>30% Inhibition) 10 (10.9)
Sex n (%): Female 25 (27.2) Male 67 (72.8)
Blood Group n (%): A 16(17.4), B 20(21.7), AB 7(7.6), O 49(53.2)
Comorbidities: n (%)
Hypertension 75 (81.5) Diabetes 8 (8.7%) Opioid Drug Misuse 9(9.7%)
BMI n (%): Underweight 7(7.6) Normal 26(28.3) Overweight 40(43.5) Obese 15(16.3), Morbid Obese 4(4.3)
Serostatus n (%): Non-Convalescent 91(98.9) Convalescent 1(1.1)

In terms of age distribution of the participants 67% were young adults aged 18-45 years 31.9% as middle age 46-65 years, while the remaining 1.1% were of the elderly population above 65 years of age, this is keeping with age distribution in the general population in Nigeria where life expectancy is believed to be estimated at 52 years. [21] For sex distribution 72.8% identified as male, 27.2% as females, for co-morbidities 81.8% of study participants had systemic hypertension, 9.1% diabetic, 9.1% admitted to previous opioid misuse. 4.3% percent of

participants were morbidly obese (BMI above 40), 16.3% were obese (BMI, 30 to 39.9) % 43.5% overweight (BMI 25-29), 28.3% normal (BMI18.5-24.9) and 7.6% were found to be underweight (<18.5).

98.9% were non-convalescent, while 1.1% were convalescent (previous confirmed PCR COVID positive). In terms of Blood group 53.6% belong to blood group 0, 21.7% B,17.4% A and 7.3% AB blood group
Demographic characteristics of the baseline seronegative population were similar to those of the overall population (Table 1) above.

DISCUSSION

In this study, we found that one dose of the ChAdOx1 nCoV-19 vaccine had 81.5% efficacy against the wildtype SARS-COv-2 S protein which implies from the study findings are that the ChAdOx1 nCov-19 vaccine may protect against severe COVID-19 caused by infection by several SARS-CoV-2 variants.The responses to the original SARS-CoV-2 virus as determined by cPass surrogate neutralization assays in recipients of the ChAdOx1 nCoV-19 vaccine in our study were similar to the responses in vaccinated participants in the studies conducted in the United Kingdom and Brazil. [17,18]

It is worthy of note that 10.9% of our study participants had low humoral response to the vaccination. Though previous studies on SARS-CoV and SARS-CoV-2 suggested that RBD - targeting Nabs are the immunodominant during both infections. [22,23] One reason for the result of this study might be the fact that not all RBD binding antibodies are NAbs as past SARS-CoV-2 studies have shown antibodies to other regions in the S1 or S2 protein can also play a role in virus neutralization.[24] The other obvious reason being the 1st dose is a priming dose and it is only after the 2nd dose (the booster dose) that humans fully establish full immune response. A longitudinal study several months after 2nd dose is administered in the same study subjects would be desirable to determine the rate of waning of the neutralising antibody and the longevity of immunity to COVID-19 infection. The last reason for this trend of results where over 10.9% of the vaccinated participants had low neutralizing antibodies may be due to delayed immune response. Delayed response has been documented in study where a small group that showed an unexpected increase of neutralising antibodies during late convalescence (at 90 or 180 days after infection or vaccination).[25]

Mutations like Delta Variant Indian strain being experienced in UK and the rest of the world is becoming a concern in Nigeria. The extent to which the effectiveness of the authorized COVID-19 vaccines may be affected by variants with mutations would depend on the magnitude of neutralizing antibody induced by vaccination. Whether an enhanced antibody response resulting from a longer interval between the first and second doses of the ChAdOx1 nCov-19 vaccine, as described [17,18] might confer better residual neutralizing activity against the worldwide dominant strains like B.1.351 variant is not known.

A recent multinational study that included South Africa evaluated the efficacy of a single dose of the Ad26.COV2. S non-replicating adenovirus type 26 vaccine (Janssen). Interim results from South Africa reported a vaccine efficacy of 60% against moderate-to-severe COVID-19 and 89% against severe COVID-19 mainly due to the B.1.351 variant.[26]

Despite 10.9% of the study participants exhibiting low humoral response as extrapolated from this present study, it is not all worrisome news. It is well known that the correlation between antibody response and vaccine efficacy is high, which suggests that the neutralizing antibody response is important, however T-cell responses may contribute to protection from COVID-19 even in the presence of lower neutralizing antibody titres.

Although efforts to develop second-generation COVID-19 vaccines targeted against B.1.351 and P.1-like variants are under way, the only COVID-19 vaccines likely to be available for most of 2021 have been formulated against the original virus from these results have proven efficacious. ChAdOx1 nCoV-19 is likely to be one of the most accessible of all the currently authorized COVID-19 vaccines to most Africa countries including Nigeria [27, 28] with expected manufacture of approximately 3 billion doses during 2021.

Relative resistance to human neutralizing antibody responses is expected to be a feature of the pandemic coronavirus in the years ahead, in countries like Nigeria with low endemicity it might pose a big problem.
The fact that there was no statistically significant association in antibody response after vaccination with socio-economic and clinical variables like age, sex, hypertension, diabetes, blood group, and BMI is not surprising as this have been previously documented study conducted in Italy; analysed the antibody titre seven days after the second dose of BNT162b2 (Pfizer) vaccine in a group of 248 healthcare workers (HCWs) and how antibody titre changes in correlation with age, gender, BMI and hypertension , the variables were found to be not associated with difference in immune response to the vaccine. [29]

If the resources were available, a follow-up study would be advantageous on the same 92 study cohorts to look at longitudinal immune response to the AstraZeneca vaccine after 2nd dose and up to a year or more afterwards, to give a full picture of immune response this vaccine confers in the general population in Nigeria and rest of Africa. This would go a long way in allaying the fears of anti-vaxxers and reposing public confidence in advocating high vaccine intake as the only exit strategy from this pandemic that has held the whole world including Africa to ransom

Funding: Study funded by PreciseMed, PreciseMed has legal responsibility as sponsor of the study, heartfelt appreciation goes to its director Daniel Onifade for funding the study.

Authorship contributions: Dr Adedapo Adesokan, Dr Aisha Lawal and Dr Mohammad Obeid were involved in conception and design of the study, data collation, analysis and interpretation, Mr Chinedu Egejuru conducted the ELISA tests, Dr Adeola Adefioye made contributions to the study methodology.

The views expressed in this article are those of the authors and not necessarily those of the PreciseMed, UK.

Competing interests: There is no conflict of interest

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