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Antibody response to receptor-binding domain of SARS-CoV-2 spike protein following vaccination and natural infection with SARS-CoV-2

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Abstract

Background and objectives: Antibody to SARS-CoV-2 develops both after natural infection with SARS-CoV-2 and vaccination. This study was undertaken to determine the antibody response to SARS-CoV-2 among population after natural SARS-CoV-2 infection and vaccination.

Material and methods: The study was carried out on adults aged 18 years and above. Study population consisted of four groups. Group-1 (control): healthy and history of no prior SARS-CoV-2 infection and vaccination, Group-2: had past SARS-CoV-2 infection and no vaccination, Group-3: received two doses of recombinant adenoviral vector vaccine ChAdOx1 (Oxford–AstraZeneca) without past SARS-CoV-2 infection, and Group-4: had past SARS-CoV-2 infection and received 2 doses of ChAdOx1 vaccination.

Blood was collected 1 and 7 months after the second dose of vaccination from Group-3 and 4 individuals. Single blood sample was collected from participants of Gr-1 and 2 at the time of enrolment. Immunoglobulin G (IgG) antibodies to receptor-binding domain (RBD) of SARS-CoV-2 spike protein S1 (anti-RBDS1 IgG) was determined in serum by ELISA method.

Results: Total 176 participants aged 18 years and above were enrolled. Anti-RBDS1 IgG positivity rates were 51.9%, 66.7%, 96.8% and 100% in individuals of Group-1, 2, 3 and 4 respectively. Gr-4 had significantly ($p < 0.05$) mean higher anti-RBDS1 IgG antibody level (120.8 ± 31.9 DU/ml) compared to other groups 1 month after 2nd dose of vaccination. No significant differences in antibody response were found among the individuals of four groups across gender and comorbidities. Seven months after the 2nd dose of vaccines, the antibody concentration declined in 85.3% (112.1 ± 30.4 DU/ml to 75.9 ± 48.7 DU/ml) and 81.5% (127.3 ± 20.4 DU/ml to 92.5 ± 43.6 DU/ml) individuals of Group-3 and Group-4 respectively. Decline of antibody was 40.6% and 34.7% in 7 months, but all remained positive except 1 in Group-3. Fever (34.4%) and headache (24.8%) were the most common adverse effects noted after vaccination.

Conclusion: The study revealed that ChAdOx1 nCoV-19 vaccine induces high concentration of persisting anti-RBDS1 IgG antibody after 2nd dose and previous infection with SARS-CoV-2 acts as immune priming. Therefore, antibody screening test prior to booster dose could be a good option to maximize coverage of vaccination.

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Introduction

The world is currently facing pandemic due to severe acute respiratory syndrome corona virus–2 (SARS-CoV-2) since its origin in December, 2019 in Wuhan, China [1]. As of 3rd May, 2022, around 511,965,711 cases and 6,240,619 deaths have been recorded around the world [2]. Development of immunity to SARS-CoV-2 is important for the containment of the disease. Antibody to SARS-CoV-2 develops both after natural SARS-CoV-2 infection and vaccination. Several studies have reported that almost 100% of naturally SARS-CoV-2 infected individuals develop IgG antibodies to virus by day 30 [3-5]. Wei et al., determined antibody response after SARS-CoV-2 infection in 7,256 general populations in UK and found 24% of the participants as 'non-responder' meaning that they did not develop anti-spike antibodies [6]. The non-responders were older and had lower viral burden. Studies have reported that IgG antibodies to SARS-CoV-2 persist for several months in patients recovering from SARS-CoV-2 infection [5,7]. In a linear mixed model analysis, using data from 4553 participants of Texas antibody response survey, Swartz et al., has showed that expected antibody response increases for 100 days post SARS-CoV-2 infection and may remain positive beyond 500 days from the time of infection depending on age, body mass index and disease severity [8].

Antibody response following vaccination against SARS-CoV-2 varies depending on the types of vaccines and doses. Antibody level against the SARS-CoV-2 nucleocapsid protein following 2 doses of the SARS-CoV-2 messenger RNA (mRNA) vaccine (mRNA-1273, Moderna) was found 3836 U/ml whereas the antibody response following 2 doses of BNT162b2 mRNA vaccine (Pfizer-BioNTech) was 1444 U/ml [9]. Whole inactivated virus COVID-19 BIBP vaccine (Sinopharm) induced a median anti-spike antibody level of 52.15 RU/ml (equivalent to 166.88 BAU/ml) one month following 2 doses of vaccine among 95.7% individuals [10]. For a recombinant adenoviral vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca), median spike antibody level of 1201 U/ml was observed at 0-20 days [11]. The recombinant adenoviral vector vaccine Ad5-nCoV (CanSino Biologics Inc) induced neutralizing antibodies against SARS-CoV-2 among 92.6% of individuals without prior COVID-19 disease following 21-25 days of vaccination [12]. Townsend et al., estimated the durability of anti-spike IgG antibody levels following vaccination by BNT162b2, mRNA-1273, ChAdOx1, and recombinant adenoviral vector vaccine Ad26.COV2.S (Johnson & Johnson/Janssen) by applying comparative evolutionary framework [13]. Messenger RNA vaccines (BNT162b2 and mRNA-1273) were predicted to yield protection against breakthrough infections for median time of 29.6 months whereas the expected median time of breakthrough infection following vector vaccination with ChAdOx1 and Ad26.COV2.S as 22.4 and 20.5 months respectively.

Bangladesh initiated mass vaccination with ChAdOx1 (Oxford–AstraZeneca) in January 2021 [14]. This study was designed to determine the IgG antibody response to RBD (receptor binding domain) of SARS-CoV-2 spike protein S1 in individuals suffered from SARS-CoV-2 infection and in those vaccinated with ChAdOx1 vaccine. Persistence of antibody after a defined period was also determined in those individuals.

Material and methods

The study was approved by the Institutional Research Review Board of Ibrahim Medical College. Informed consent was obtained from all participants after explaining the nature and purpose of the study. The laboratory work was conducted at K.A. Monsur Research Laboratory at the Department of Microbiology, Ibrahim Medical College.

Study population: This study was carried out on adults aged 18 years and above. Study population consisted of four groups. Group-1 (control): healthy and history of no prior SARS-CoV-2 infection and vaccination, Group-2: had past SARS-CoV-2 infection (RT-PCR positive) within 1-10 months of enrolment in the study and no vaccination, Group-3: received two doses of recombinant adenoviral vector vaccine ChAdOx1 (Oxford–AstraZeneca) without past SARS-CoV-2 infection, and Group-4: past SARS-CoV-2 infection within 1-10 months plus received 2 doses of recombinant adenoviral vector vaccine ChAdOx1 (Oxford–AstraZeneca) vaccination. ChAdOx1 vaccine was a replication-deficient

adenoviral vector vaccine manufactured by Oxford–AstraZeneca. A pre-tested structured questionnaire (closed ended) was used to record the age, gender, co-morbid condition and adverse effects of vaccination.

Collection of blood sample: Single blood sample from participants of Gr-1 was collected at the time of enrolment. Sample from Gr-2 participants were collected within 1-10 months of recovery from SARS-Cov-2 infection (COVID-19). Two blood samples were collected from Gr-3 and Gr-4 individuals. First blood samples from Gr-3 cases were collected 1 month after the 2^{nd} dose of vaccination. First blood samples from Gr-4 individuals were collected 1 month after the 2^{nd} dose of vaccination and within 1-10 months of recovery from SARS-Cov-2 infection (COVID-19). Second blood samples from Gr-3 and Gr-4 individuals were collected 7 month after the 2^{nd} dose of vaccination having antibody level of >30 DU/ml. About 5 ml of blood was collected aseptically from each participant by venipuncture. After collection, blood was kept at room temperature for at least half an hour followed by centrifugation at 1500 rpm for 10 minutes. Then the serum was separated and stored at -20^0C until tested.

Estimation of IgG antibodies to receptor binding domain (RBD) of SARS-CoV-2 spike protein S1: IgG antibodies to RBD of SARS-CoV-2 spike protein S1 (anti-RBDS1 IgG) was determined in serum by ELISA using DRG ELISA kit (EIA-6150; Marburg, Germany). ELISA test was performed according to manufacturer's instruction. Concentration of anti RBDS1 IgG antibody was expressed in DU/ml. Any sample showing antibody concentration above the cut off value of 5.4 DU/ml (1DU/ml=5.15IU/ml) was considered as positive.

Results

Total 176 participants were enrolled of which Group-1, 2, 3 and 4 consisted of 27, 24, 93 and 32 individuals respectively. The age range of the participants was 18-85 years. Of the total, male and female were 111 (63.1%) and 65 (36.9%) respectively. About one-third of participants (30.1%) had comorbid condition which included diabetes, hypertension, asthma and cancer (Table-1).

Table-1: *Distribution of groups, gender and co-morbid condition of study population (N = 176)*

Study population	Number (%)
Group 1: Healthy, without past SARS-CoV-2 infection and not vaccinated (control)	27 (15.3)
Group 2: Had only past infection with SARS-CoV-2[a]	24 (13.6)
Group 3: Received 2 doses of ChAdOx1 vaccine	93 (52.8)
Group 4: Had past infection with SARS-CoV-2[a] and had 2 doses of ChAdOx1 vaccine	32 (18.2)
Gender	
Male	111 (63.1)
Female	65 (36.9)
Comorbid condition	
Present	53 (30.1)
Absent	123 (69.9)

Note: a=RT-PCR positive.

Table-2 shows the anti-RBDS1 IgG antibodies of participants belonging to four groups. Anti-RBDS1 IgG was positive in 51.9%, 66.7%, 96.8% and 100% participants of Group-1, 2, 3 and 4 respectively and the mean antibody concentrations of the positive participants were 16.5 ± 10.6, 39.9 ± 39.8, 97.7 ± 42.1 and 120.8 ± 31.9 DU/ml respectively. Seropositivity rate was significantly ($p<0.001$) higher in Group-3 and 4 individuals compared to that of Gr-1 and 2. No significant ($p=0.284$) difference in seropositivity rate was found between healthy control and individuals with past SARS-CoV-2 infection (Gr-1 vs Gr-2). Individuals who were previously infected and vaccinated (Gr-4) had significantly higher ($p<0.05$) anti-RBDS1 IgG antibody level (120.8 ± 31.9 DU/ml) compared to participants who were naturally infected but not vaccinated (Gr-2, 39.9 ± 39.8 DU/ml) as well as those who were vaccinated without prior infection (Gr-3, 97.7 ± 42.1 DU/ml). There were no significant differences in positivity rate and antibody levels between male and female individuals of any groups (Table-3). No significant ($p>0.05$) difference of anti-RBDS1 IgG antibody level was found between individuals with and without co-morbidity of any four groups (Table-4). Comorbid conditions included diabetes, hypertension, asthma and cancer.

Seven months after the 2nd dose of vaccination blood samples were collected from 61 and 22 individuals of Group- 3 and 4 respectively having > 30 DU/ml anti-RBDS1 IgG antibodies. Seven months after receiving the 2nd dose of vaccines, the antibody concentration declined in 85.3% and 81.5% of individuals of Group-3 and Group-4 respectively. Mean antibody concentration declined significantly (p≤0.05) from 112.1 ± 30.4 DU/ml to 75.9 ± 48.7 DU/ml and from 127.3 ± 20.4 DU/ml to 92.5 ± 43.6 DU/ml in Group-3 and Group-4 individuals respectively seven months after receiving the 2nd dose of vaccines (Table-5). Decline of antibody was 40.6% and 34.7% in 7 months. Only 1 (2.9%) out of 63 cases of Group-3 became negative (level <5.4 DU/ml). Out of total 176 participants, 103 reported adverse events following second dose of vaccination. Fever was the most common systemic adverse effect (41.7%) followed by headache (30.1%), myalgia (21.4%) and anorexia (6.8%) among the reported adverse events (Table-6).

Table-2: *Anti-RBDS1 IgG antibody response in different groups of study population (N = 176)*

Study population	Number	Anti-RBDS1 IgG antibody			
		Positive n (%)	Concentration (DU/ml) Mean (± SD)[b]	Negative n (%)	Concentration (DU/ml) Mean (± SD)
Group 1	27	14 (51.9)	16.5 ± 10.6	13 (48.2)	2.5 ± 1.4
Group 2	24	16 (66.7)	39.9 ± 39.8	8 (33.3)	2.7 ± 1.4
Group 3[a]	93	90 (96.8)	97.7 ± 42.1	3 (3.2)	3.2 ± 1.4
Group 4[a]	32	32 (100)	120.8 ± 31.9	0 (0)	0

Note: a= Tested 1 month after 2nd dose of vaccination; b= The Kruskal-Wallis test showed significant differences (p < 0.05) in positive antibody concentrations between group 1, 2, 3 and 4; SD – Standard deviation.

Table-3: *Anti-RBDS1 IgG antibody response in male and female participants of study population (N = 176)*

Group	Male			Female			p value
	Total Number	Positive n (%)	Anti-RBDS1 IgG (DU/ml) Mean ± SD	Total Number	Positive n (%)	Anti-RBDS1 IgG (DU/ml) Mean±SD	
Group-1	16	10 (62.5)	11.5 ± 6.8	11	4 (36.4)	29.2 ± 6.7	> 0.05[a]
Group-2	17	11(64.7)	32.6 ± 29.6	7	5 (71.4)	56.3 ± 57.1	> 0.05[b]
Group-3*	58	55 (94.8)	98.3 ± 42.7	35	35 (100)	96.7 ± 41.7	> 0.05[a]
Group-4*	20	20 (100)	120.6 ± 36.8	12	12 (100)	121 ± 23.3	> 0.05[a]

*Note: *Tested 1 month after 2nd dose of vaccination; a= p value determined by independent t test; b= p value determined by Mann-Whitney U test; SD – Standard deviation.*

Table-4: *Anti-RBDS1 IgG antibody concentration in study population with and without comorbidities (N = 176)*

Group	Co-morbidity present (n=53)		Co-morbidity absent (n=123)		p value
	No	Anti-RBDS1 IgG Mean ± SD	No	Anti-RBDS1 IgG Mean ± SD	
Group-1	4	2.8 ± 2.4	23	11.2 ± 10.7	> 0.05[a]
Group-2	5	22.3 ± 13.6	19	28.5 ± 41	> 0.05[a]
Group-3*	27	91.9 ± 44.3	66	95.8 ± 45.1	> 0.05[b]
Group-4*	17	121.1 ± 36.9	15	120.4 ± 26.4	> 0.05[b]

*Note: *Tested 1 month after 2nd dose of vaccination; a= p value determined by Mann-Whitney U test; b= p value determined by independent t test; SD – Standard deviation.*

Table-5: *Anti-RBDS1 IgG levels of Group-3 and Group-4 individuals 1 and 7 months after 2nd dose of vaccination (N = 83)*

Group	Number	Mean ± SD anti-RBDS1 IgG (DU/ml)			Change in anti-RBDS1 IgG 7m after 2nd dose		
		1 m after 2nd dose	7 m after 2nd dose	p	Declined n (%)	% Decline of Ab	Negative N (%)
Group-3	61	112.1± 30.4	75.9± 48.7	< 0.05	52 (85.3)	40.6	1 (2.9)
Group-4	22	127.3± 20.4	92.5 ± 43.6	< 0.05	18 (81.8)	34.7	0

Table-6: *Adverse effects after 2nd dose of vaccination among participants (N = 103)*

Side effects	Number (%)
Fever	43 (41.7)
Headache	31 (30.1)
Myalgia	22 (21.4)
Anorexia	7 (6.8)

Discussion

In this study, we report antibody response in adults who contracted SARS-CoV-2 and who were vaccinated with ChAdOx1 nCoV-19 vaccine and both. The antibody response of those participants was compared with that of a control group of adults who were not previously infected with SARS-CoV-2 or vaccinated.

Our results show that after 2 doses of ChAdOx1 nCoV-19 vaccine the antibody concentration increased substantially with seropositivity rate over 96%. Antibody positivity is only one measure of a multifaceted immune response. SARS-CoV-2 vaccines have been shown to induce a Th1-dominated T cell response, which persists for at least 6-8 months and continues to mature [15]. B cell-mediated immunity can sustain at least for 12 months after initial infection [16,17].

In our study, the concentration of antibodies was significantly higher in response to the vaccine than after natural infection. These results are in agreement with the previous studies [18,19]. This finding may be related to heterogeneity within the COVID-19 recovered persons including variations in timing and severity of prior illness.

In our study, significantly higher antibody response to the vaccine was noted in previously SARS-CoV-2 infected individuals than in infection-naïve individuals. This observation is similar with previous studies [20,21]. In naturally infected individuals subsequent vaccination serves as booster. This aspect is important to preserve vaccine in the context of scarcity. The serological data suggests a potential approach is to include antibody screening at or before the time of booster to prioritize the use of booster doses for individuals with no previous infection. This would help in maximizing the use of vaccine.

In the present study, among 27 participants of the control group who had no history of natural infection with SARS-CoV-2 and vaccination, 14 (51.9%) were found positive for anti-RBD IgGS1 antibodies though the level of antibody concentration was low. The reason behind their positivity might be due to the presence of cross-reactive antibodies against other prevalent corona viruses than SARS-CoV-2. In fact a study in 2019 in Dhaka found that 4.57% of viral respiratory tract infections were due to corona viruses other than SARS-CoV-2 (corona virus 229E, corona virus NL63) [22]. However, in addition our Gr-1 population could have asymptomatic SARS-CoV-2 infection in this pandemic period.

We found no differences in antibody level between male and female which was in agreement with previous study [23]. However, this is in contrast to the results of some reports where female showed higher antibody response than male to a range of vaccines [24]. Our findings showed that the antibody responses of naturally infected persons, infection-naïve vaccinees and previously infected vaccinees with comorbidities were similar to those without the comorbidities. The findings indicate that the recombinant adenoviral vector vaccine ChAdOx1 nCoV-19 is capable of inducing antibody

response irrespective of gender and presence of comorbidities.

Although our study found significant decrease in antibody level 7 months after 2nd dose of vaccine, the persisting antibody level was still high. This presence of persisting antibody to SARS-CoV-2 suggest antibody screening test prior to booster dose to maximize coverage and impact. For example, estimation of antibody titer is recommended before giving booster dose against hepatitis B virus. If the titer is found below the protection level of 10mIU/ml, only then booster dose is recommended [25].

The implications of detectable antibodies to SARS-CoV-2 are not yet well understood. Presence of high antibody concentration does not necessarily mean protection from infection, just as a negative result does not correlate susceptibility to infection. Cavanaugh et al., studied individuals infected with SARS-CoV-2 during April-December, 2020 and subsequently re-infected during May-June, 2021 [26]. They have found 20.3% had two doses of vaccination between first and second infection which implies re-infection is possible in spite of having high titer of antibody after natural infection and vaccination. In our study population, no serious adverse effect was noted after vaccination that warranted hospitalization. Mild constitutional symptoms recorded were similar to reported study [23].

The limitation of our study was that we could not assess the persistence of antibody to SARS-CoV-2 over a longer period of time. Also, we could not determine the neutralizing antibody and cell-mediated immune response and our sample size was small. Our study revealed that ChAdOx1 nCoV-19 vaccine induces high concentration of persisting anti-RBDS1 IgG antibody after second dose irrespective of gender and comorbidities. Previous infection with SARS-CoV-2 acts as immune priming and subsequent vaccination serves as booster. Therefore, antibody screening test prior to booster dose could be a good option to maximize coverage of vaccination.

Competing interest

The authors declare no competing interests.

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