

Evaluation of Antibody Response to Two Doses of Covishield Vaccine with a 5-Week Gap between Doses after 21 Days Post Second Dose: A Cross-sectional Study

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ABSTRACT

Introduction: The Coronavirus Disease-2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) resulted in unprecedented global morbidity and mortality. Covishield (ChAdOx1 nCoV-19), a recombinant chimpanzee adenoviral vector vaccine manufactured by the Serum Institute of India under licence from Oxford-AstraZeneca, was the primary vaccine used in India's national COVID-19 immunisation programme that commenced on 16 January 2021. Although most studies have evaluated 4-week or extended 8-12 week dosing intervals, real-world evidence regarding the immunogenicity of an intermediate 5-week dosing schedule remains limited, representing an important gap in knowledge.

Aim: To evaluate the SARS-CoV-2 IgG antibody response 21 days after the second dose of Covishield vaccine administered with a 5-week interval and to assess its association with age, sex, and co-morbidities among healthcare workers at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, India.

Materials and Methods: A cross-sectional observational study was conducted at Vydehi Institute of Medical Sciences and Research Centre (VIMS and RC), a tertiary care teaching hospital in Bengaluru, Karnataka, India, between March and June 2022. A total of 326 vaccinated healthcare workers were enrolled; 324 were analysed (2 excluded due to equivocal results). Participants

included healthcare workers and hospital staff who received two doses of Covishield with a 5-week (35-day) inter-dose interval. SARS-CoV-2 IgG antibodies against the spike protein were measured 21 days after the second dose using Chemiluminescent Immunoassay (CLIA). Spearman's rank correlation assessed the association between age and antibody levels; Mann-Whitney U test was used for gender and co-morbidity comparisons. A p-value <0.05 was considered statistically significant.

Results: Out of total 324 participants, 171 (52.8%) were male and 153 (47.2%) female, with a mean age of 36.8±11.2 years. Detectable IgG antibodies (≥ 1 S/CO) were observed in 320 participants (98.8%). The median IgG titre was 4.84 S/CO (IQR: 2.00-13.90); mean 11.20±14.56 S/CO. The IgG distribution was significantly right-skewed (Shapiro-Wilk p-value <0.0001). Spearman's rank correlation showed no significant association between age and IgG levels ($\rho=0.106$, p-value=0.057; $R^2=0.011$). No statistically significant difference was observed in antibody levels based on sex ($U=13,005.000$, p-value=0.856) or co-morbidity status ($U=1,656.500$, p-value=0.058).

Conclusion: Two doses of Covishield administered with a 5-week interval induced a robust humoral immune response in 98.8% of participants. Antibody levels were independent of age, sex, and co-morbidity status, indicating consistent immunogenicity across demographic and clinical subgroups in this working-age healthcare worker cohort.

Keywords: Neutralising antibodies, Occupational exposure, Serologic tests, Vaccination schedule, Vaccine immunogenicity

INTRODUCTION

The COVID-19 pandemic, caused by SARSCoV-2, first identified in Wuhan, China in December 2019, rapidly evolved into a global public health emergency, resulting in unprecedented morbidity and mortality worldwide [1]. By 8 December 2021, over 266 million confirmed cases and 5.26 million deaths had been reported globally, with the United States, India, and Brazil accounting for the highest disease burden [1].

Vaccination emerged as the most effective strategy to prevent severe illness, hospitalisation, and mortality associated with COVID-19 [2]. Previous studies found that neutralising antibody levels correlated strongly with protection against symptomatic infection [3], while vaccine effectiveness against severe outcomes was well demonstrated at the population level [4]. However, accumulating evidence indicated that antibody levels declined over time following vaccination, underscoring the importance of postvaccination serological assessment [5]. Breakthrough infections

in vaccinated individuals were also reported, highlighting the need for continued monitoring [6]. SARS-CoV-2 enters host cells through the interaction of its spike (S) glycoprotein with the Angiotensin-Converting Enzyme 2 (ACE2) receptor, making the spike protein the principal immunological target for vaccine development [7]. Several vaccine platforms- including mRNA, viral vector, protein subunit, and inactivated vaccines-demonstrated varying degrees of safety, immunogenicity, and protective efficacy [8-10]. Large-scale global vaccination efforts were implemented worldwide [11].

In India, the national COVID-19 vaccination programme commenced on 16 January 2021, with Covishield manufactured by the Serum Institute of India being widely used as part of the nationwide vaccination drive [12]. By August 2021, over 50.8 crore vaccine doses were administered, with healthcare workers forming the earliest vaccinated cohort [12]. Systematic assessment of postvaccination antibody responses in this population was considered critical to guide vaccination strategies and booster policies. Among available vaccines,

the chimpanzee adenoviral vector vaccine ChAdOx1 nCoV-19 (Covishield; AZD1222) was widely used. Clinical trials demonstrated good safety and immunogenicity across age groups [13,14], and further analyses showed that longer dosing intervals were associated with improved vaccine efficacy [15]. Real-world evidence from India demonstrated high seroconversion rates among healthcare workers, with follow-up studies confirming a gradual decline in antibody titres over time [16,17].

Age- and host-related variations in immune response were also documented, with reduced antibody responses observed in older individuals [18,19]. Additionally, prior SARS-CoV-2 infection was shown to enhance postvaccination antibody responses (hybrid immunity) [20]. Recent studies demonstrated waning of antibody responses over time [21], along with occurrence of breakthrough infections [22]. Evidence also indicated that antibody responses showed waning followed by stabilisation [23,24], while booster doses significantly enhanced antibody responses and restored immunity [25,26]. These findings emphasised the need for continued evaluation of vaccine-induced immune responses.

Although most studies evaluated 4-week or extended 8-12 week dosing intervals, real-world evidence on an intermediate 5-week dosing schedule remained limited, particularly in Indian healthcare settings, representing an important knowledge gap. Concerns regarding waning antibody levels, breakthrough infections, and the emergence of viral variants further emphasise the need for continued evaluation of vaccine-induced immune responses.

Aim: To evaluate the SARS-CoV-2 IgG antibody response 21 days after administration of the second dose of Covishield vaccine given at a 5-week interval, and to assess its association with age, sex, and co-morbidities among healthcare workers at a tertiary care institution.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the Department of Biochemistry at Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bengaluru, Karnataka, India between March and June 2022. The study was carried out after obtaining approval from the Institutional Ethics Committee (IEC Reg No: ECR/747/Inst/KA/2015/RR-21; Approval No: VIEC/2021/APP/010; Date: 20 July 2021). The study adhered to the ethical principles outlined in the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants prior to enrollment.

Inclusion criteria: Healthcare workers aged 18 years and above who had completed two doses of Covishield vaccine with a 5-week interval between doses and from whom blood samples were collected 21 days after administration of the second dose were included in the study.

Exclusion criteria: Individuals with acute illness at the time of sample collection, those with known immunodeficiency disorders, and those receiving immunosuppressive therapy were excluded from the study.

Sample size: 326 healthcare workers were enrolled; 324 were analysed after excluding 2 with equivocal results and institutional staff who had completed two doses of Covishield vaccine with a 5-week (35-day) inter-dose interval were enrolled. No formal sample size calculation was performed; all eligible staff presenting during the study period were enrolled (convenience sample). A retrospective power analysis indicates that with $n=324$ and an assumed seroconversion rate of 95%, the study achieves >99% power to detect a rate of $\geq 90\%$ at $\alpha=0.05$, confirming adequacy for the primary outcome. However, the co-morbidity subgroup ($n=15$) was underpowered for subgroup comparisons.

Data collection: Demographic details (age, sex) and clinical information including co-morbidities (hypertension, diabetes mellitus,

thyroid disorders, autoimmune diseases, bronchial asthma, allergic disorders), medication history, and prior COVID-19 infection were recorded using a structured proforma.

Laboratory analysis: Venous blood samples (5 mL) were collected by standard venepuncture, and serum was separated by centrifugation at 3000 rpm for 10 minutes. SARS-CoV-2 IgG antibodies targeting the spike protein were measured using a CLIA on the Access Immunoassay System (Beckman Coulter Inc.) following the manufacturer's instructions. Antibody levels were expressed as Signal-to-Cut-off ratio (S/CO) and interpreted as: <0.8 S/CO- Non reactive; 0.8-0.9 S/CO- Equivocal; ≥ 1.0 S/CO- Reactive [27].

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ Standard Deviation (SD) or median (interquartile range, IQR) based on data distribution. Categorical variables were expressed as frequencies and percentages. Normality of data was assessed using the Shapiro-Wilk test. Since IgG antibody levels showed a significantly non normal distribution, non parametric tests were used throughout. Spearman's rank correlation coefficient (ρ) was used to assess the relationship between age (continuous) and antibody levels. Mann-Whitney U test was used to compare antibody levels between sexes and between participants with and without co-morbidities. Chi-square test was applied for categorical comparisons. A p -value <0.05 was considered statistically significant.

RESULTS

[Table/Fig-1] presents the demographic and clinical profile of the 324 enrolled participants. The study population was predominantly young, with the 21-30-year age group accounting for 191 (59.0%) participants, reflecting the composition of an active healthcare workforce. Sex distribution showed near-equal representation, with 171 (52.8%) males and 153 (47.2%) females. The mean age of the participants was 36.8 ± 11.2 years. The vast majority of participants, 309 (95.4%), had no co-morbidities, while only 15 (4.6%) had one or more co-morbid conditions.

Variables	Category	Frequency (%)
Gender	Male	171 (52.8)
	Female	153 (47.2)
Mean age $\pm$ SD (years)	-	36.8 $\pm$ 11.2
Age group (years)	<21	9 (2.8)
	21-30	191 (59.0)
	31-40	66 (20.4)
	41-50	40 (12.3)
	51-60	13 (4.0)
	61-70	4 (1.2)
	>70	1 (0.3)
Co-morbidity	Absent	309 (95.4)
	Present	15 (4.6)

[Table/Fig-1]: Demographic and clinical profile of study participants.

*Note: 2 participants excluded from analyses due to equivocal IgG values (0.8-0.9 S/CO); analysed N=324

[Table/Fig-2] presents descriptive statistics for IgG antibody titres. A seroconversion rate of 98.8% confirms that nearly all participants mounted a detectable humoral immune response. The median IgG titre of 4.84 S/CO (IQR: 2.00-13.90) is the appropriate measure of central tendency given the markedly right-skewed distribution confirmed by the Shapiro-Wilk test ($W=0.820$, p -value <0.0001). The wide IQR and extreme range (0.09 to 100 S/CO) reflect well-described inter-individual variability.

Statistical parameter	Value
Total participants enrolled	326
Total analysed (2 equivocal excluded)	324
Participants with detectable IgG (≥ 1.0 S/CO)	320 (98.8%)
Non reactive participants (< 0.8 S/CO)	4 (1.2%)
Mean $\pm$ SD (S/CO)	11.20 $\pm$ 14.56
Median (S/CO)	4.84
Interquartile Range- IQR (S/CO)	2.00-13.90
Minimum value	0.09
Maximum value	100.00
Shapiro-Wilk Normality Test (p-value)	< 0.0001 (Non normal distribution)
Distribution pattern	Positively skewed (right-skewed)

[Table/Fig-2]: Descriptive statistics of SARS-CoV-2 IgG antibody titres measured 21 days after the second dose of Covishield.
*Equivocal values (0.8-0.9 S/CO) were excluded from analysis

Categorised IgG antibody response: [Table/Fig-3] presents the distribution of categorised IgG responses among the 324 analysed participants (2 excluded for equivocal values). An overwhelming 87.7% achieved a high IgG response category (> 3.0 S/CO), confirming the strong immunogenic potential of the two-dose Covishield schedule at a 5-week interval.

IgG category	n (%)
Low response (1.00- < 1.0 S/CO)	35 (10.8)
Moderate response (2.00- 1.0-3.0 S/CO)	5 (1.5)
High response (3.00- > 3.0 S/CO)	284 (87.7)

[Table/Fig-3]: Distribution of IgG antibody response categories among study participants.

[Table/Fig-4] presents the sex-stratified distribution of IgG antibody response categories along with the comparison of antibody levels between male and female participants. High IgG response (> 3.0 S/CO) was observed in 135 (41.7%) females and 149 (46.0%) males, indicating a comparable distribution across sexes. The Mann-Whitney U test showed no statistically significant difference in IgG antibody levels between males and females ($U = 13,005.000$, $p = 0.856$), confirming that the antibody response was not significantly influenced by sex in this study population.

[Table/Fig-5] shows that the majority of participants (87.7%) had high antibody titres (> 3.0 S/CO). Participants with co-morbidities demonstrated a higher mean rank of antibody levels compared to those without. However, this difference was not statistically significant (p -value=0.058). Hence, no significant association was observed between co-morbidity status and antibody response.

[Table/Fig-6] presents the age group-wise distribution of IgG antibody response categories among the study participants. High antibody response (> 3.0 S/CO) was observed across all age groups, with the majority of participants demonstrating a strong humoral immune response following vaccination. Although the largest proportion

of participants belonged to the 21-30-year age group (59.0%), no clear age-related trend in antibody response was observed.

[Table/Fig-7] presents a weak positive correlation between age and SARS-CoV-2 IgG levels ($p = 0.106$). However, this association was not statistically significant (p -value=0.057). The findings indicate that age has minimal influence on antibody response. Thus, no significant correlation was observed between age and IgG levels in this study population.

DISCUSSION

The present study assessed the humoral immune response following two doses of Covishield administered at a 5-week interval among healthcare workers. A high seroconversion rate of 320/324 (98.8%) was observed, with the majority demonstrating a high IgG antibody response (284/324; 87.7%). These findings indicated that the selected vaccination schedule elicited a robust immune response in this cohort. The right-skewed distribution of antibody titres suggested inter-individual variability, possibly influenced by prior asymptomatic infection and host immune factors.

These findings were comparable with those reported in clinical trials of adenoviral vector vaccines. Folegatti PM et al., demonstrated strong immunogenicity following ChAdOx1 nCoV-19 vaccination in early-phase trials [13]. Similarly, Ramasamy MN et al., reported consistent antibody responses across different age groups [14]. Voysey M et al., further showed that extended dosing intervals were associated with improved immunogenicity and vaccine efficacy [15]. In comparison, the present study demonstrated that even an intermediate 5-week dosing interval yielded high seroconversion rates, suggesting that shorter intervals also produce substantial immune responses in real-world settings.

Real-world evidence from India by Singh AK et al., reported a seroconversion rate of 98.1% among healthcare workers, which closely aligned with the 98.8% observed in the present study [16]. Longitudinal follow-up by Singh AK et al., demonstrated a gradual decline in antibody titres over time [17]. Similarly, Levin EG et al., reported waning of humoral immunity within six months following vaccination [21]. In addition, Srivastava K et al., showed that antibody levels exhibited waning followed by stabilisation [23]. These findings were consistent with the present study, which captured peak postvaccination responses but highlighted the need for longitudinal monitoring.

Population-based data by Rosenberg ES et al., demonstrated significant vaccine effectiveness in reducing infection, hospitalisation, and mortality [6]. However, breakthrough infections among vaccinated individuals, as reported by Bergwerk M et al., emphasised the clinical relevance of declining immunity [22]. More recent studies by Wu J et al., Liu M et al., and Pradenas E et al., demonstrated that booster doses significantly enhanced antibody responses and restored waning immunity [24-26]. Compared to these findings, the present study demonstrated a strong primary immune response but did not evaluate booster effects, indicating a need for further research.

Sex	Low (< 1.0 S/CO) n (%)	Moderate (1.0-3.0 S/CO) n (%)	High (> 3.0 S/CO) n (%)	Total n (%)	Mean rank	Sum of ranks	U statistic	p-value
Female	16 (4.9)	2 (0.6)	135 (41.7)	153 (47.2)	164.00	25,092.00		
Male	19 (5.9)	3 (0.9)	149 (46.0)	171 (52.8)	162.11	27,883.00	13,005.000	0.856
Total	35 (10.8)	5 (1.5)	284 (87.7)	324 (100)	-	-		

[Table/Fig-4]: Sex-stratified IgG antibody response and comparison of antibody levels.

Co-morbidity	Low (< 1.0 S/CO) n (%)	Moderate (1.0-3.0 S/CO) n (%)	High (> 3.0 S/CO) n (%)	Total n (%)	Mean rank	Sum of ranks	U statistic	p-value
Absent	34 (10.5)	5 (1.5)	270 (83.3)	309 (95.4)	161.33	49,850.50		
Present	1 (0.3)	0	14 (4.3)	15 (4.6)	208.57	3,128.50	1,656.500	0.058
Total	35 (10.8)	5 (1.5)	284 (87.7)	324 (100)	-	-		

[Table/Fig-5]: Co-morbidity-stratified IgG antibody response and comparison of antibody levels.

Age group (years)	Low (1.00)	Moderate (2.00)	High (3.00)	Total (N)	% Total
<21	1	0	8	9	2.8%
21-30	20	3	168	191	59.0%
31-40	7	0	59	66	20.4%
41-50	5	0	35	40	12.3%
51-60	1	1	11	13	4.0%
61-70	1	1	2	4	1.2%
>70	0	0	1	1	0.3%
Total	35	5	284	324	100.0%

[Table/Fig-6]: Age group-stratified distribution of IgG antibody response categories.

Parameters	Correlation coefficient (ρ)	p-value	N
Age vs SARS-CoV-2 IgG (S/CO)	0.106	0.057	324
R ² (linear approximation)	0.011	-	-

[Table/Fig-7]: Correlation analysis between age and SARS-CoV-2 IgG antibody levels.

High IgG response (>3.0 S/CO) was observed in 135 of 153 females (88.2%) and 149 of 171 males (87.1%), indicating comparable immune responses between the sexes. The Mann-Whitney U test showed no statistically significant difference in antibody levels between males and females ($U=13,005.000$, $p\text{-value}=0.856$). This was consistent with findings reported by Terpos E et al., who observed minimal sex-based differences [18]. However, studies on mRNA vaccines reported variable immune responses, suggesting possible platform-specific differences [8,9].

Similarly, no statistically significant association was observed between co-morbidity status and antibody response ($U=1,656.500$, $p=0.058$). Although a higher mean rank was observed among participants with co-morbidities, this finding was interpreted cautiously due to the small subgroup size (15/324; 4.6%). In contrast, Singh AK et al., reported relatively lower antibody responses in individuals with co-morbidities [16,17]. Thus, while the present study did not demonstrate a significant association, the findings may have been limited by sample size.

Age demonstrated a weak positive correlation with antibody levels ($\rho=0.106$, $p\text{-value}=0.057$), which was not statistically significant. This may have been due to the predominance of younger participants in the study population. In contrast, Müller L et al., demonstrated reduced immune responses in older individuals due to immunosenescence [19]. Compared to these findings, the present study may have underestimated age-related differences due to limited representation of elderly participants.

The skewed distribution of antibody titres justified the use of non parametric statistical methods. Elevated antibody levels in a subset of participants may have been attributable to prior asymptomatic SARS-CoV-2 infection, leading to hybrid immunity, as demonstrated by Krammer F et al., [20]. However, this could not be confirmed due to the absence of baseline serological assessment.

Overall, the findings suggested that a 5-week inter-dose interval of Covishield induced a strong humoral immune response in healthcare workers. However, the absence of statistically significant associations with demographic and clinical variables should be interpreted cautiously, particularly in view of borderline p-values and sample distribution characteristics.

Limitation(s)

The study had several limitations. Being a single-centre study, the findings may have limited generalisability to other settings. Baseline serology was not assessed, making it difficult to exclude pre-existing SARS-CoV-2 immunity, which could have contributed to the higher antibody titres observed. The small number of participants with co-morbidities limited the statistical power for subgroup comparisons. Additionally, no a priori sample size calculation was performed; while the study was adequately powered for the primary seroconversion

outcome, it may not have been sufficient for subgroup analyses. The use of convenience sampling rather than random selection may also introduce selection bias. Furthermore, neutralising antibody titres and T-cell-mediated immunity were not evaluated, and there was no longitudinal follow-up beyond 21 days after the second dose. Finally, potential confounding factors such as body mass index, smoking status, blood group, and medication use were not accounted for.

CONCLUSION(S)

Two doses of Covishield administered at a 5-week interval produced a strong humoral immune response in 98.8% of healthcare workers, with no significant variation across age, sex, or co-morbidity status, indicating consistent immunogenicity within this cohort. Borderline associations with age and co-morbidities suggest the need for further validation in broader populations. These findings support the effectiveness of the 5-week dosing schedule in real-world settings. Future research should focus on larger, multicentre and age-diverse populations, including the elderly, with baseline serology to distinguish prior infection. Longitudinal studies assessing antibody persistence and T-cell responses, along with comparisons across dosing intervals and vaccine platforms, are recommended. Correlating immunological markers with clinical outcomes such as breakthrough infections will further strengthen vaccination policy decisions.

Data availability: De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request.

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