ORIGINAL PAPER

Antibody Response against SARS-CoV-2 Following ChAdOx1(AstraZeneca AZD 1222) Vaccine in Health Care Workers in a Tertiary Care Hospital in India

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Abstract

BACKGROUND: The ChAdOx1 nCoV-19 vaccine against COVID-19 is a two-dose vaccine spread 3 to 4 weeks apart. This study aims to ascertain the antibody response to each dose with respect to age, previous infection status etc. **METHODS:** Baseline total COVID-19 antibody level was ascertained using Siemens SARS-CoV-2 Total Antibody assay in consenting health care workers before the first dose of vaccination. Adverse effects were noted in each individual and were monitored weekly for the total antibody titre following both doses. Descriptive statistical tests were used to analyse the changes in antibodies levels weekly after both doses. Association of previous COVID infection and age with antibody levels was assessed. **RESULTS:** Median (range) of age of the 30 study participants was 31.5 years.23% of the participants had a history of previous COVID-19 infection. Mild adverse events following immunisation were reported by 87% participants after first dose whereas only in 7% after second dose. Median baseline antibody titres were significantly higher among those with previous COVID infection as compared to previously uninfected individuals. Antibody titres increased consistently after first dose and showed a declining trend following the second dose in all participants and showed no significant association with previous COVID-19 infection or age. **CONCLUSIONS:** Antibody titre response was similar amongst the various age groups. Higher response in the previously infected individuals following first dose may make them ideal candidates for a single dose vaccine regimen. Individuals showing lower levels of neutralising antibodies can be ideal candidates for a booster dose.

Keywords: COVID-19 vaccine, ChAdOx1 nCoV-19, influenza vaccines, vaccination and immunity.

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INTRODUCTION

As a global response to the COVID-19 pandemic, several vaccines against the SARS-Cov2 virus have been simultaneously developed by various agencies and are forming the backbone of humanities fight against the disease through targeted and mass vaccinations[1,2].

Developed by Oxford University and AstraZeneca, the COVID-19 vaccine, codenamed AZD1222 or ChAdOx1 nCoV-19 vaccine, is sold under the brand names Covishield and Vaxzevria. The vaccine uses the modified chimpanzee adenovirus ChAdOx1 as a viral vector and is administered intramuscularly in two doses spread 3 to 4 weeks apart.

ChAdOx1 nCoV-19 is a replication-deficient simian adenoviral vector that expresses the full-length SARS-CoV-2 spike protein. In preclinical studies, either a single dose or two doses of

ChAdOx1 nCoV-19 vaccination prevented SARS-CoV-2-mediated pneumonia in rhesus macaques[3].

Further clinical studies have shown that even a single dose of this vaccine is producing a strong antibody response in more than 80 percent of the human recipients[4].

Even though antibody response and T cell response are the main arms of the adaptive immune response following vaccination against viral pathogens, the mechanisms and duration of protective immunity in COVID-19 remain to be elucidated.

Earlier this year, the health care workers (HCWs) at our facility were administered both the doses of this vaccine at an interval of 4 to 6 weeks. This study aims to ascertain the safety and the antibody response to each dose and study its pattern with respect to age, previous infection status and duration between doses.

MATERIAL AND METHODS

A pilot study group of 30 HCWs was identified between the ages of 25 to 50 and their previous medical history was noted. After obtaining informed consent to participate in this study, a baseline total COVID-19 antibody (Ig G + Ig M) level was ascertained using Siemens automated biochemistry analyser parameter SARS-CoV-2 Total Antibody assay (COV2T) which is a chemiluminescent assay detecting the concentration of total antibodies to SARS-CoV-2 in human serum and plasma and an absorbance value of greater than 1000 QUAL units is considered as positive. The absorbance is directly proportional to the concentration of antibodies in the serum/plasma.

Following the first dose of vaccination, adverse effects were noted in each individual and all the study subjects were monitored serially on a weekly basis for the total antibody titre using the same test as before.

This was followed by the second dose of vaccination at an interval of 4 to 8 weeks and the gap between the doses for each individual, adverse effects after the second dose and weekly total antibody titres were recorded as before.

Statistical analysis

Data was summarised by median, inter-quartile range and proportions. Antibody levels in two groups were compared by Mann Whitney test. Linear mixed effect models were used for analyzing the changes in antibodies levels over time after first and second vaccine dose. Association of previous COVID infection and age with antibody levels was also assessed. Variables with $p < 0.1$ in univariable analysis were included for multivariable analysis. R software ver 3.6.3 was used for statistical analysis and nlme package was used for linear mixed effect modelling. p value of less than 0.05 was statistically significant.

Ethical issues

Approval of the study was obtained from Institutional Ethics Committee. Informed consent of all study participants was taken.

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RESULTS

A total of 30 HCW participated in this study, out of whom only 2 (7%) were female. Median (range) of age of study participants was 31.5 (25 - 50) years. No study participant had any comorbidity. Seven (23%) of the participants had a history of previous COVID-19 infection, of which 2 recovered from mild, 4 from moderate and 1 from severe disease. Median (range) gap between previous infection and first dose of vaccination was 153 (132 -214) days for these seven individuals. Mild adverse events following immunisation were reported by 26 (87%) study participants after first dose - most common being myalgia (16 HCW, 53%) and fever (13 HCW, 43%). Only 2 (7%) HCW reported mild fever and myalgia after second dose.

Baseline titres

Median (IQR) baseline antibody titres before first dose of vaccine were 437 (234 -826) IU/L. These titres were significantly higher among those with previous COVID infection as compared to individuals with no documented COVID infection (5000 IU/L vs 292 IU/L). Baseline antibody titres of 6 (85.7%) of previously infected individuals were > 1000 Qual units.

Change in antibody titres after first dose

Antibody titres increased consistently after first dose in all participants till 3 weeks after first dose (Figure 1).

Median (IQR) antibody titres after first, second and third week following prime dose of vaccine were 7046 (5429 – 14106), 29835 (16295 – 45252) and 45093 (25438 – 51765) respectively. Though antibody titres were higher among previously infected HCW, the difference was not statistically significant except after first week (Table 1). Average increase in antibody titres (after adjusting for previous COVID infection) was around 13000 QUAL units every week for the first three weeks. No significant association of increase in titres after first dose was observed with history of previous COVID-19 infection or age (Table 2 & Figure 2).

Table 1. Week wise Antibody Values with Inter Quartile Range

	Total (n =30)	**No previous COVID infection group (n =23)**	**Previous COVID infection group (n =7)**	**P value**
Baseline	437 (233.8 – 826)	292 (197 – 356)	5000 (1759 – 10610)	0.0001
D + 7 days	7046 (5429 – 14106)	6555 (4739 – 12367)	26783 (14605 – 44668)	0.0077
D +14 days	29835 (16295 – 45252)	28742 (16502 – 42399)	45379 (18688 – 61353)	0.3478
D + 21 days	45093 (25438 – 51765)	42744 (25764 – 51088)	48806 (24512 – 63499)	0.6005
D + 28 days	15434 (10511 – 31306)			
DD+7 days	39609 (23212 – 44872)	39474 (25628 – 44861)	39823 (28738 – 47011)	0.6692
DD+14 days	29837 (15400 – 38776)	28843 (14690 – 37661)	33677 (19837 – 42691)	0.4467
DD+21 days	16545 (8832 – 18712)	16545 (8832 – 18712)		
DD + 28 days	9665 (6439 – 12100)	8924 (6180 -10733)	19255 (10735 – 27506)	0.0799

Table 2. Linear mixed model analysis showing average difference per week following first dose of vaccination

	Univariable Analysis		**Multivariable analysis**	
	Regression Co-efficient	**P value**		
Time (Per Week)	13023 (8722, 14982)	< 0.0001	13009 (11050, 14967)	< 0.0001
Previous COVID infection (Yes Vs No)	11412 (- 87, 22912)	0.0516	11103 (-241, 22446)	0.0547
Age	16 (- 637, 668)	0.9610	-	-

Change in antibody titres after second dose

As depicted in Fig 1 and Table 3, average decline of 8096 units per week was observed in antibody levels after second dose of vaccine. Median (IQR) antibody titres fell from 39609 (23212 – 44872) one week after second dose to 9665 (6439 – 12100) after four weeks. This declining trend was observed in individuals with previous COVID infection as well as in those with no history of previous COVID infection (Figure 3).

Table 3. Linear mixed model analysis showing average difference per week following second dose of vaccination

	Univariable Analysis	
	Regression Co-efficient	**P value**
Time (Per Week)	- 8096 (-9543, - 6649)	< 0.0001
Previous COVID infection	4157 (-6485, 14800)	0.4287
Age	- 96 (-625, 433)	0.7121

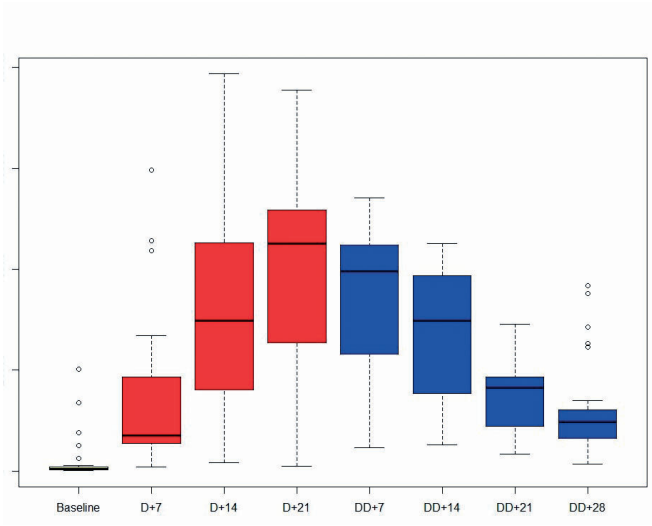

Figure 1. Box and whisker plot showing antibody titres post first dose(D) and second dose (DD).

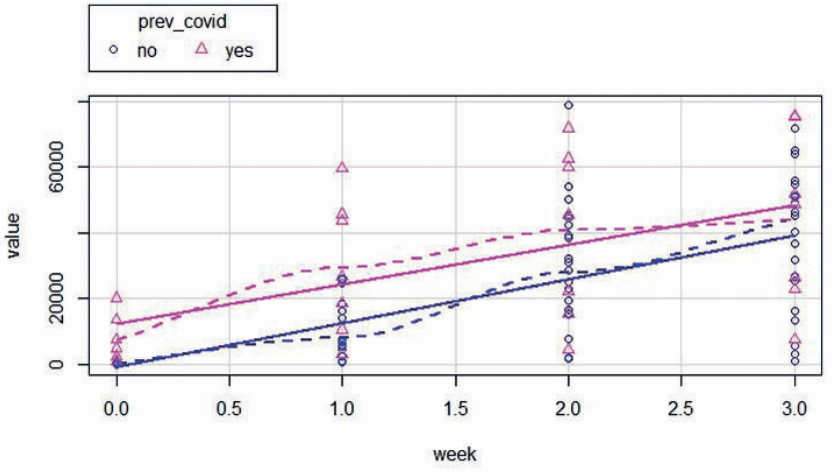

Figure 2. Linear mixed model showing a rising trend in the antibody titres during the first three weeks post first dose

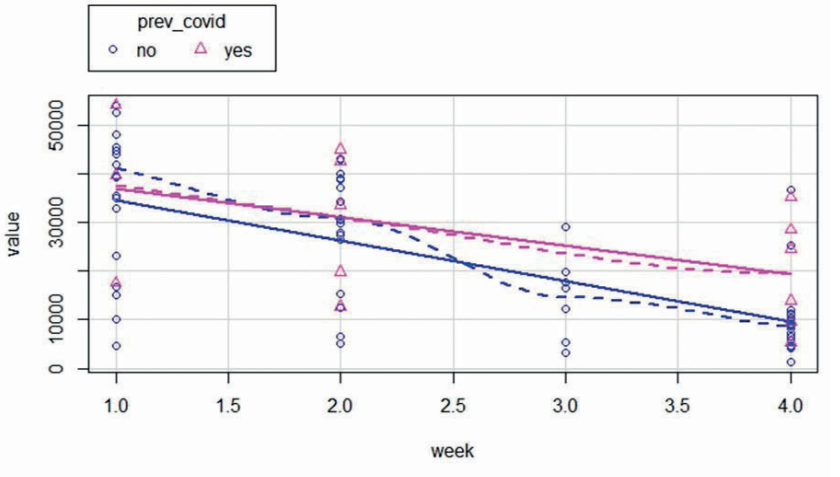

Figure 3. Linear mixed model showing a decreasing trend in the antibody titres during the weeks post second dose.

DISCUSSION

The adaptive immune response to SARS-CoV-2 virus comprises T and B cell immunity and antiviral neutralizing antibodies. The antibody-mediated immune response against the SARS-CoV-2 virus is primarily aimed at the spike glycoprotein and N (nucleocapsid) protein[5,6].

The AstraZeneca AZD1222 vaccine is a safe double dose vaccine ideally to be administered at an interval of 4 to 6 weeks.

Mild Systemic and local side effects were noted in all previously uninfected individuals which were alleviated by single dose of NSAIDS which was similar to the findings of the phase 1 and 2 randomized control trials[7].

However, amongst the previously infected and recovered individuals who received the vaccine in our study, only 57 percent exhibited mild systemic side effects like fever and myalgia. These results contrast with the observations by Menni et al who found a low adverse effect rate of 33.7 percent with the ChAdOx1 vaccine compared to the 88 percent in the phase 2 and 3 trials. They also noted that that Individuals with evidence of past SARS-CoV-2 infection were more likely to have adverse effects than those without past infection with this vaccine[8].

Inspite of initial recommendations of a 4-to-6-week interval between the two doses, in many regions, the second dose of the vaccine was delayed by up to 3 months to ensure greater population coverage of the first dose[9].

The findings of our study show definite advantage of this strategy as the rate of seroconversion following the first dose of the vaccine was greater than 90 percent suggesting adequate interim protection following a single dose.

Jeewandara et al elicited similar results in Sri Lanka where a robust rate of seroconversion was seen after the initial dose of the two-part vaccine.in addition ACE 2 blocking antibodies were formed in more than 97 percent of their naïve vaccine recipients[10].

Similarly, a metaanalysis by Voysey et al demonstrated a high efficacy of a single dose of vaccine in the first 90 days with better immunogenicity with a longer duration between doses[11].

This suggests that a single dose provides adequate protection for a duration for as long as 90 days, and this may be exploited to maximise the first dose coverage of the population.

It was noted that the baseline titres of all the previously COVID-19 infected individuals in the current study was significantly higher than the previously uninfected group which suggests that previous infection provides a sound immune response to the disease. However Various studies have suggested that the principle functional immunity is governed by the memory B cells and memory T cells and decreases over time even if it doesn't disappear[12,13]. Therefore vaccine should not be denied to the previously infected and recovered individuals. They may however be ideal candidates for a single dose regimen or may be placed low on the vaccination priority list as antibody response amongst the previously infected individuals following the first dose of vaccination was higher than the previously uninfected population initially which suggests a higher response to a single dose of vaccine amongst the previously infected. Like our findings, Saadat et al also observed that Health care workers with previous COVID-19 infection had higher antibody titre responses to a single dose of mRNA vaccine than those who were not previously infected[14].

In our study, the antibody response increased consistently following the first dose in all the individuals. The previously infected individuals who had received the vaccine showed a greater response in terms of rising antibody titre in the initial 3 weeks, but no significant difference was seen in the response thereafter. This suggests that the antibody response following the first dose of the vaccine is as potent as previous infection in terms of seroconversion.

With respect to the age groups, no significant difference was seen in the immune response to the vaccine across various age groups. Ramasamy et al also observed that in participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses were similar across the three age cohorts in their study[15].

The overall trend of total antibody titres in our study shows an initial rise in the total titres followed by a steady fall in the total titres following the second dose. This corroborates the observations in the systematic review conducted by Post et al in which levels of IgM antibody peaked between 2 to 5 weeks and declined over the next 3 to 5 weeks. IgG peaked around weeks three to seven post-symptom onset then plateaued, generally persisting for at least eight weeks[16].

None of the subjects included in this study contracted COVID-19 infection post vaccination till date which suggests good vaccine efficacy. This may be due

to the limited sample size of our study as various reports of post vaccination breakthrough infection have been reported worldwide with the incidence dramatically decreasing with each passing week post vaccination[17].

CONCLUSION

1. ChAdOx1 nCoV-19 Vaccine, also known as Astra Zeneca AZD1222 and Covishield is a safe and effective vaccine with a very robust rate of seroconversion even after the first dose.
2. No difference was seen in the antibody titre response amongst the various age groups.
3. The previously infected individuals mount a higher antibody response in the first few weeks following the first dose of vaccination, however no significant difference is noted thereafter between the infected and the uninfected group.
4. The previously infected group may be ideal candidates for a single dose vaccine regimen or can be placed low on the priority list.
5. Since the total titres fall over an extended period, specific tests can be done to detect neutralising antibodies and to detect the cellular response. Individuals showing lower levels of either can be ideal candidates for a booster dose.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.