Serosurveillance among healthcare workers vaccinated with ChAdOx1 nCoV-19 Corona vaccine in a tertiary hospital of Kerala, India: prospective cohort study[1]

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Abstract

Aim. To evaluate antibody responses following two doses of ChAdOx1 nCoV-19 Corona vaccination in a tertiary care setting and the association of host factors like age, body mass index and comorbidities in determining this antibody response.

Materials and methods. This prospective serosurveillance study was done among healthcare workers of Jubilee Mission Medical College, vaccinated during January- April 2021. Blood samples were drawn from 170 participants after their first dose and from 156 participants after their second dose of Covishield™ to measure the specific Ig G antibodies against the recombinant S1 subunit of the S protein of SARS-CoV-2.

Results. The median level of anti-SARS-CoV-2 Ig G antibody 28–56 days after the first dose vaccination was 3.64 S/C (1.33, 7.24) and 11.6 S/C (8.61, 14.27) after 14 days of second dose vaccination. Protective levels of anti-SARS CoV-2 Ig G antibodies (≥ 9.5 S/C) was developed by 25 participants (14.7%, 95% confidence interval: 9.8% to 20.9%) after 28–56 days of first dose of vaccination and by 109 participants (69.9%, 95% confidence interval: 62% to 77%) after 14 days of second dose. Health care workers in the age group below 60 years (p = 0.027) and without comorbidities (p = 0.079) showed higher protective Ig G levels. But on multiple logistic regression only age under 60 years was found to be statistically significant.

Conclusion. After the first dose of the ChAdOx1 nCoV-19 vaccine, the formation of Ig G antibodies was observed, the level of which increased after the second dose. Among the various associated factors studied only the age of the participants below 60 years was found to be statistically significant for protective antibody levels. Follow up studies involving larger and different ethnic population is key to decoding the antibody response especially in the elderly and high-risk groups.

Keywords: antibody response; ChAdOx1COVID-19 vaccine; health care workers; neutralizing antibodies; protective level; SARS-CoV-2

MeSH terms:
COVID-19 – IMMUNOLOGY
COVID-19 – PREVENTION & CONTROL
CHADOX1 NCOV-19 – THERAPEUTIC USE
CHADOX1 NCOV-19 – PHARMACOLOGY
IMMUNITY, HUMORAL – DRUG EFFECTS
COVID-19 – SEROLOGICAL TESTING
HEALTH PERSONNEL
INDIA

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[1] Preprint of the paper is published in Medrxiv: https://doi.org/10.1101/2021.06.29.21259686

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УДК [616.98:578.834.1]-085.371.015:[616-092:612.017.1:614.25]

Серологический ответ среди медицинских работников, вакцинированных «ChAdOx1 nCoV-19 Corona» в больнице третичного уровня в Керале, Индия: проспективное когортное исследование

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Аннотация

Цель. Оценить гуморальный ответ после введения двух доз вакцины «ChAdOx1 nCoV-19 Corona» в учреждении третичного звена здравоохранения и оценить взаимосвязь факторов хозяина, таких как возраст, индекс массы тела и сопутствующие заболевания, с уровнем антител.

Материалы и методы. Проспективное исследование было проведено среди медицинских работников Медицинского колледжа Jubilee Mission, вакцинированных в период с января по апрель 2021 года. Образцы крови для определения специфических антител IgG против рекомбинантной субъединицы S1 белка S SARS-CoV-2 были взяты у 170 участников после первой дозы и у 156 участников после второй дозы Covisield™.

Результаты. Медиана уровня антител IgG к SARS-CoV-2 через 28–56 дней после введения первой дозы составляет 3,64 S/C (1,33, 7,24) и через 14 дней после второй – 11,6 S/C (8,61, 14,27). Протективные уровни антител IgG против SARS CoV-2 (≥ 9,5 S/C) достигнуты у 25 участников (14,7%, 95% доверительный интервал: от 9,8 до 20,9%) через 28–56 дней после введения первой дозы вакцины и 109 участников (69,9%, 95% доверительный интервал: от 62 до 77%) через 14 дней после второй дозы. У медицинских работников моложе 60 лет (p = 0,027) и без сопутствующих заболеваний (p = 0,079) выявлен более высокий уровень защитных IgG. Но при множественной логистической регрессии статистически значимым оказался только возраст до 60 лет.

Заключение. После введения первой дозы вакцины «ChAdOx1 nCoV-19» наблюдается образование антител IgG, уровень которых повышается после введения второй дозы. Среди изученных факторов только возраст участников моложе 60 лет оказался статистически значимым для достижения протективного уровня антител. Последующие исследования с участием более крупного и разнообразного этнического населения являются ключом к расшифровке ответа антител, особенно у пожилых людей и групп высокого риска.

Ключевые слова: гуморальный ответ; вакцина ChAdOx1 nCoV-19; медицинские работники; нейтрализующие антитела; защитный уровень; SARS-CoV-2

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List of abbreviations
CI – confidence intervals
COVID-19 – COronaVIrus Disease 2019
HCWs – healthcare workers
Ig G – immunoglobulin gamma
S/C – signal/cut-off
SARS-CoV-2 – severe acute respiratory virus coronavirus-type 2

The COronaVIrus Disease 2019 (COVID-19) pandemic entered a second peak in India towards early April of 2021 and by June 2021 it was declining in all the states, including Kerala. The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has already affected more than 171 million people and caused more than 3 million deaths worldwide, as of June 04, 2021[2]. To try to contain this, several novel vaccines recently received an emergency use authorization (EUA) by the U.S Food and Drug Administration (FDA), the European Medicine Agency, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) and the Indian Central Drugs Standard Control Organization as well as the Drugs Controller General of India. After receiving EUA, these vaccines were administered to healthcare workers (HCWs), frontline workers, elderly, and at-risk individuals, including people with comorbidities, in a phased roll-out.

The vaccination program in India started on January 16, 2021 after the approval of two candidate vaccines namely Covishield™ (ChAdOx1-nCOV or AZD1222, acquired from Oxford University and AstraZeneca, manufactured by Serum Institute of India, Pune) and Covaxin™ (BBV-152, manufactured by Bharat Biotech, Hyderabad in collaboration with Indian Council of Medical Research, India) [1].

Our institute also started the vaccination programme with the two dose-regimen of ChAdOx1 nCoV-19 coronavirus vaccine (Covishield™), administered intramuscularly 4–6 weeks apart. Covishield™ is

[2] World Health Organization COVID-19 dashboard:www.covid19.who.int (assessed on June 4, 2021).

a recombinant, replication deficient, chimpanzee adenovirus vector encoding the SARS-CoV-2 spike (S) glycoprotein produced in genetically modified human embryonic kidney 293 cells. It contains 5×10^5 viral particles. Trials have shown that the vaccine induced a clear antibody response at 28 days after the first dose, across all age groups, including the elderly [2]. As total antibody levels correlate with the neutralizing antibody levels [3, 4]; we decided to measure the SARS-CoV-2 Immunoglobulin gamma (Ig G) antibody and total antibody to estimate the immune response to the vaccine. The immune response among individuals vaccinated against SARS-CoV-2 is hitherto less known. In the light of the current vaccination drive by the government with frequently changing dosage intervals, it is imperative to measure the antibody responses to ascertain the protection from SARS-CoV-2 infection among individuals.

The aim of the study was to evaluate the antibody responses among HCWs following two doses of Covishield™ vaccination in a tertiary care setting and the association of host factors like age, body mass index and comorbidities in determining this antibody response.

MATERIALS AND METHODS

Jubilee Mission Medical College & Research Institute (JMMC & RI) is a teaching hospital with 1600 beds and around 3000 staff on regular pay rolls, daily wagers, and workers of service contractors. The institute started vaccinating its staff with ChAdOx1 nCoV-19 coronavirus vaccine, according to the Government of India guidelines, using the vaccine supplied by the Kerala Health Services on 19 January 2021. Baseline antibody levels of individuals against SARS-CoV-2, prior to vaccination, was available as part of the study conducted in our institute during September to December 2020 [5]. The current study is a prospective cohort-serological surveillance study (initiated after obtaining the Institutional Ethics Committee approval from January 2021 to April 2021. The study protocol 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). Written informed consent was obtained from each participant prior to enrolment and blood sample draw.

Participants of the study were HCWs aged $\geq$ 18 years of JMMC & RI: (a) who have provided their pre-vaccination serum sample for SARS-CoV-2 antibody estimation and were found negative (b) who have taken the first dose of ChAdOx1 nCoV-19 Coronavirus vaccine (c) with no history or test result suggestive of COVID-19 infection. Satisfaction of all the three criteria was essential to be included in the study. Health staff on short term contract and those who were not willing to provide repeated blood samples were excluded from the study. After obtaining informed consent a self-administered

questionnaire in Google forms was filled out by each participant.

During our study period the recommended dosage was two doses of Covishield™ given intramuscularly (0.5 ml each) with an interval of 28 days. (From May 2021 the interval for second dose extended to 12–16 weeks in India. From January 2022 booster was given to those who completed 9 months after their second dose).

Flowchart of study design and inclusion of patients is shown in Figure 1.

On the day of the second dose of vaccination, which ranged from 28 to 56 days after the first dose, a 5 ml blood sample was drawn by a trained phlebotomy team. Similarly, blood samples were also drawn 14 days after the 2nd dose from the same set of participants. A total of 170 individuals provided their blood samples after the first dose of vaccination. Fourteen participants were excluded from the second analysis of the study as they refused to provide consent for repeat blood samples.

The blood samples collected were centrifuged and the plasma separated and frozen at -20° Celsius for batch testing. The samples were subjected to SARS-CoV-2 Ig G and total antibody testing using the VITROS anti-SARS CoV-2 Ig G/Total Chemiluminescence kit manufactured by Ortho Clinical Diagnostics, USA. Both the VITROS anti-SARS-CoV-2 Total and Ig G assays (Ortho Clinical Diagnostics) are based on CLIA using luminol-horseradish peroxidase-mediated chemiluminescence. Both assays were performed on the VITROS 3600 automated immunoassay analyser (Ortho Clinical Diagnostics) according to the manufacturer's instructions. In these assays, the specific antibodies against the recombinant S1 subunit of the S protein of SARS-CoV-2 were automatically analysed. Results are reported as signal/cut-off (S/C) values and as qualitative results indicating non-reactive (S/C < 1.0; negative) or reactive (S/C $\geq$ 1.0; positive). The VITROS anti-SARS-CoV-2 total assay can detect total antibodies (IgA, Ig M, and Ig G) against SARS-CoV-2 S protein. Anti-SARS-CoV-2 Ig G antibody levels have been tested using various platforms especially for the extraction of high titre COVID-19 convalescent plasma. The protective levels post vaccination has not yet been validated. The protective level for convalescent plasma is considered to be above 9.5 S/C according to the US FDA document published for use in the manufacture of high titre COVID-19 Convalescent Plasma[3].

Statistical analysis

Data collected was entered into Microsoft Excel (Microsoft Corporation, USA) spread sheets and analysed using Statistical Package for Social Sciences (SPSS) v.25 (SPSS: An IBM Company, USA). Categorical variables are expressed as proportions/percentages with 95% confidence intervals (CI); continuous variables as median and 25th, 75th percentile.

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[3] Table of Tests Acceptable for Use in the Manufacture of High Titre COVID-19 Convalescent Plasma. https://www.fda.gov/media/141477/download (assessed on June 4, 2021).
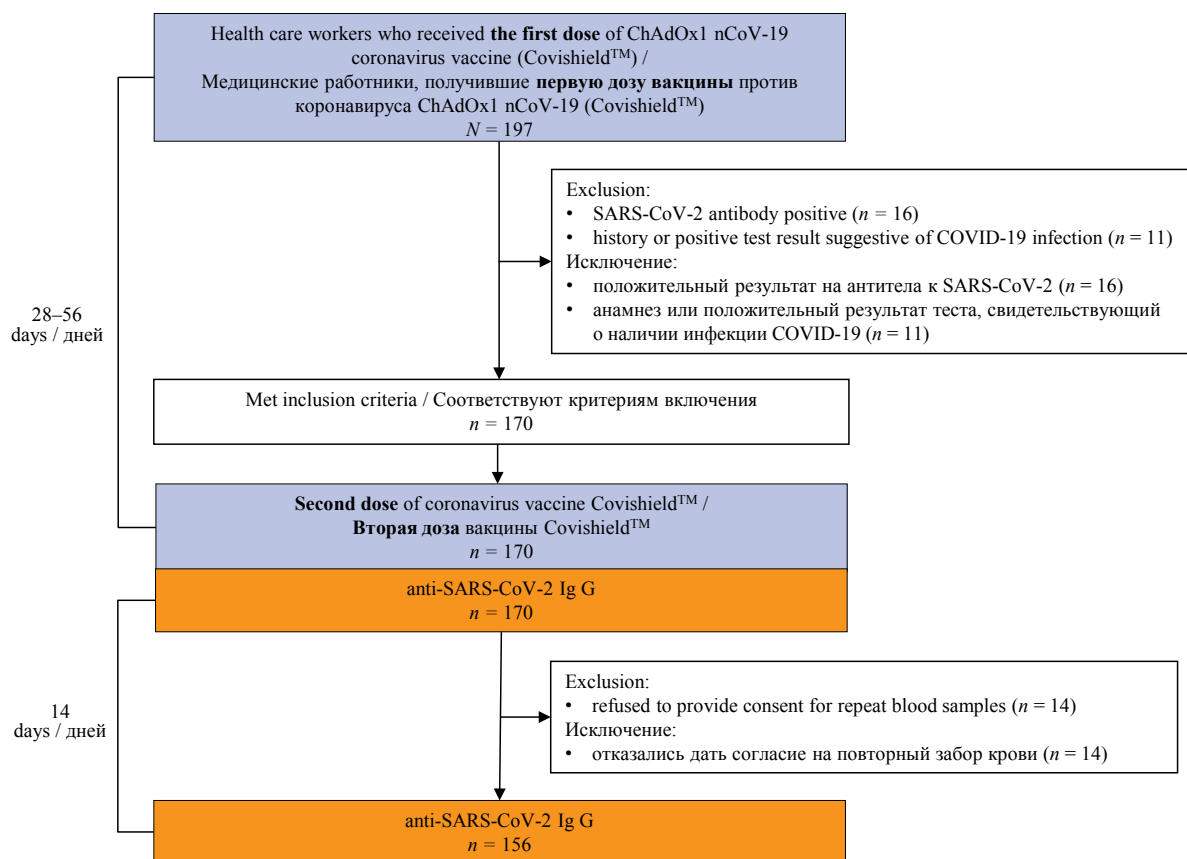
FIG. 1. Study design and patient enrollment flowchart.
РИС. 1. Дизайн исследования и потоковая диаграмма включения пациентов.

Mann-Whitney U test was used to test the significance of age with antibody protective level and Chi square / Yates correction test for categorical variables. The correlation of age and interval between the two doses of vaccine with antibody levels were calculated using Spearman's rank correlation. Association of age and comorbidities with immune response were estimated by regression method. The p value <0.05 is considered as statistically significant.

RESULTS

Table 1 describes baseline characteristics of 170 HCW who received Covishield™ vaccination. The mean age of the study population was 37.09 years (SD = 12.6). 126 (74.1%) belong to the 18–44 years age group, 30 (17.6%) to the 45–59 years age group and 14 (8.2%) to the 60 years and above age group. Males constituted 23.5% and females 76.5%. The body mass index categories according to the Asian classification[4] show that 21 (12.4%) are underweight, 45 (26.5%) normal, 40 (23.5%) overweight and 64 (37.6%) obese. 23 (19.4%) participants have comorbidities like diabetes, hypertension, bronchial asthma etc. 144 (84.7%) have a

previous history of Bacillus Calmette-Guérin vaccination and 17 (10%) have a history of influenza vaccination.

Adverse events following vaccination were reported by 141 (82,9%) participants. The most common symptom was fever, which was reported in 88 (51.8%), followed by pain at the injection site in 59 (34.7%), myalgia in 59 (34.7%), and headache in 45 (26.5%) of participants.

Protective levels of anti-SARS-CoV-2 Ig G antibodies (≥9.5 S/C) were observed in 25 (14.7%, 95% CI: 9.8% to 20.9%) from 170 participants after the first dose and in 109 (69.9%, 95% CI: 62% to 77%) from 156 individuals after the second dose.

Figure 2 depicts the distribution of serum antibodies 28 to 56 days after first dose of vaccine. The median level of anti-SARS-CoV-2 Ig G antibody in the serum of 170 participants was 3.64 (1.33; 7.24). The median antibody level after 14 days of second dose vaccination for 156 participants was 11.6 (8.62; 14.27) S/C.

Sub-group analysis (Table 2) of the participants who developed protective levels of Ig G following vaccination revealed that 80% of the participants after the first dose and 75.2% of participants following the second dose belong to the 18–44 years age group.

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[4] World Health Organization (WHO). International Association for the Study of Obesity (IASO) and International Obesity Task Force (IOTF). The Asia-Pacific Perspective: Redefining Obesity and its Treatment. Geneva: World Health Organization; 2000. p. 18 https://apps.who.int/iris/handle/10665/206936 (assessed on June 4, 2021).

Table 1. Baseline characteristics of study population
Таблица 1. Исходные характеристики исследуемой популяции

Characteristic / Характеристика	Value / Значение (*n* = 170)
Age, years / Возраст, годы	34 (27.75; 45)
18–44	126 (74.1%)
45–59	30 (17.7%)
≥60	14 (8.2%)
Sex / Пол	
Male / Мужчины	40 (23.5%)
Female / Женщины	130 (76.5%)
Body mass index (kg/m^2) / Индекс массы тела (кг/м^2)	
Underweight / Дефицит веса (<18.5)	21 (12.4%)
Normal / Норма (18.5–22.9)	45 (26.5%)
Overweight / Избыток массы тела (23.0–24.9)	40 (23.5%)
Obese / Ожирение (≥ 25)	64 (37.6%)
Comorbidity / Коморбидность	33 (19.4%)
Previous BCG vaccination / Наличие вакцинации БЦЖ	
Yes / Да	144 (84.7%)
No / Нет	12 (7.1%)
Unknown / Неизвестно	14 (8.2%)
Previous influenza vaccination / Наличие вакцинации от гриппа	
Yes / Да	17 (10%)
No / Нет	115 (67.6%)
Unknown / Неизвестно	38 (22.4%)

Note: BCG – Bacillus Calmette-Guérin vaccine (given against Tuberculosis).
Примечание: БЦЖ – Бацилла Кальмета – Герена (вакцина против туберкулеза).

Independent analysis of various factors for association with serum Ig G levels of anti-SARS CoV-2 antibodies after second dose vaccination (Table 2) showed that HCW below 60 years of age had significant association (p = 0.027) in building up protective antibody levels.

No significant correlation was found between age (r = –0.19, & r = –0.13) and interval between two doses (r = 0.19) of vaccine with Anti SARS Cov-2 Ig G antibody levels in individuals 28 to 56 days after the first dose and 14 days after the second dose of Covishield™ vaccine.

Logistic regression of age of the individuals as well as the presence of comorbidities with protective antibody levels after second dose of vaccination, showed significant relation with age of the individuals only (Table 3).

DISCUSSION

Antibody response plays a major role in developing protective immunity during SARS-CoV-2 infection [4, 6]. Even though seropositivity based on different cut off values of Ig G titres does not necessarily translate into direct protection from SARS-CoV-2 infection, it can be used as a surrogate biomarker of immunity in assessing the human humoral response to COVID-19. In this study, we assessed the humoral immune response after the first and second doses of Covishield™ vaccine in HCWs in a tertiary hospital in Kerala. The samples were subjected to SARS-CoV-2 Ig G and total antibody testing using the VITROS anti-SARS CoV-2 Ig G/Total

Chemi luminescence kit manufactured by Ortho Clinical Diagnostics, USA, which has already been validated to have a high specificity in the detection of antibodies in convalescent plasma of COVID-19 infected patients [7]. However, the protective levels of antibody post vaccination have not yet been validated. Hence, we followed the cut-off value of 9.5 S/C as hypothetical protective level as prescribed by the manufacturer based
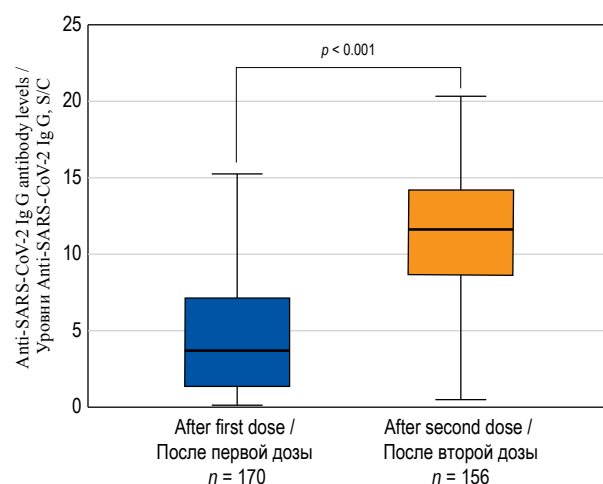
FIG. 2. Anti SARS-CoV-2 Ig G antibody levels in individuals 28 to 56 days after the first dose and 14 days after the second dose of Covishield™ vaccine
РИС. 2. Уровни антител IgG против SARS-CoV-2 через 28–56 дней после первой дозы и через 14 дней после второй дозы вакцины Covisield™

Table 2. **Association with host factors in individuals who developed protective Ig G levels (≥9.5 S/C) after vaccination with Covisield™**

Таблица 2. **Ассоциация с факторами хозяина у лиц с защитным уровнем IgG (≥9,5 S/C) после вакцинации Covisield™**

Characteristic / Характеристика	Participants with protective antibody levels after first dose / Участники с протективным уровнем антител после первой дозы (25/170)	p value / значение p	Participants with protective antibody levels after second dose / Участники с протективным уровнем антител после второй дозы (109/156)	p value / значение p
Age, years / Возраст, годы				
18–44	20 (80%)		82 (75.2%)	
45–59	4 (16%)	n.s.	22 (20.2%)	0.027
≥60	1 (4%)		5 (4.6%)	
Sex / Пол				
Male / Мужчины	3 (12%)	n.s.	27 (24.8%)	n.s.
Female / Женщины	22 (88%)		82 (75.2%)	
Body mass index (kg/m²) / Индекс массы тела (кг/м²)				
Underweight / Дефицит веса (<18.5)	4 (16%)		12 (11%)	
Normal / Норма (18.5–22.9)	3 (12%)		33 (30.3%)	
Overweight / Избыток массы тела (23.0–24.9)	6 (24%)	n.s.	25 (22.9%)	n.s.
Obese / Ожирение (≥25)	12 (48%)		39 (35.8%)	
Comorbidity / Коморбидность	5 (25.0%)	n.s.	17 (15.6%)	0.079
Previous BCG vaccination / Наличие вакцинации БЦЖ				
Yes / Да	20 (80.0%)		90 (82.6%)	
No / Нет	3 (12.0%)	n.s.	8 (7.3%)	n.s.
Unknown / Неизвестно	2 (8.0%)		11 (10.1%)	
Interval between two doses of vaccination / Интервал между двумя дозами вакцины				
≤42 days / дней (*n* = 123)			86 (78.9%)	n.s.
>42 days / дней (*n* = 33)			23 (21.1%)	

Note: BCG – Bacillus Calmette-Guérin vaccine (given against Tuberculosis); n.s. – not significant.
Примечание: БЦЖ – Бацилла Кальмета – Герена (вакцина против туберкулеза); n.s. – не значимо.

Table 3. **Logistic regression of protective antibody level with different age group and presence of comorbidities**

Таблица 3. **Логистическая регрессия уровня защитных антител с разной возрастной группой и наличием коморбидности**

Variables / Переменные	Coefficient / Коэффициент	SE / CO	OR / ОШ	95% CI for OR / 95% ДИ для ОШ	p value / значение p
45–59 years / лет	1.380	0.606	3.976	1.212-13.045	0.023
18–44 years / лет	1.769	0.733	5.867	1.395-24.673	0.016
Comorbidities (No) / Коморбидность (Нет)	0.625	0.485	1.868	0.722-4.834	0.198

Note: OR – odds ratio, CI – confidence interval, SE – standard error.
Примечание: ОШ – отношение шансов, ДИ – доверительный интервал, СО – стандартная ошибка.

on protective levels required for convalescent plasma[5]. It has already been proved in various studies [8, 9] that Ig G levels following natural infection with SARS CoV-2 can persist for several months, including an ongoing study on a cohort of Belgian hospital workers, which shows persistence of Ig G till up to 199 days [10]. This principle may also be applied for antibody response following vaccine administration.

In a pooled analysis of four randomized trials on immunogenicity and efficacy ofChAdOx1 nCoV-19 (AZD1222) vaccine by Voysey M. et al. [2], where antibody responses were measured by immunoassay and by pseudovirus neutralisation, it is already known that individuals aged 18–55 years who received a second dose vaccine more than 12 weeks after the first had antibody titres more than two-fold higher than those who received the second dose within 6 weeks of their initial vaccination. In our study, among the 170 HCWs, protective antibody levels were found in 14.7% after the first dose, which rose to 69.9% after the second dose of Covishield™ vaccine.

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[5] Table of Tests Acceptable for Use in the Manufacture of High Titre COVID-19 Convalescent Plasma.

Ewer K.J. et al. [11] report an increase of spike protein specific IgG activity between day 28 and 56 after dosing. Folegatti P.M. et al. [12] report an increase in protective neutralizing antibody levels after second dose. Here humoral responses at baseline and following vaccination were assessed using a standardised total IgG enzyme-linked immunosorbent assay (ELISA) against trimeric SARS-CoV-2 spike protein, a muliplexed immunoassay, three live SARS-CoV-2 neutralisation assays. Our observations are in concordance with these two studies. However, an Indian study by Singh A.K. et al. [13] among HCWs reports 79.3% positivity which is higher than our findings. The IgG antibodies directed against the spike protein (S-antigen, both S1 and S2 protein) were measured using chemiluminescence immunoassay (CLIA). Inclusion of subjects with a history of COVID-19 could be a reason for the faster high antibody level in this report. We excluded participants with a history of COVID-19 infection from our study. In a study by Hoque A.et al. in Bangladesh [14], Spike-specific IgG antibody responses elicited after the first and second doses of vaccine were 99.9% and 100%. A study performed in Kuwait by Ali H. et al. [15] report high levels of IgG, IgA, and neutralizing antibodies in vaccinated subjects with previous COVID-19 infections than in those without previous infection.

Subgroup analysis of those participants who built up protective antibody levels in our study reveals a preponderance of 18–44 years age group ($p = 0.027$). 80% of the participants who developed IgG more than 9.5 S/C following the first dose vaccination and 75.2% following second dose belong to this particular age group. The majority of the 60 years or above age group remained to be 'low-responders' despite two doses of vaccination. Similar findings were reported in age-dependent immune response studies to the BioNTech/Pfizer BNT162b2 Covid-19 vaccine and AstraZeneca vaccine by Iacobucci G. et al. and Wei J. et al. [16, 17]. Perhaps aging and resultant immunosenescence may have a role in the decreased response to vaccinations in the elderly population [18, 19].

In the current study, even though 73% of participants without comorbidities like diabetes, hypertension and bronchial asthma developed protective levels of antibody,

it is not significant statistically ($p = 0.079$). The literature shows no differences in immune responses with presence or absence of comorbidities following natural infection with the virus [20]. The limited studies available following vaccination also show no significant association of comorbidities with antibody response [14].

The time interval between the two doses of the vaccine in our study ranges from 28 to 56 days. Even though there is enough evidence to show that an increasing time interval between the two doses of Covishield™ is beneficial in building up antibody response [21], we observed no significant association (Fig. 3). This might be a function of the small sample size of our study.

This is a prospective serosurveillance study following up a cohort of vaccinated HCW for one year where the antibody levels of participants at 3 months, 6 months, and 12 months following second dose of the Covishield™ vaccination will be studied. These are the preliminary results of the study. The small sample size, especially the small number of participants over 60 was the main limitation of our study. We have also not investigated the cell-mediated immune responses which could augment responses against COVID-19 virus.

CONCLUSION

The evidence base for optimal vaccine dosage, timings of doses, adverse events following immunization and need for booster dose remains scarce for COVID-19 vaccinations. The current study observed positive antibody response to the first dose of Covishield™ vaccine which is enhanced after the second dose. Antibody response in younger age groups is higher and the influence of body mass index and co-morbidity is not significant. Given the current scenario in India where there is scarcity of hospital beds, oxygen and ventilators coupled with a low supply of vaccines, an effective strategy for vaccination is needed. Our study results provide a baseline data and supplement the evidence for the early response to the vaccine but further follow up studies are required to decide on the further optimal boosting interval and dynamics of antibody response.

DECLARATIONS

Availability of data and material

Data collected was compiled into Excel sheets by Sree Raj V. & Aboobacker M. Rafi under the supervision of Susheela J. Innah. Data cleaning, analysis and review was done by Swathi K. Njarekkattuvalappil, Uttumadathil G. Unnikrishnan and Ponnu Jose.

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