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Neutralizing IgG antibody seroprevalence, efficacy and safety post covishield vaccination: A follow up study

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***Abstract*---**COVID-19, a pandemic caused by severe acute respiratory syndrome (SARS) corona virus-2 has been a worldwide challenge for the entire mankind. However, a safe and efficacious vaccine would be

clinically valuable to reduce the risks of COVID-19. In this study, we aimed to assess the seroprevalence of the Neutralizing IgG Antibodies six months after completion of both the doses of Covishield Vaccination (ChAdox1 nCoV-19) and compare it with the IgG titres one month after the first dose and one month after the second dose of the vaccine respectively. The efficacy, safety and comorbidities related to the vaccine were also assessed at different time intervals. The levels of IgG antibodies were estimated in 72 subjects from the Teerthanker Mahaveer Medical College & Research Centre (who turned up after six months of the complete regimen of Covishield Vaccination) using the Enzyme-Linked Immunosorbent Assay (ELISA) Technique. A highly significant increase (p= 0.00) in the neutralizing Antibodies titre was seen in fully vaccinated individuals post six months when compared to the titres of post one month of 1st & 2ndDoses. It can therefore be concluded that (ChAdox1 nCoV-19) Covishield Vaccination if administered in full regimen has both acceptable efficacies as well as safety profile. Hence, a complete vaccine regimen may prove as an effective strategy against COVID-19 and consequent minimization of long-term morbid effects.

***Keywords*---**COVID-19, vaccine, covishield, neutralizing IgG antibodies titres, efficacy, safety.

Introduction

The Severe Acute Respiratory Syndrome (SARS) corona virus 2, belonging to the coronaviridae family is a novel coronavirus and the culprit pathogen in the ongoing pandemic which started at the end of 2019.[1] The World Health Organisation (WHO) termed the respiratory illness as COVID-19 which is believed to have originated from Wuhan, China. The structural proteins that constitute the corona virus-2 are spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. The functional receptors for the spike (S) protein of SARS-COV-2 are Angiotensin Converting Enzyme-2 (ACE-2) receptors of respiratory epithelial cells. [2] The pandemic has been a worldwide challenge for the entire mankind. All the countries have focused on developing effective vaccines to get rid of the highly contagious and lethal virus. The WHO has approved numerous vaccines since then, as vaccination could be of paramount significance in developing population immunity and thus, helping to prevent severe disease. Effective vaccination could be clinically valuable in reducing the risks of an ongoing health crisis.[3]

In June 2021, WHO licensed some vaccines that had fulfilled the required criteria laid down for the safety and efficacy against COVID-19, these include Pfizer, Moderna, Johnson and Johnson's Janssen, AstraZeneca / Oxford vaccine, Sinopharm and Sinovac. [4] Moving to the Indian scenario of Vaccination details, three COVID-19 vaccines have been approved for immunization to combat COVID-19 infection, they include Covaxin, Covishield and Sputnik V manufactured by Bharat Biotech, Serum Institute of India and Gamaleya Research Institute of Epidemiology & Microbiology, Russia respectively.

The chAdox1 nCoV-19 vaccine (Covishield) has been developed by Oxford University which consists of the SARS-Cov-2 structural surface glycoprotein antigen gene (Spike protein; nCov-19).[5] The safety and immunogenicity of the ChAdox1 nCov-19 vaccine had been studied in four different Randomized Controlled Trials in Brazil, the United Kingdom, South Africa, and Kenya. They assessed the seroprevalence of neutralizing antibodies in the trials to determine the immunogenicity of the vaccine. The immunogenicity outcomes from COV001, a phase 1/2 UK study in 1077 healthy individuals of age group 18–55 years, and COV002, a phase 2 cohort in elderly individuals (>56 years), have shown a safety profile for the vaccine, with induction of binding and neutralizing antibodies as well as production of interferon- enzyme-linked immunological responses, and higher Antibodies titres after the second dose of vaccine. [6]

It has been seen that the natural infection with coronavirus in the form of vaccine or the inoculation of attenuated or killed coronavirus induces the production of IgM and IgG neutralising antibodies in the serum of the individual. Here production of IgM neutralising antibodies signifies early response which is seen in acute phase of natural infection or an early response to the vaccination. This response is short lived and the isotype switching occurs to IgG neutralising antibodies. IgG Antibodies production signifies secondary immune response imparting long term immunity possibly, due to the activation of memory cells against the pathogen. The actual efficacy and effectiveness of Covishield Vaccine at the ground level is the biggest common query for vaccine manufacturers, researchers involved in the area, the medical professionals and most importantly the common population who are the major beneficiaries of this vaccine.

Thus, this study aimed to assess the seroprevalence of the neutralizing Ig G Antibodies six months after the completion of both the doses of Covishield Vaccination (ChAdox 1 nCoV- 19) and compare it with the Ig G titres one month after the first dose and one month after the second dose of the vaccination respectively. The manufacturer of Covishield, Serum Institute of India and various researchers have claimed that the Covishield vaccine is safe and effective. In a recent study it has been claimed that efficacy of Covishield vaccine is to be around 81.3%.[7] In a study done by ICMR it was found that efficacy of Covishield vaccine is around 80%.[8] In general, the efficacy of any vaccine is expected to be influenced by many confounding factors such as ethnicity, geographical distribution, lifestyle patterns and associated comorbidities of the participants. The present study has taken most of these facts into consideration.

Materials and Methods

The present study was a hospital-based cross-sectional, prospective study conducted to assess the levels of IgG Antibodies after the administration of Covishield vaccine on subjects attending the Department of preventive and Social Medicine, at Teerthanker Mahaveer Hospital, Moradabad. The investigation was performed in the Central Biochemistry Laboratory of the hospital. In our previous study “IgG Antibodies Seroprevalence Post Covishield vaccination in a tertiary care hospital in Western Uttar Pradesh: A Hospital Based Study” the blood samples of 215 subjects of age group above 18 years were collected one month after the administration of the first dose of Covishield. Follow-up of the subjects

was done and out of 215 subjects, 101 subjects turned up for participation. The samples of these individuals were collected post one month after the second dose of Covishield Vaccine. The neutralizing IgG Antibodies titres of the subjects of both groups were analysed.

In this present study, 72 subjects from the previous group of participants who had taken both the doses of Covishield vaccine reported, were assessed for their IgG Antibodies titres six months after the complete course of the Covishield Vaccination Program. A duly filled consent form was taken from the subjects before sample collection and before performing the serum assay. The exclusion group comprised of participants who were administered with anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma or the ones who did not receive both the dosages of the Covishield vaccine or who did not give the consent. Neutralizing IgG Antibodies titre (Spike & Nucleocapsid) to COVID-19 was estimated using commercially available ELISA Kit.[9] The test results for IgG were calculated using the following formula on mean Optical density 450nm/620-630nm,

NC+0.250 = Cut-off Value (NC: Negative Control)

The interpretation of results was done on the following basis:

S/Co	Interpretation
< 0.9	Negative
0.9 - 1.1	Gray-zone
> 1.1	Positive

IgG Antibodies titre less than 0.9 means a negative result (seronegative), which suggests that after the administration of Covishield vaccination, the antibodies were not developed in the subjects. IgG Antibodies titre more than 1.1means the result is positive i.e., seroprotective, signifying the development of antibodies after Covishield vaccination.

Results

The data has been analysed using SPSS version 22. In this study, mean + SD have been calculated for all the parameters which were analysed and compared using the Student t-test. Significance was assessed at a 5% level of significance. One way ANOVA has also been used to compare the Neutralizing IgG titres at different time intervals post-Covishield vaccine.

The interpretation of results was done on the following basis

- p-value <0.05 – Significant (S)
- p-value <0.01- Highly significant (HS)
- p-value > 0.05 – Not significant (NS)

Table 1 shows that 63.9% females and 36.1% males turned up post six months of Covishield vaccine for evaluation of their Neutralizing IgG Antibodies titres. The percentage of males is more as compared to that of females which may be

attributable to various socio-demographic factors prevalent in the region. Table 2 shows the mean height, weight, and BMI of the individuals. The BMI ranged from as low as 12.9kg/m^2 to 37.2kg/m^2 with the mean 24.69 + 3.70kg/m^2. This signifies that the study sample comprised of individuals with a wide range of anthropometric measurements.

Table 3 shows that there is a significant rise in the Neutralizing IgG Antibodies titres post six months of Covishield Vaccine with the titres being in the seroprotective range with the mean value of 7.07 + 1.36 (Protective cut off titre > 1.1) Table 4 shows that there is a significant increase in Neutralizing IgG Antibodies titres post six months of Covishield Vaccination when compared with the titres post one month after the second and third dose with p-value = 0.00.Table 5 shows the comparison of different clinical variables at different time intervals post-Covishield Vaccine. There is a significant rise in IgG Antibodies titres in covid sufferers as compared to non-covid sufferers with a p-value = 0.01 post 6 months of Covidshield vaccination.

There was no significant effect of comorbidities on the immune response. It was seen that 72.2% of the individuals had trivial adverse effects post Covishield vaccination. Only 19.4% of the subjects had some anaphylactoid reactions which were managed easily through medical intervention thus proving the safety and efficacy of the Covishield vaccine. Table 6 shows the comparison of immunogenicity at different time intervals. It was seen that 28% of the participants were in the seroprotective range post month of the 1st dose of Covishield Vaccine which rose to 37.5% post one month of the second dose. Table 6 shows that all the vaccinated individuals (100%) were seroprotective by the end of six months post-Covishield vaccination.

Table 1: Gender-wise distribution of participants

Gender	Frequency	Percent (%)
Male	46	63.9
Female	26	36.1

Table 2: Anthropometric parameters of the participants post 6 months Covishield vaccination

Parameter	MEAN±SD	Minimum	Maximum
Age (Years)	39.26±13.98	19	69
Height (cm)	165.2+ 0.08	147	182
Weight (kg)	67.54 ± 12.07	36	98
BMI (kg/m^2)	24.69 + 3.70	12.90	32.74

Table 3: Neutralizing Antibodies (IgG) status based on different sampling timeline

Neutralizing Antibodies	MEAN±SD	Minimum	Maximum
IgG-post 1 month	1.09 ± 1.62	0.113	8.07
IgG-post 2 month	1.22 ± 1.63	0.014	7.64
IgG-post 6 month	7.07 ± 1.36	3.11	8.17

Table 4: Comparison of Neutralizing Antibodies (IgG) Titre of individuals at different time intervals post-Covishield Vaccination

Pair	IgG Status	t -value	p-value	Level of significance
1	IgG titre Post 1 month IgG titre Post 2 month	-0.956	0.342	NS
2	IgG titre Post 1 month IgG titre Post 6 month	23.79	0.00	HS
3	IgG titre Post 2 month IgG titre Post 6 month	22.99	0.00	HS

Table 5: Comparison of Neutralizing Antibodies (IgG) titre with COVID-19 status & clinical variables at different time intervals post-Covishield Vaccination

Variables	Status	No.	IgG titre Post 1-month Vaccination			IgG titre Post 2 months Vaccination			IgG titre Post 6 months Vaccination		
Covid status			Mean± SD	t-value	p-value	Mean± SD	t-value	p-value	Mean± SD	t-value	p-value
	YES	11	1.62 ± 1.22	1.47	0.15	1.75 ± 1.21	1.465	0.16	7.78 ±0.81	2.74	0.01**
	NO	61	0.99 ±1.67			1.12 ± 1.68			6.94 ±1.41		
Comorbidities	YES	15	0.72 ± 0.88	1.40	0.16	1.46 ± 2.26	0.49	0.62	7.08 ±1.39	0.03	0.97
	NO	57	1.18 ± 1.76			1.16 ± 1.44			7.07 ±1.37		
Adverse effects	YES	52	1.15 ± 1.64	0.53	0.59	1.29 ± 1.72	0.685	0.49	7.13 ±1.27	0.49	0.62
	NO	20	0.92 ± 1.61			1.03 ± 1.38			6.93 ±1.61		
Anaphylactoid Reactions	YES	14	1.11 ± 2.17	0.05*	0.95	0.95 ± 1.70	-0.67	0.51	6.72 ±1.42	1.04	0.30
	NO	58	1.08 ± 1.48			1.29 ± 1.62			7.16 ±1.35		

* Significant; ** Highly significant

Table 6: Frequency distribution of Immunogenicity at different time intervals post

Immunogenicity	Post 1 Month		Post 2 Months		Post 6 Months	
	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Seroprotective	21	29.2	27	37.5	72	100
Seronegative	51	70.8	45	62.5	0	0

Discussion

COVID-19 pandemic has caused much havoc to mankind in terms of morbidity and mortality, which has resulted in the collapsed and jeopardized health systems across various countries.[10] From there on major concerns by the researchers, health care providers, scientists, epidemiologists etc. has been raised

to develop various measures to curtail and limit the spread of the COVID-19 pandemic. Such a medical health catastrophe gave advent to numerous treatment options like anti-inflammatory drugs, anti-viral agents, monoclonal antibodies, immune boosters etc. which served to provide only palliative treatment and none of those could be documented as definitive measures to combat the disease. [11]

Finally, vaccination was the ultimate resort to combat the disease and the only robust measure to get rid of the pandemic completely. Never in the history of the medical world, have clinical trials been conducted and completed in such a short period and at such a fast pace. Vaccination came out as the only measure to fight the disease at the individual level by stimulating an active immune response and at the community level by generating herd immunity.[12] A multitude of vaccines like Pfizer, Moderna, Johnson and Johnson's Janssen, AstraZeneca / Oxford vaccine, Covaxin, Sinopharm and Sinovac have been approved by WHO after completion of clinical trials. Phase IV trials or post-marketing surveillance have been coming up from the various government and non-government health agencies from time to time, the results of most of which are quite convincing but, quantitatively a lot of variation still ensue in terms of efficacy and safety assessment of these vaccines.[13]

In the current follow-up study, we have tried to elucidate and document the immunogenicity and safety of the Covishield vaccine in a representative sample of the population from Western Uttar Pradesh, India. Moreover, certain variables like the previous history of COVID-19, the occurrence of comorbidities, adverse reactions, anaphylactoid reactions and certain demographic variables have also been taken into consideration while interpreting and exploring the titre of neutralizing IgG antibodies post-Covishield vaccination down the timeline at defined time intervals.

The demographic and anthropometric parameters of the volunteers recruited for the 1st dose of Covishield at our centre are as indicated in Table 1 & Table 2 which shows that the entire age groups from >18 years had been covered and BMI of whom ranged from as low as 12.9 kg/m^2 to 32.7 kg/m^2 making external validity prove feasible signifying that the study sample comprised of individuals with a wide range of demographic characteristics which might help to explore a wide range of variables which might influence the outcomes of vaccination in terms of efficacy, immunogenicity, safety profile etc.

Table 3 & Table 4 describes that the total neutralizing antibodies (spike and nucleocapsid) were measured in a time-bound manner. The first quantification of IgG neutralizing antibodies was done 28 days post 1st dose of Covishield vaccination whereby, neutralizing antibodies were detected ranging from 0.113 to 8.07 with the mean level of 1.09 + 1.62. Following the manufacturers' guidelines values > 1.1 were considered protective. Most of the individuals who had a COVID positive history yielded a higher IgG neutralizing antibodies titre post 1 month of 1st dose heralding that natural infection might have already initiated active immunity in such individuals.[14] However, most of the individuals showed a titre towards the lower end of the quoted range.

The duration between 1 & 2nd dose was 4 -6 weeks as advocated by the Government of India. The 2nd sample was taken 4 weeks after 2nd dose. The IgG neutralizing antibodies detected were in the range of 0.014 to 7.64, mean value being 1.22 +1.63. Contrary, to the usual belief, that the titre would rise significantly as compared to 1st dose in many participants the titre was a little lower as compared to the previous value. Possibly, this can be attributed to the immediate consumption of already formed IgG neutralizing antibodies in neutralizing the protein component of attenuated virion particles introduced by the 2nd dose post-Covishield vaccination.[15]

This is well concerted with a fact which has been earlier explained by various immunologists that, after the introduction of an antigen into a system with the Antibodies in circulation, the interaction between the antigen and the Antibodies causes a transient drop in the quantity of circulating Antibodies. This is referred to as the Negative phase. It is later accompanied by a rise in Antibodies titre beyond the initial level. [16]

Third chronological quantification was scheduled 6 months post complete Covishield vaccine regimen for which 72 participants (Males: n = 46and Females: n= 26) were compliant enough to get their Antibodies titre done and reported. In comparison, female participation for the follow-up was much lesser than the males indicating better compliance of the males which probably may be attributable to socio-demographic factors in this geographical area.

The results obtained 6 months post-vaccination regimen was found to be very convincing as the titre obtained were all in the protective range starting from 3.11 to 8.17 with the mean value being 7.07 ± 1.36, speculating that in long term immunological regulation, varied mechanisms could be held responsible for the development of immunogenicity. Some of the hypotheses/ theories which have been proposed worldwide and unanimously are as follows:

As evident from details in Table 4, there was no significant difference in IgG neutralizing titre post 1 month and 2 months (p=0.34), thus indicating that a single dose might be too meagre to elicit a detectable immune response in terms of immunogenicity. Comparison between IgG neutralizing Antibodies titres post 1 month, and 6 months revealed a significant rise in the neutralizing Antibodies titre post 6 months (p=0.00), indicating the clearcut onset of secondary immune response which is said to be characterized by a lag period and much higher amplitude of secondary response as shown in figure no.1.[17]

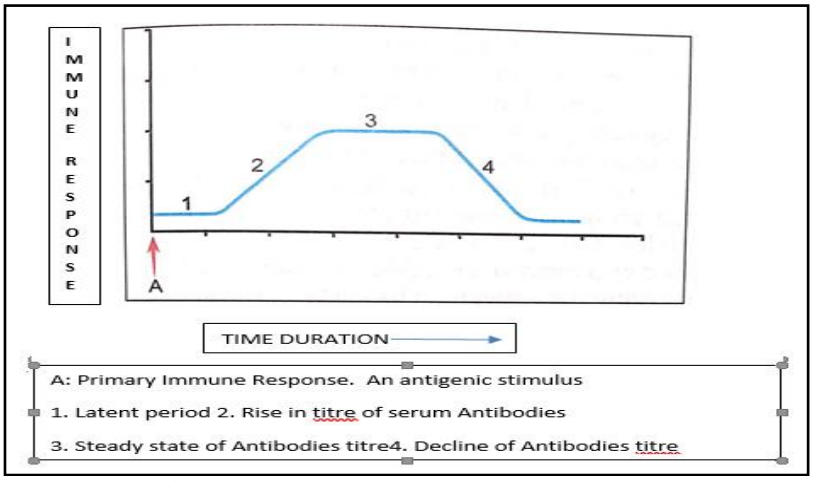

Figure 1: Primary immune response[17]

Like the figure above, the comparison of IgG Neutralizing Antibodies titre among post 2nd month and post 6 months, the titres were almost comparable signifying that the complete Antibodies titre indicates both primary and secondary immune response and that the latter requires a longer period to set in probably allowing memory immune cells to come into play and generate an appreciable and detectable immune response as shown in figure no.2.[17]

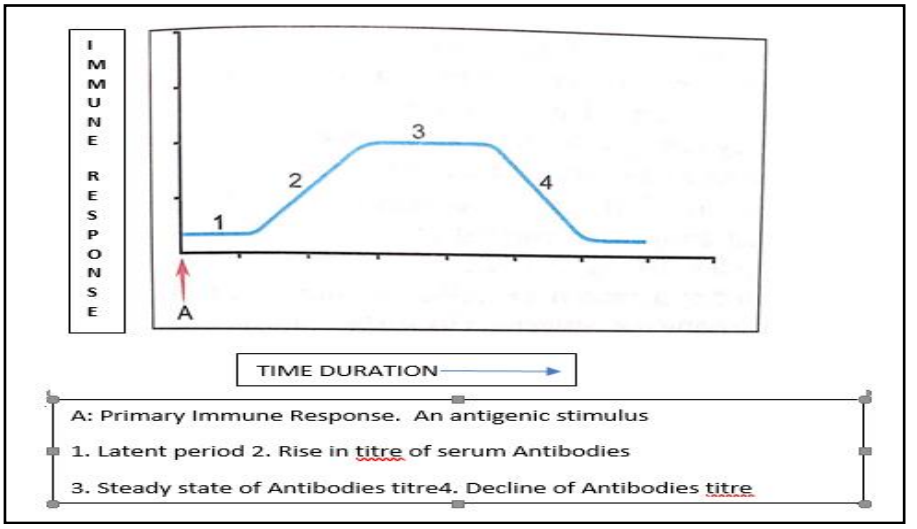

Figure 2: Effect of repeated antigenic stimulus[17]

Influence of other clinical variables, confounding factors on immune response after various time intervals post-Covishield regimen (viz, Table 5) Eleven out of 72 (15.27%) participants in post 6 months IgG Antibodies titre evaluation had COVID -19 positive status before 1st dose of regimen and neutralizing Antibodies titre was significantly higher as compared to COVID -19 non-sufferers. This could be seen possibly in a view of the fact that the individuals with prior COVID -19 infection might have responded to the virion particles' natural inoculation like the effect of

1st dose of vaccination. Thereafter, the 1st dose of the Covishield vaccine might have triggered the secondary immune response and the 2nd dose of the vaccine most probably might have played the role of booster immune response, thus showing heightened immunogenicity in such study participants. The long-term degree of protection was more after a complete immunization regimen in justifying that the natural (Innate) and adaptive (acquired) immunity could have played a cumulative role for higher protective Antibodies titres in fully immunized participants.[18]

On comparing the immune response in different individuals with varied comorbidities, it was observed that the neutralizing IgG Antibodies titres were not significantly different after the six months of Covishield vaccination thus showing that there is no interference of any systemic illness with the immune response generated in participants after immunization with Covishield vaccine. This explains that the Covishield vaccine is equally safe and effective in comorbid patients at all times.[19]

None of the 72 participants exhibited any severe adverse reactions post-vaccination. Minor to moderate temporary symptoms like fever, headache, nausea, dizziness, myalgias, etc was seen in 72.22 % participants, these were relieved with symptomatic treatment modalities. Apparently higher titres were seen in individuals with adverse reactions, but they were not significantly different. Slightly higher protective Antibodies levels in individuals' encountering adverse reactions signify a rapid and prompt response of the immune system. In most of the cases, the adverse reactions were trivial enough to subside naturally within 1-2 days, thus confirming the remarkable safety of the Covishield vaccination regimen.[20]

Fourteen out of the 72 (19.4 %) participants suffered from anaphylactoid reactions which were controlled immediately with the emergency kit available on site and no untoward events were reported, thereafter. No significant difference was observed in the Antibodies titre of the two groups that experienced anaphylactoid reactions. Since the anaphylactoid reactions were seen only in a minor percentage of participants, which were manageable with considerable ease, hence, efficacy along with safety could be estimated in most of the participants. In a nutshell, as shown in Table 6, 29% of participants were protective after 1st sampling (post-1stdose Covishield (28 days)), these population rose to 37.5 % post 2nd dose of Covishield (28 days) and attained 100% immunoreactivity post 6 months after a complete regimen of Covishield.

Assumptions

i. In the government policy regarding the duration from 1st to 2nd dose -8-12 weeks could Change be justified scientifically considering the time-lapse which occurs between primary and secondary immune response.
ii. Rapid onset and heightened immune response in COVID-19 positive participants indicates the role of B and T cell responses.
iii. Insidious onset of response in some participants and especially COVID-19 negative individuals indicates that there might be varied mechanisms by which the immune system of different individuals is intricately regulated.

Immunogenicity is a complex mechanism/interplay of varied immune responses.

iv. It can be assumed that the Covishield vaccine has a high safety margin as no untoward event had occurred during the entire study period.

Implications

i. Single-dose may suffice for COVID-19 positive patients for the attainment of protective neutralising IgG Antibodies titres, especially where resources are limited as in economically backward countries or third world countries.
ii. In the long run, a full regimen must be given to achieve the full protective range.
iii. As the vaccine is found to be highly efficacious and safe, it is administered in full regimen to the entire population to develop herd immunity paving way for community-level protection leading to complete eradication of the disease, bringing pandemic to a halt.
iv. Duration of 8-12 weeks between 1st and 2nd dose was justified on scientific grounds for the time-lapse which is seen between the development of primary and secondary immune response.

Recommendations

i. In the present study 33.4% participants had turned up for the final Neutralized IgG Antibodies titre evaluation. If a higher percentage of participants would have reported for the evaluation, the generalizability of the study would have increased further. Hence, a larger sample size is recommended for further studies to increase the validity of the findings.
ii. Further study is warranted to see the impact of various demographical and social factors on long term immunogenicity after full regimen with Covishield vaccination.
iii. In the present study, results could not be segregated according to different variants of the Coronavirus. Results of the study apply only to delta variant infection which was rampant at the time of the study.
iv. Determination of efficacy on infection by other Coronavirus variants can be a matter of further research and/or evaluation.
v. Although profound development of immunogenicity could be documented in this study, immunoreactivity couldn't be deduced.
vi. Anamnestic immune responses need to be considered while interpreting the status of seroprotective IgG Antibodies in further studies in order to yield information regarding vaccine efficacy.

Conclusion

Conclusively, it can be inferred that ChAdox1 nCoV-19 Covishield Vaccination, if administered in full regimen, has both acceptable efficacies as well as safety profiles (similar in line to other clinical trials) to vaccinate a large proportion of population which, may prove to be an effective strategy for reducing the disease burden of COVID-19 and consequent long term morbid effects. This would also aid in coming out of the pandemic completely in near future.

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