Original Article

DOI: 10.7860/NJLM/2022/52643.2582

Public Health Section

Rise in Levels of Anti-SARS CoV-2 Immunoglubulin G by Covishield Vaccine- A Cohort Study in Rural Medical College, West Bengal, India

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ABSTRACT

Introduction: The Coronavirus Disease-2019 (COVID-19) pandemic was declared by the World Health Organisation (WHO) on 11th March 2020 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). As a preventive measure, valid information concerning the development of antibodies is being collected for assessing the progress towards herd immunity of COVID-19.

Aim: To assess the level of Anti-SARS-CoV-2 IgG before and after vaccination by two doses of ChAdOx1 nCoV 19 vaccine in a rural Medical College of West Bengal.

Materials and Methods: The present interventional cohort study was conducted in a rural Medical College and Hospital, West Bengal, India, from February 2021 to August 2021. Total 248 willing subjects were included for this interventional study from the same socio-economic and geographical distribution depending upon a vaccine population of a rural Medical College of West Bengal. To measure the anti-SARS-CoV-2 IgG antibody authors used Indian Council of Medical Research-National Institute of Virology (ICMR-NIV) certified Anti-SARS-CoV-2 human IgG ELISA COVID KAVACH MERILISA kit and approved protocol by the ICMR.

Results: The median age of study population was 39 years (range 25-64) with 97 (39.1%) females and 151 (60.9%) males. It was found that antibody response induced by two doses of vaccination was significantly high (t-value: 28.421, p<0.001) in the vaccinated population.

Conclusion: Thus, present study suggests that vaccination may be critical to develop anti-SARS-CoV-2 IgG antibody. This would lead to a better understanding of the immunisation program and prevention of severe disease and deaths due to COVID-19.

Keywords: Acquired immunity, Corona vaccine, Coronavirus disease-2019, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

A COVID-19 pandemic was declared by the WHO on 11th March 2020 caused by SARS-CoV-2 [1]. The disease was first reported in December 2019 in Wuhan, China [2]. Numbers of cases and deaths reported globally were increasing with high rapidity [3]. The COVID-19 pandemic has posed a severe threat to global economy and health [4]. Scientific communities at international level were trying tirelessly to treat health problems in this current pandemic and to get answers in terms of therapeautics and vaccines to manage the COVID-19 in future. Scientific community is aware that few vaccines like Covaxin-BBV152 [5], Covishield-ChAdOx1 nCoV-19 [6], Johnson and Johnson-Janssen Ad26.COV2.S [7], Moderna-mRNA [8,9], Sputnik V-Gam-COVID-Vac [10] and Zydus Cadila-ZyCoV-D [11,12] vaccines have already been established for prevention of COVID-19 at this time.

For emergency use several vaccines have recently gained authorisation. Currently we don't have enough knowledge regarding the efficacy and duration of immunity of these vaccines. Information on other coronaviruses after natural infection suggests that immunity to SARS-CoV-2 might be short-term, and groundwork evidence indicates declining antibody titers next to SARS-CoV-2 infection [13,14]. A cautious validation of efficacy in terms of antibody titer (Anti-CoV2 IgG) and adverse reactivity presented by biochemical parameters are required for the target vaccine population for a successful immunisation [14]. After a tedious literature search, we found limited and conflicting data related to the response to COVID-19 immunisation globally. This type of finding may be due to different socio-economic status and ethnicity [15-18].

The updated number of vaccines under development for prevention of severe disease and deaths by the novel SARS CoV-2 is more than 190. Whereas, neutralising antibodies in opposition to the viral spike protein may correlate with protection and added antibody functions may also be essential in preventing infection, as was exposed by animal studies [17]. A phase 1/2, single-blinded randomised controlled trial conducted by Oxford COVID-19 vaccine trial group, described the safety and tentative humoral and cellular immunogenicity of the vaccine. A homologous full dose (SD/SD d56; n=25) or half dose (SD/SD d56; n=32) Covishield booster vaccine was given to all the participants in the trial after 56 days following prime vaccination. In this study, they found stronger antibody responses in case of a booster dose vaccine than a dose-sparing half-dose booster. Either of the booster doses failed to increase the magnitude of T-cell responses. These phase three clinical trials also support the two-dose vaccine regime after evaluation [17].

Between 23rd April to 4th November, 2020, 23848 participants were included and 11636 participants (7548 in the UK, 4088 in Brazil) were enrolled in three randomised, single blinded, controlled trials one phase 1/2 study in the United Kingdom (COV001), one phase 2/3 study in also the same place (COV002), and a phase three study performed in Brazil (COV003)-and one double blinded phase 1/2 study conducted in South Africa (COV005) for the interim primary efficacy analysis by Voysey M et al., [19]. Twenty one days following the initial dose, in this study there were 10 hospitalised cases for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. Participants who received two standard doses, vaccine effectiveness was 62.10% and in participants who received a low dose followed by a standard dose,

effectiveness was 90%. They reported overall vaccine effectiveness across both groups was about 70.4% [18]. With this background the present study was being proposed to assess the level of Anti-SARS-CoV-2 IgG before and after vaccination by two doses of ChAdOx1 nCoV 19 vaccine in a rural Medical College of West Bengal.

MATERIALS AND METHODS

The present study was an interventional cohort study in a rural Medical College and Hospital, West Bengal, India, for a period of approximately six months (February 2021-August 2021) to achieve the required sample size (N=248) after getting the approval from the Institutional Ethics Committee (IEC/2021/02/005, 12.02.2021). Authors followed the guidelines of the Helsinki declaration of 2009 in every aspects of the study [20]. Blood samples were collected after getting informed consent from the willing subjects at the hospital vaccination centre and measurements of IgG level was done at the clinical laboratory of the Department of Biochemistry of the Government Medical College and Hospital, West Bengal, India.

Sample size calculation: Considering the prevalence 62.1% [18], the required sample size for this study was calculated. $N=4pq/l^2$ {p=0.62, q=0.38, allowable error l=10% of prevalence} $N=4\times0.62\times0.38/0.0038=0.9424/0.0038=248$. Systematic random sampling was used.

Inclusion criteria: Participants were included in this study after getting their voluntary informed consent from each subject by systematic random sampling irrespective of their previous COVID-19 status. The people who attended for vaccination were the target population.

Exclusion criteria: Those who did not gave their consent to be enrolled in this study were automatically excluded.

Study Procedure

About 3 mL of blood was collected from the willing subjects after getting voluntary, informed written consent by venipuncture in a clot sample vial before the scheduled 1st dose of non replicating viral vector vaccine {ChAdOx1 nCoV 19 vaccine (recombinant) COVISHIELD™: Serum Institute of India Private Limited, 212/2 Hadapsar, off Soli Poonawalla Road, Pune 411028, India} by the vaccination centre at our rurally situated Government Medical College and Hospital, by the college assigned vaccinators. Another sample was also collected after 28 days (four weeks later) from the 2nd dose of the vaccine as studied by widely divergent researcher [21-23]. Assessment of the test parameters was done on the same day of collection of the sample; if not so, then samples were stored at 2-8°C for the next day. Every sample was discarded as per biomedical waste disposal protocol after the testing had been performed.

Estimation of test parameters [24-26]: To measure the Anti-SARS-COV-2 IgG antibody authors used ICMR NIV certified anti-SARS-CoV-2 human IgG ELISA COVID KAVACH, MERILISA kit and approved protocol by the ICMR.

Principle of the assay: Microtitre plate/ELISA wells coated with the SARS CoV-2 virus whole cell antigen binds to the IgG antibodies from serum/plasma of human to be intended to measure by the kit. Human IgG antibodies were then captured by the anti-human IgG-Horseradish Peroxidase (HRP) in the next step. Subsequently chromogenic substrate Tetramethylbenzidine (TMB/H_2O_2) was added and 1N H_2SO_4 was used to stop the reaction. At λ=450 nm the intensity of colour/optical density was measured. The kit is in support of in-vitro use for monitoring anti-SARS CoV-2 binding antibodies in human only. The method is indirect ELISA which requires about 130 minutes time for assay with the diagnostic sensitivity and specificity of about 100% and 93%, respectively. Authors followed the approved ELISA protocol by the ICMR as mentioned in the kit insert [25,27,28].

STATISTICAL ANALYSIS

After getting the completed master chart, the data were analysed by means of statistical software Statistical Package for the Social Sciences (SPSS) version 21, (SPSS inc. Chicago II, USA). Descriptive statistics was done to calculate the mean, Standard Deviation (SD) and Standard Error of the Mean (SEM). Association between two variables was checked by bivariate Pearson's correlation analysis between pre and postvaccination levels of antibody. Paired sample student's t-test was used to weigh against the means of the two sets of pre and postvaccination data.

RESULTS

Out of 248, the median age of study population was 39 years (mean±SD; 39±8.12, range; 25-64 years) with 97 (39.1%) females and 151 (60.9%) males of approximately same socio-economic condition and geographical distribution. Responses were evaluated before 1st dose and after 28 days from the 2nd dose of ChAdOx1 nCoV-19 vaccines. The mean and SD before 1st dose (0.601±0.525) and 28 days after 2nd dose (1.151±0.441) as follows [Table/Fig-1].

	Mean	Sample size (N)	Standard deviation (SD)	Standard error of mean (SEM)
Pre vaccination	0.6015	248	0.52557	0.03337
Postvaccination	1.1519	248	0.44189	0.02806

[Table/Fig-1]: Showing descriptive statistics of pre and postvaccination levels of antibody.

Statistically highly significant paired samples Pearson's correlation (r=0.815, p<0.001) between the samples of pre and postvaccination was found [Table/Fig-2].

	N	Correlation coefficient (r)	Significane (p-value)
Pre and postvaccination	248	0.815	<0.001

[Table/Fig-2]: Showing Pearson's correlation between pre and postvaccination.
p-value <0.05 considered significant

By doing paired sample t-test between pre and postvaccination samples authors found high rise (t-value: 28.421, p<0.001) of antibody titer after 28 days of 2nd dose vaccination which is statistically significant as shown in [Table/Fig-3].

Paired samples test	Mean	Standard deviation	Standard error mean	t-value	Significance (p-value, 2-tailed)
Pair of pre and postvaccination	0.55040	0.30497	0.01937	28.421	0.001

[Table/Fig-3]: Showing pre-postvaccination antibody titer after 28 days of 2nd dose vaccination.
p-value <0.05 considered significant

DISCUSSION

A two dose regimen of the Oxford, AstraZeneca ChAdOx1 (Covishield) COVID-19 vaccine with an inter dose gap of three months was implemented in many countries in the midst of limited vaccine supply [29]. The efficiency of heterologous prime boost COVID-19 vaccination is at present unknown [30]. A number of studies have previously been available concerning the antibody response to COVID-19 vaccination [2,4,5,9,11,13,17-19,31-34]. Immunogenicity and safety of the AZD1222 (ChAdOx1 nCoV 19) vaccine was evaluated in Japanese adults in continuing phase 1/2, randomised, double blinded, parallel group, placebo controlled, multicenter trial (NCT04568031). The AZD1222 elicited a powerful immune response against SARS-CoV-2 and was well-tolerated in Japanese participants, including elderly participants [32]. In a double-blinded, randomised, placebo-controlled, ongoing phase three clinical trial to determine safety and effectiveness of the AZD1222 (ChAdOx1 nCoV-19) vaccine in a large, varied population concerning participants from United States, Chile, and Peru by

two doses of AZD1222 done by Falsey AR et al., (2021) involving a total of 32,451 participants undergo randomisation, in a 2:1 ratio, they pointed out that AZD1222 was secure, with low incidences of grave and medically attended unfavorable events of special interest. Their overall expected vaccine efficacy was 74% {95% Confidence Interval (CI), 65.3 to 80.5; p-value<0.001} and predictable vaccine effectiveness was 83.5% (95% CI, 54.2 to 94.1) in participants of 65 years of age or older. They also noted that high vaccine effectiveness was constant across a range of demographic subgroups and in the fully vaccinated study subgroup, no severe or grave symptomatic COVID-19 cases were observed amongst the 17,662 participants in the AZD1222 group [35].

The results of above discussed studies by researchers [29,30,32,35] are in agreement with each other and with this study; however, there are some discrepancies. Results of the present study suggest that the ChAdOx1 nCoV-19 vaccine boosted antibody responses with or without history of prior exposure to SARS-COV-2. Information on other Coronaviruses following natural infection suggests that immunity to SARS-CoV-2 might be short lived, and preliminary proof indicates declining antibody titers next to SARS-CoV-2 infection [13,14].

Clinical trials showed that after vaccination, there was approximately 95% efficiency in preventing severe COVID-19 disease in people without prior infection [36]. After the 1st dose, the efficiency of the preparation was estimated at approximately 52% [37]. At this stage we don't have sufficient information on safety against the rising new variants of the virus [36]. Angyal A et al., showed that the cellular response was strengthened by the administration of the first dose, they also found that the neutralising properties are strengthened in relation to the variant B.1.351 (South African) in-vitro [38]. Skelly DT et al., tested the neutralisation strength of antibodies resulting after immunisation with Pfizer/BioNTech vaccine and from natural SARS-CoV-2 infection also pointed out the same aspect [34]. Asano M et al., found positive seroresponses in all 174 participants who received two doses of AZD1222 to SARS-CoV-2 spike and Receptor Binding Domain (RBD) antigens [32].

For public health purposes it is of paramount importance to monitor the load and extend of infection with the new Coronavirus SARS-CoV-2, whether inside small communities or in huge geographical settings. Serology is the most appropriate tool for this task because it detects the host antibody response to the infection [28]. In a study by Datta P et al., showed that their ELISA procedure, which was dependent on antibody binding to the RBD of the S1 subunit of the viral spike protein expressed as a novel fusion protein, detects antibody responses to SARS-CoV-2 infection and vaccination. They also pointed out that their ELISA was precise and versatile. It was compared favorably with marketable assays extensively used in clinical apply to establish exposure to SARS-CoV-2 [28].

Liu B et al., studied a candidate vaccine based on a RBD recombinant subunit by preparing a novel glycol-engineered yeast Pichia pastoris expression system with characteristics of glycosylation modification similar to those of mammalian cells. Found that candidate vaccine efficiently stimulated mice to make high titer anti-RBD specific antibody [14]. We also utilised an extremely sensitive and specific ELISA procedure to establish the binding antibody (anti-SARS-COV-2 IgG antibody) levels in a population that was not essentially diagnosed with COVID-19. The results of this study showed that the humoral immune response induced by vaccination is significantly enhanced (t-value:28.421, p<0.001) by two doses of vaccine. Hence, this finding is in a concordance with the findings of the various authors like Falsey AR et al., [35] and other researchers [14,36,38] as described above. In a systematic review, including 11 titles out of 1766, following the PRISMA guidelines by Iheanacho CO et al., found enhanced immune response by the vaccination subsequent to deciphering the effectiveness of Covishield, COVID-19 vaccine against SARS-CoV-2 infection and COVID-19 related morbidity and mortality [33]. Also, the present study supports this enhanced immune response and was also able to establish the efficacy of the Covishield (ChAdOx1 nCoV-19) vaccination program in target vaccinee population.

Limitation(s)

Estimation of neutralising antibodies by Plaque Reduction Neutralisation Test 50% (PRNT50) was beyond the scope of our study in a rural Medical College and Hospital. The study would have been improved by confirming the findings by PRINT50 involving a large scale population.

CONCLUSION(S)

The course of humoral immune response to COVID-19 in both vaccinated and convalescent patients can be assessed by testing the concentration of antibodies to the S protein. Whether the patients responded to vaccination, and if so, how strongly, can also measured quantitatively by determining anti-SARS-CoV-2 IgG antibodies. The present study established the effectiveness of the Covishield (ChAdOx1 nCoV-19) vaccination program in target vacinated population of West Bengal. This encourages continued practice of preventive measures and reinforces the need for a second dose, a better understanding of the immunisation program, treatment and prevention of COVID-19.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 30, 2021
- Manual Googling: Nov 15, 2021
- iThenticate Software: Nov 26, 2021 (15%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 29, 2021**
Date of Peer Review: **Oct 28, 2021**
Date of Acceptance: **Dec 08, 2021**
Date of Publishing: **Jan 01, 2022**