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Research Paper

Sequential Observation of Antibody Response Pattern at 3 and 6 Months Following ChAdOx1 nCoV-19 Vaccination Among Health Care Workers-A Prospective Single Cohort Study

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Running Title Six Month Trend of ChADoX1nCoV-19 Vaccine Response

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ABSTRACT

Background: The duration of the immune response induced by ChAdOx1 nCoV-19 vaccination in a real-world setting is unknown.

Objectives: This study is aimed to estimate the 6-month trend of SARS-CoV-2 antibody titer after Covishield vaccination among Health Care workers (HCW) and their associated factors.

Materials & Methods: A prospective single cohort study of health care workers was done in a tertiary care-teaching institute of central Kerala from January 2021 to October 2021. HCWs who have given pre-vaccination serum sample for SARS-CoV-2 antibody estimation and negative for SARS-CoV-2 antibody were included. They were followed up and their blood samples to check for antibody levels were taken 28 days after first dose, 2 weeks after second dose, and 3 and 6 months after first dose of ChAdOx1 nCoV-19 vaccine. Samples taken from 102 HCW were sent for SARS-CoV-2 IgG antibody testing.

Results: Mean age of the study participants was 39.3 (age range:19 - 71) yrs. and 71.6% were females. Antibody levels of participants at 3rd month ranged from 0.28 S/C to 21.2 S/C with a mean of 8.01. Only 34 (33.3%) HCW had IgG antibody levels >9.5 S/C. Mean antibody level further declined to 6.09 S/C at 6th month. Only 19 (28.4%) had antibody levels more than 9.5 S/C at 6th month. HCW with aged less than 50 years and those who had COVID disease during

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the study period had a significantly higher level of IgG antibody titres. Quantitative results were reported as signal to cut-off (S/C) value.

Conclusion: The study found that after vaccination with Covishield vaccine IgG levels peaked at 14 days following second dose of vaccine, then getting decreased in the third month and further in sixth month confirming the need for a booster dose. COVID antibody levels were significantly higher in COVID infected HCW and in young age participants.

Keywords: Antibody response, ChAdOx1 nCoV-19 vaccine, Health care workers, Prospective cohort

1. Introduction

Since November 2019 the world has been witnessing the various phases of SARS-CoV-2 pandemic. There have been 251,788,329 confirmed cases of COVID-19, including 5,077,907 deaths, reported to World Health Organization (WHO) till November 15th 2021 [1]. Tremendous tireless work by mankind resulted in a number of safe and effective COVID vaccines. A number of vaccine was listed for emergency use by WHO Emergency Use Listing (EUL) [2]. As of 15th November 2021, a total of 7,160,396,495 doses of vaccine have been administered worldwide [1].

India started vaccinating its people from January 16, 2021 with two vaccines; ChAdOx1 nCoV- 19 coronavirus vaccine (CovishieldTM) and CovaxinTM/BBV-152, manufactured by Bharat Biotech, Hyderabad in collaboration with Indian Council of Medical Research (ICMR). These vaccines have been given in a phased manner in India. As on 15 November 2021, India have administered 123,430,478 vaccine doses. Jubilee Mission Medical College & Research Institute (JMMC&RI), Thrissur, a tertiary care hospital of South India, started vaccinating its Health Care Workers (HCW) with Covishield which has two dose regimen given at an interval of 4-6 weeks. Covishield is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein, produced in genetically modified human embryonic kidney (HEK) 293 cells. From the results of clinical trials, it is evident that Covishield induces a sufficient antibody response, 28 days after its first dose, including the elderly [3]. Even though it's a 2 dose vaccine regimen, the dynamics of antibody response following vaccination in a real world setting is not much known. Only on-going research can find the duration of protection of COVID-19 vaccines and how the various intrinsic and extrinsic factors influence its effectiveness. The need for a booster especially for front line workers like HCW should be explored at the earliest. Therefore, in this study, we report the antibody titre of HCW of JMMC&RI at their 3rd and 6th month of first dose of their Covishield vaccination and factors associated with it.

2. Methods

Study design and participants

The study is part of an ongoing prospective single cohort study of HCW, who had taken two doses of Covishield with an interval of minimum 28 days in between. The study is done at JMMC & RI, Thrissur, a tertiary care & teaching center of central Kerala with around 3000 health staff. On 19 January 2021 the institution initiated COVID vaccination for the public, after completion of vaccinating its own HCW in the first phase. This study started from January 2021 to October 2021. HCW of JMMC & RI who have given their pre-vaccination serum sample for SARS-CoV-2 antibody estimation and negative for SARS-CoV-2 antibody were included in the study. Informed consent was obtained from 170 volunteers and a self-administered questionnaire in Google forms was sent to the participants for providing basic demographic, anthropometric and comorbidity details. These HCW were followed up and their blood samples to check for antibody levels were taken 28 days after first dose of vaccine, 2 weeks after the second dose, 3 months and 6 months post first dose. Dates were confirmed by cross checking of the employee health records. A 5 ml blood sample was taken from each participant on these 4 time points by a trained phlebotomy team from the department of transfusion medicine. Samples were taken from 170 HCW before the second dose ,154 HCW 14 days following the first dose, 137 HCW in 3rd month and 117 HCW in the 6th month. We excluded HCWs who had active COVID diseases (14 days from the diagnosis) at the time of blood collection, who failed to provide any one of the 4 blood samples i.e., on 28 days after first dose of vaccine, 2 weeks after the second dose, 3 months and 6 months post first dose, and who refused to give consent for repeat blood samples. The final sample size was 102. COVID-19 disease was reported by 10

participants during the study period between the third and sixth month of the first dose.

Antibody testing

The blood samples collected at 3 months and 6 months post the first dose of vaccination were centrifuged, separated immediately and frozen at -20 degrees for batch testing.

SARS-CoV-2 IgG antibody testing was done using the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack in combination with the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Calibrator (Ortho Clinical Diagnostics, US) on the VITROS 5600 immunodiagnostic integrated system, intended for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum. The sensitivity and specificity at >/= 8 days was 90.0% and 100.0% respectively [4].

Sample results are reported as signal to cut-off (S/C) values for quantitative and as non-reactive (S/C < 1.0; negative) or reactive (S/C ≥ 1.0; positive) for qualitative report. The protective levels observed post vaccination have not yet been validated. The value above 9.5 S/C is considered as the protective level for convalescent plasma according to the US FDA document published for use in the manufacture of high titre Covid-19 Convalescent Plasma [5]. Although, the magnitude of the measured result above the cut-off is not indicative of the total amount of antibody present in the sample, the measured levels at specified intervals can be as an indicator of recent or prior infection or of presence or absence of protective immunity [6].

Statistical analysis

Data was collected and entered into Microsoft Excel and analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 25. A total of 102 samples were analyzed for the baseline characteristics but for further calculation, 10 participants with positive COVID history were excluded. Qualitative variables were presented as proportions or percentages; continuous variables as mean with standard deviation or median with interquartile range. Antibody levels at different time points were compared using Friedman's two-way Analysis of Variance by rank. Post-hoc comparison was made using Conover test. Association of selected factors with immune response at 6 month were assessed by chi-square test and Mann Whitney U test.

3. Results

General characteristics

We studied 102 participants who took two doses of ChAdOx1 nCoV- 19 coronavirus vaccine (CovishieldTM), filled the questionnaire and consistently gave 4 samples to check for antibody levels. Baseline characteristics of study participants are shown in Table 1. The mean age of the study participants was 39.3yrs which ranged from 19 to 71 yrs. The majority (73 subjects, 71.6%) were females. Only 51 had a normal body mass index. Among 13 (12.7%) HCW with comorbidities, hypertension (28%), thyroid disorders (16%), and bronchial asthma (16%) were the most common diseases. Fever (54.9%) was the most common Adverse Event Following Injection (AEFI), followed by pain at the injection site 33(32.4) and myalgia 31(30.4). No AEFI was reported by 16(15.7%) HCW. History of any vaccination within past five years was given by 53(53%) participants and 16(15.7%) took flu vaccine during the same period. BCG vaccine scar was found in 81(79.4%) HCW.

Antibody levels

Antibody levels in third month

Antibody levels of participants at 3rd month ranged from 0.28 to 21.2 with a mean level of 8.01 S/C. Only 34(33.3%) of HCW had IgG antibody levels >9.5. None reported a history of COVID disease before the blood sample collection of third month.

Antibody levels in 6th month

IgG antibody levels of participants significantly decreased from 8.01 in the 3rd month to a mean of 6.09 at 6th month and ranged from 0.05-19.7. Only 19 (28.4%) had antibody levels more than 9.5 (Table 2).

Antibody levels of HCW at various time points

The antibody levels were at the maximum level at two weeks following the second dose and it started weaning off from that point to a level similar to the antibody level of 28 days after the first dose. There was significant difference on antibody levels over time (P<0.001). On multiple comparison test, antibody levels at all the different time points were significantly different except for the Antibody levels after 28 days post first dose and at 6 months (Table 3).

Table 1. General characteristics of study participants

Variables		No. (%) (n=102)
Gender	Male	29(28.4)
	Female	73(71.6)
BMI	Under Weight	11(10.8)
	Normal	52(51.0)
	Over Weight	39(38.2)
	Comorbidities	13(12.7)
Duration of Comorbidities (n=13)	≤3 years	4(33.3)
	3-5 years	1(8.3)
	5-10 years	6(50.0)
	> 10 years	2(16.7)
BCG Vaccination status	Vaccinated	81(79.4)
	Not aware	21(20.6)
Flu Vaccination status	vaccinated	16(15.7)
	Not vaccinated	65(63.7)
	Not aware	21(20.6)
Time period of prior Vaccination before Covishield	In Childhood	14(13.7)
	Within 5 years	54(52.9)
	5 to 10 years	17(16.7)
	More than 10 Years	17(16.7)
AEFI	Fever	56(54.9)
	Myalgia	31(30.4)
	Pain at Injection Site	33(32.4)
	Chills	18(17.6)
	Head ache	29(28.4)
	No Reaction	16(15.7)

AEFI: Adverse Events Following Injection; BMI: Body Mass Index.

Table 2. Percentage of health care workers with antibody levels >9.5

Follow Up	No. (%)
28 Days after First dose	13(12.7)
14 days after Second dose	69(67.6)
3 Months after First Dose	34(33.3)
6 Months After First dose	19(28.4)

Table 3. Comparison of antibody levels of health care workers at various time points

Follow Up Time Point	N	IgG Antibody (S/C)		P
		Mean±SD	Median (IQR)	
28 Days after First dose	102	4.82±4.77	3.36 (1.37-7.18)	<0.001
14 days after Second dose	102	11.08±4.19	11.55 (8.06-13.80)	
3 Months after First Dose	102	8.01±4.87	7.57 (4.03-11.53)	
6 Months After First dose	102	6.09±6.00	3.51 (1.32-10.65)	

Table 4. Factors associated with antibody level among health care workers at 6-month post vaccination

Variables		IgG antibody (S/C)		P
		≥ 9.5	< 9.5	
		No. (%)		
Age	< 50	19(25.3)	56(74.7)	0.019
	≥ 50	0(0.0)	17(100.0)	
Sex	Male	5(20.0)	20(80.0)	0.925
	Female	14(20.9)	53(79.1)	
BMI	Under Weight	3(37.5)	5(62.5)	0.186
	Normal Weight	12(24.0)	38(76.0)	
	Over Weight	4(11.8)	30(88.2)	
Any Comorbidities	present	1(8.3)	11(91.7)	0.258
	Not present	18(22.5)	62(77.5)	
AEFI	Yes	1(7.1)	13(92.9)	0.175
	No	18(23.1)	60(76.9)	
BCG vaccination status	vaccinated	14(18.7)	61(81.3)	0.512
	Not aware	5(29.4)	12(70.6)	

S/C: Signal to cutoff ration; BMI: Body mass index; AEFI: Adverse Events Following Injection.

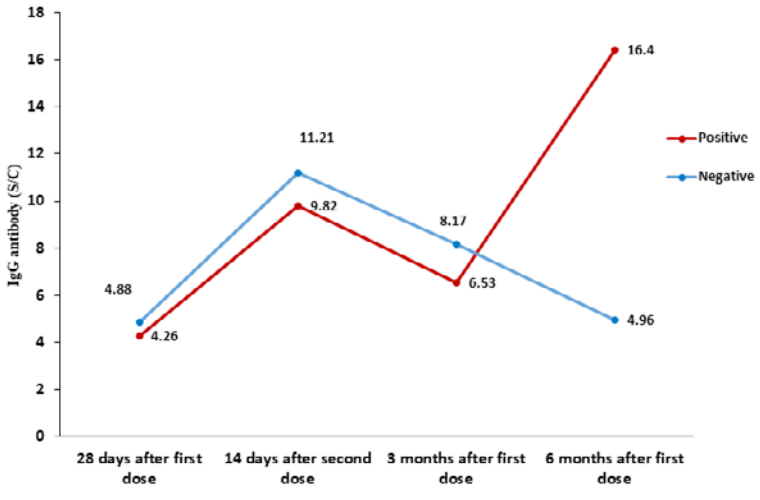

Figure 1. Trend of antibody levels of COVID infected and non-infected health care workers

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COVID Disease

Among the 102 participants, 10 gave history of COVID disease in between 3rd and 4th sample. When the mean antibody titre of non-COVID infected participants (n=92) decreased to 4.96, the mean of COVID infected HCW increased to 16.4 in the 6th month (Figure 1).

Associated factors of post-vaccination antibody level

Analysis of the associated factors were performed only on non-COVID infected participants. HCW of age less than 50 yrs. had a significantly higher level of IgG antibody than those above 50 yrs. Other factors like gender, comorbidity, BMI, history of any vaccination, BCG vaccine, and AEFI following Covishield vaccine injection had no significant association with the antibody levels (Figure 4).

4. Discussion

SARS-CoV-2 IgG antibody testing of the collected samples were done using the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Chemi-luminescence kit manufactured by Ortho Clinical Diagnostics, USA. It was validated and found to have a high specificity in detection of antibodies in convalescent plasma of Covid infected patients, with sensitivity reported as 83.3% (12-15 days) & 90.0% (>/= 8 days) and Specificity of 100.0%, in a comparative study by Padoan A et al comparing five SARS-CoV-2 antibody assays [4]. We followed the cut-off value of 9.5 S/C which is prescribed by the manufacturer based on protective levels required for convalescent plasma since the protective levels of antibody, post vaccination, have not yet been validated. The clinical utility behind the use of VITROS™ Anti-SARS-CoV-2 IgG test platform in our study was based on the proven fact that estimation of vaccine responses and population seroprevalence are enhanced, if it is known that the antibodies detected correlate with neutralizing capacity. It is widely reported that anti-spike antibodies, as used in VITROS™ Anti-SARS-CoV-2 IgG kit, correlate more closely with neutralizing antibodies [7, 8] than anti-nucleocapsid antibodies and. VITROS™ Anti-SARS-CoV-2 IgG showed high sensitivity, specificity, and positive predictive value, suggesting that the selected assay will be useful for assessment of population seroprevalence and response to vaccines [9].

We report the IgG antibody response after vaccination with Covishield vaccine among 102 health care workers who had consistently given 4 serum samples for estimation of antibody titres. The mean antibody titre decreased significantly from third month to sixth month post vaccination. The protective antibody levels at three months post vaccination were found in 33.3% participants, which considerably reduced to 28.4% at sixth month. A similar finding was reported by Naaber et al. [10], (BNT 162b2 vaccine) who reported that, the S-RBD IgG levels decreased to 5226 AU/mL (IQR 3097 – 6924) at 12 weeks (P<0·0001) and further to 1383 AU/mL (IQR 893 – 2463) at 6 months (P<0.0001).

Another study by Swadźba et al. [11] on the humoral response induced by the Pfizer/BioNTech Comirnaty COVID-19 vaccine reported that the concentration of antibodies significantly decreased between days 90 and 120.

We analyzed and compared the trend of antibody levels between those who had a history of COVID-19 and those who did not. Nine participants had tested COVID positive between third and fourth sample collection time points. The mean antibody titre was significantly higher among those with history of COVID infection (14.70) than those without COVID history (5.04). Our observation is in concordance with two different studies by Erpos et al. [12] and Modenese et al. [13] which reported superior antibody response over time to be associated with prior COVID-19 infection

HCW of age less than 50 yrs. had a significantly higher level of IgG antibody than those above 50 yrs. This finding is consistent with that of Erpos et al. [12] where, younger age group participants had a significantly higher antibody response (young individuals had higher values at Day 36, Day 50, and Day 111). Shachor-Meyouhas et al. [14] analysed immunogenicity trends one and three months after second BNT162B2 vaccination among healthcare workers in Israel and reported that older age was associated with lower mean antibody levels (-1.22 AU/ml, P<0.001, 95%CI -1.43 - -1.01). Elderly individuals are also known to be poor responders to other vaccines such as influenza and pneumococcal vaccines by virtue of developing lower antibody levels and decreased cell-mediated immune responses [15].

No association was found between gender and antibody response at third and sixth months post vaccination. However, Swadźba et al. [11] reported that women were able to produce more persistent humoral response as compared to men.

Our study reports that BMI, history of any other vaccination, BCG vaccine, or AEFI following Covishield

vaccination had no significant association with the antibody titress. This is in contrast to the findings by Erpos et al. [12] that, presence of underlying comorbidities (-10.86AU/ml, P= 0.007, 95% CI -18.81 -2.91) and treatment with immunosuppressive drugs (-28.57AU/ml, P=0.002, 95% CI -46.85 -10.29) were associated with significantly lower mean antibody levels. The same study found that occurrence of allergic reactions after vaccination was not correlated with antibody levels, which was consistent with our finding.

10 patients among our 102 participants had given a history of COVID disease in between 3rd and 4th sample. The mean antibody titre of non-COVID infected participants (n=92) decreased to 4.96, while the mean of COVID infected HCW increased to 16.4 in the 6th month. This finding could be due to the difference in the circulating antibodies and the memory B cells which are formed in response to vaccination and natural infection. Immediately after vaccination/infection, the circulating antibodies usually rises and decreases a few months later but the memory B cells can persists to prevent severe disease for decades. And they evolve over time, learning to produce successively more potent "memory antibodies" that are better at neutralizing the virus and more capable of adapting to variants. Greater amounts of circulating antibodies are produced by vaccination than natural infection, whereas, a new study suggests that all memory B cells are not created equal. While vaccination gives rise to memory B cells that evolve over a few weeks, natural infection could produce memory B cells that continue to develop over several months [16].

One of the limitations of current study is under representation of males and elderly since majority of HCW are female adults. Among the 3000 staff, only those volunteered for the study were included in the study which may lead to volunteer bias. Since blood sample was taken 3 months after the third sample the exact point of time antibody level started to decline could not find out.

5. Conclusion

The study found that Covishield vaccine showed an initial vaccine response after two doses of vaccine, but it declined later in COVID uninfected HCW. The IgG levels peaked at 14 days following second dose of vaccine, then getting decreased in the third month and further in sixth month confirming the need for a booster dose. The antibody levels at sixth month was similar to the antibody levels developed after first dose of Covishield vaccine. COVID antibody levels were significantly higher in COVID infected HCW and in young age participants. Follow-up studies in larger population is vital in determining the further trend of serum antibody levels in persons immunized with covid vaccines.

Ethical Considerations

Compliance with ethical guidelines

The study proposal was approved by the Institutional Ethic Committee of Jubilee Mission Medical College & Research Institute, Thrissur (IEC study ref no: 38/21/IEC/JMMC & RI dated 18-02-2021).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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