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ORIGINAL RESEARCH ARTICLE

Impact of Covishield Vaccination in Terms of SARS CoV-2 Neutralizing Antibody Expression

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Abstract The vaccination efficacy can indirectly be assessed through the quantification of neutralizing antibodies. Very few data are available on Covishield efficacy in terms of neutralizing antibody expression upon vaccination. This study is focused on profiling of neutralizing antibody expression during and after the Covishield two shot vaccination and observing COVID-19 infection in vaccinated participants during the period. SARS CoV-2 neutralizing antibody concentrations in samples were estimated using electrochemiluminescence immunoassay kit for Lifotronics eCL8000. The sampling had been done sequentially at 45th, 85th day after 1st dose and 15th day after 2nd dose Covishield vaccination. Parallelly, in order to confirm the total SARS CoV-2 IgG response in COVID-19 infection, measured the IgG using SARS CoV-2 IgG lateral flow immunoassay test kit. The subjects previously infected with COVID-19 before 1st dose vaccination demonstrated high neutralizing antibody (> 10AU/ml). In COVID-19 uninfected subjects, there was a sudden incline in neutralizing antibody after the 2nd dose. Infection with SARS CoV-2 between 1st and 2nd dose of Covishield vaccination implicate that the level of neutralizing antibody in serum after 1st dose was not adequate to combat the virus and prevent infection. We observed COVID-19 infection in participants even after 2nd dose of vaccination. Interestingly, there was no protection against SARS CoV-2 even with a high neutralizing antibody expression of 188.5 AU/mL after the 2nd dose. Findings of Covishield efficacy in different cohort samples before and after 2 doses of Covishield vaccination provide impetus for improvement or development of next generation vaccines.

Keywords Neutralizing antibody · Electrochemiluminescence Immunoassay · Covishield · COVID-19 · SARS CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has catastrophically affected the entire world. This deadly virus which was firstly reported in Wuhan caused 25.9 billion confirmed infections and over 5.1 million deaths worldwide as of November 25, 2021. A critical challenge is to curb the viral infection from further transmission. Initially the diagnostics tools like RT-PCR, RT-LAMP and Lateral Flow Antigen Immunoassays were the major stakeholders in early diagnosis and disease constrain [1–3]. Meanwhile, vaccine development programmes were in process and the first vaccine has been available from the end of 2020 in response to rapid efforts throughout the pharma industry. Despite the global spread, vaccination has been reported to create clinically significant outcomes of protection against COVID-19 infection and severity.

To date vaccines approved by the Indian Council of Medical Research (ICMR) and Drugs Controller General of India (DCGI) for use in India comprising, ZyCoV-D (Zydus Cadila), mRNA-1273 (Moderna), Sputnik V (Gamaleya), Ad26.COV2.S (Johnson & Johnson), AZD1222 Covishield (Oxford/AstraZeneca/Serum Institute of India), Covaxin (Bharath Biotech), COVOVAX (Serum Institute of India) & BECOV2A (Biological E Limited). The Covishield developed by the Oxford University, manufactured by AstraZeneca and the Serum Institute of India Pvt Ltd is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS CoV-2 Spike (S) glycoprotein.

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The dosage recommendation for the Covishield vaccine in India is two stage shots with a booster dose 84 days after 1st dose.

Upon vaccination, the humoral immune response triggers the antibody production against viral epitopes in the recombinant vaccine. Even though antibodies against multiple epitopes have been triggered, only the expression level of neutralizing antibodies implicates the effectiveness of vaccination. At present, very few data are available regarding the efficacy of Covishield and how it has affected the Indian population. Vaccine efficacy can be measured by focusing on invitro virus neutralization titres [4–7].

Several studies demonstrated the efficacy of different vaccination with regard to neutralizing antibodies. Previous report on neutralisation activity against variants like B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) observed lesser neutralizing antibody titre when treated with mRNA-1273 COVID-19 vaccine [8]. These reports were further substantiated with similar trends of reduced neutralising antibody against B.1.1.7 when treated with ChAdOx1 nCoV-19 [9]. Vaccine breakthrough for Delta variant were

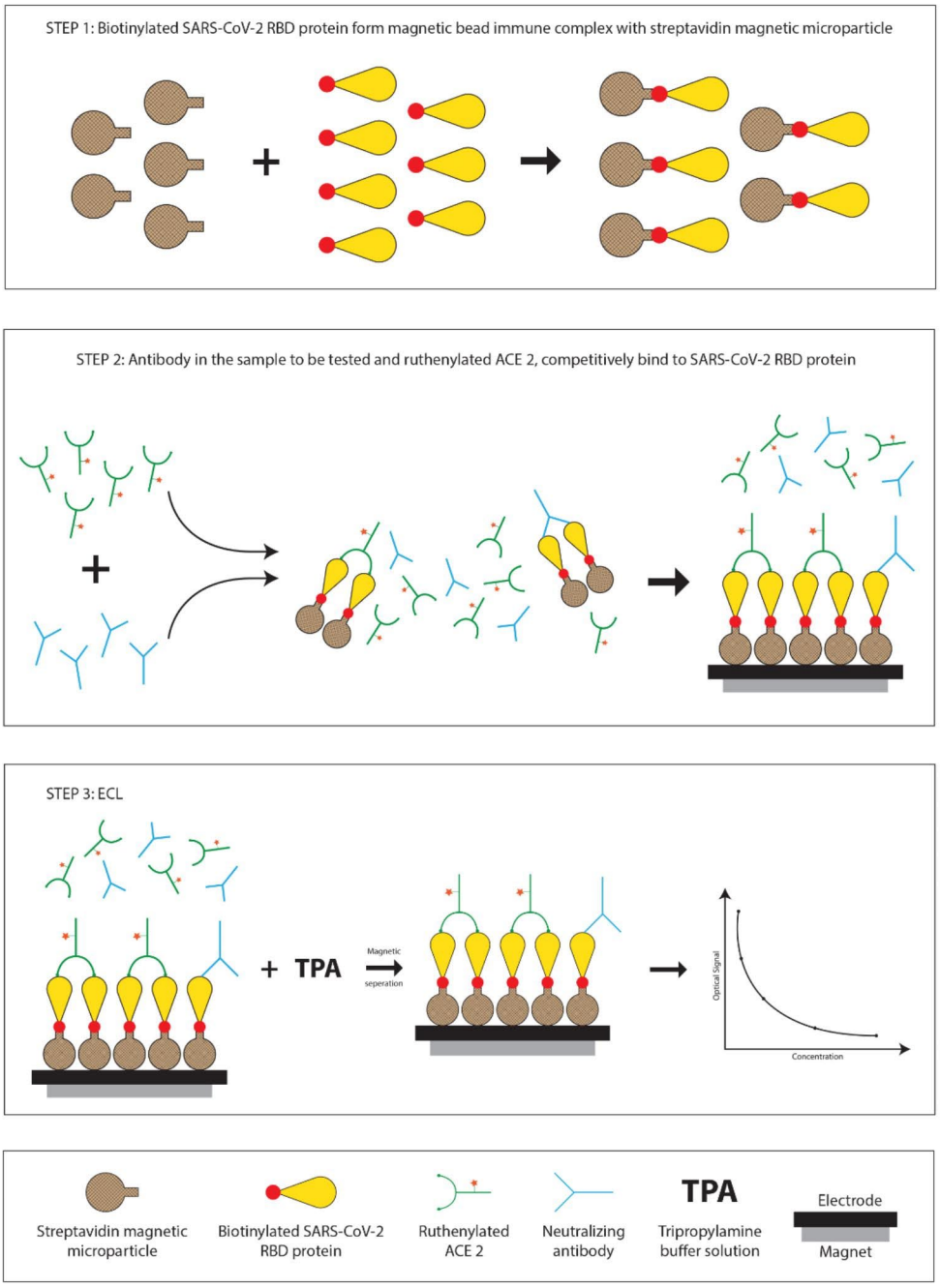

Fig. 1 Schematic representation of competitive ECLIA for detection of neutralizing antibody in patient serum. The above diagrams are not plotted according to the actual scale

observed in 6 patients that received the Pfizer BNT162b2, Moderna mRNA-1273, and Covaxin BBV152 leading to highest risk with delta variant in transmission over Alpha and other variants [10].

Neutralizing antibodies can be quantified by using different immunoassay techniques. The gold standard that measures neutralizing antibodies by invitro virus neutralization is the plaque reduction neutralization test (PRNT). Modified versions of PRNT like microneutralization test, or pseudo neutralization test are more widely used to make the process faster and easier to interpret the results [11]. Quantification of neutralization antibody expression through a chemiluminescence platform is an indirect method to assess the effectiveness of vaccination. Electrochemiluminescence Immunoassay (ECLIA) being the most specific and highly sensitive tool for detection of hormones and infection diagnosis is a ruthenium tris-bipyridine labelled model [12, 13]. Among various automated analytical platforms available, in this study we used Lifotronics eCL 8000 electrochemiluminescence analyzer to measure the COVID-19 neutralizing antibody in serum. Lifotronics eCL 8000 employs the tris (2,2' – bipyridine) ruthenium (II)- based direct

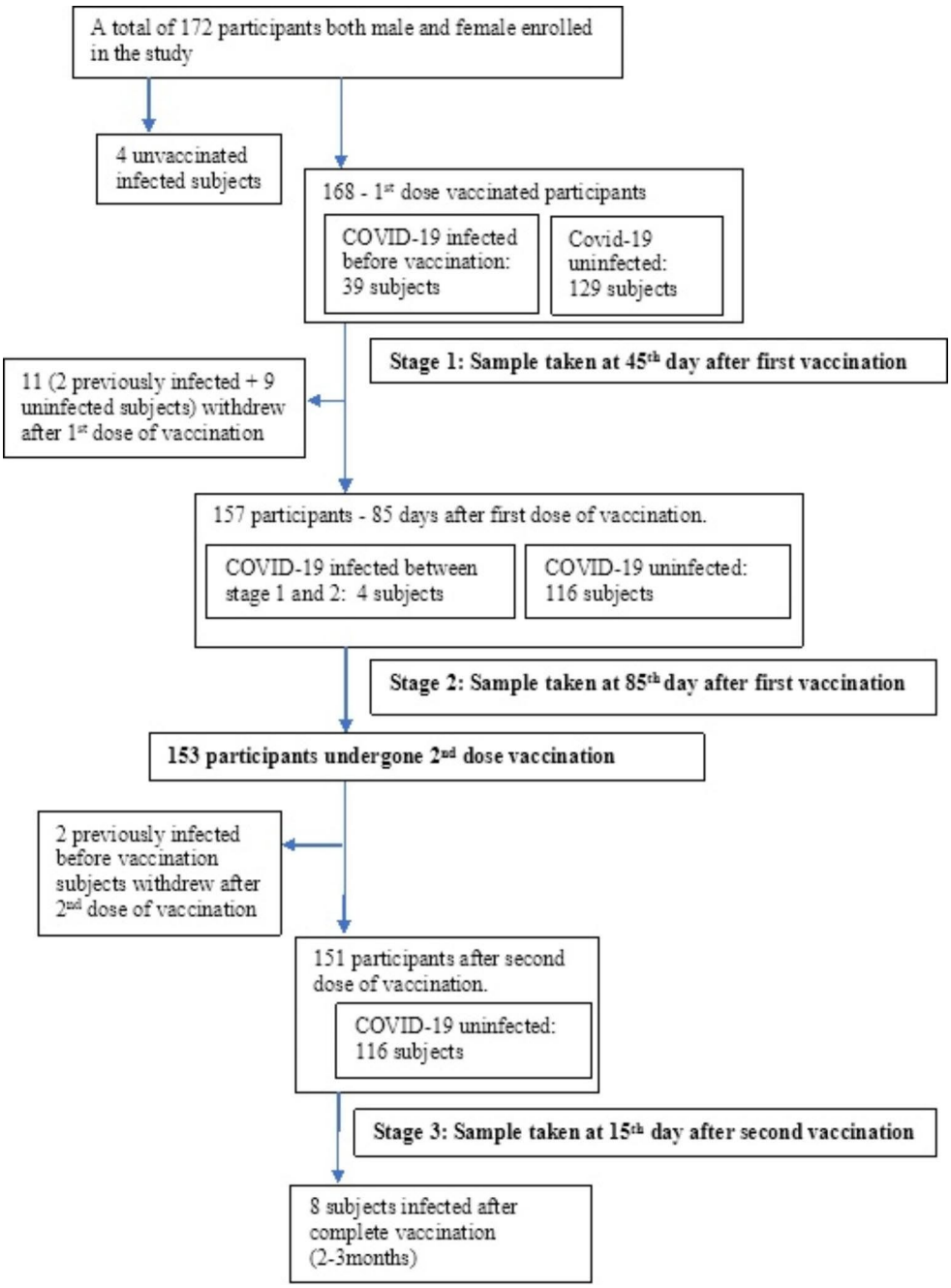

Fig. 2 Sampling representation in different cohorts

electrochemiluminescence method. Parallelly the expression of SARS CoV-2 IgG antibody was also studied with lateral flow immunoassay (LFIA) for better understanding.

Lifotronics eCL 8000 neutralizing antibody reagent works under the competitive ECLIA principle (Fig. 1). Sample, biotin labelled SARS CoV-2 RBD protein, angiotensin converting enzyme 2 (ACE2) labelled with ruthenium and streptavidin coated with microparticles are added together to react for 9 min. The SARS CoV-2 Neutralizing antibodies will bind to the RBD, the remaining reaction sites of SARS CoV-2 RBD labelled with biotin are occupied by ACE2. Meantime, the biotin labelled SARS CoV-2 RBD protein automatically attaches with streptavidin-coated microparticles forming a complex. The reaction complex is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with tripropylamine buffer (TPA). Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photocell. As per the kit insert, the cut off reference level for SARS CoV-2 neutralizing antibody is 10 AU/mL. An estimated value of > 10 AU/mL is considered as a significant level of neutralizing antibody against SARS CoV-2.

To address this relevant topic, we quantified the titres of SARS CoV-2-specific neutralizing antibodies during each stage of vaccination along with COVID-19 non-infected and non-vaccinated people as controls. Here, our aim was to present a combined analysis of the safety and efficacy of the Covishield vaccine.

Methods

Sampling

One hundred and seventy two subjects (68 females and 104 males) of the age group between 21 and 55 were enrolled in this study. Filled consent forms were given by all the participants for their samples to be stored and used for future research purposes. All the participants were physically healthy and were not undergoing any particular medical treatment. The study participants represent the entire Kerala state.

The study group received two doses of vaccination according to their respective schedule: first vaccination on 11/06/2021 and second vaccination on 11/09/2021. Serum samples were collected on 45th day after the first vaccination (Stage 1), on 85th day after 1st vaccination (Stage 2) and on 15th day after 2nd vaccination (Stage 3). The selection of days for sample collection is fixed based on our previously studied and published data on SARS C0V-2 IgG antibody expression in post COVID-19 patients. It was observed that the SARS CoV-2 IgG antibody surge occurred on 45th day of COVID-19 infection [14]. Out of 172 subjects, 4 were infected before commencement of the study and remain unvaccinated during the study period. Remaining 168 subjects taken the 1st dose vaccination; in which 39 were previously infected with COVID-19 and 129 were uninfected. 11 subjects (2 previously infected before vaccination + 9 uninfected) were withdrawn after 1st dose of vaccination leaving 157 participants in the study. Four subjects infected between the 1st and 2nd dose of vaccination. Further 2 more subjects (previously infected before vaccination) withdrew and remaining 151 subjects received a second dose of vaccination. Even after complete vaccination, 8 of the enrolled participants got infected with SARS CoV-2 within a time period of 2–3 months after 2nd dose (Fig. 2). The 39 subjects infected before 1st dose vaccination were came across the disease during the time period of July 2020 to May 2021.

Machines and assays

Neutralizing antibody and IgG antibody against SARS CoV-2 were measured using Lifotronics eCL8000 electro chemiluminescence Immunoassay analyzer, China and SARS CoV-2 IgG were measured using Lateral Flow Immunoassay test kit developed indigenously by Agappe Diagnostics Limited, India. The study design and execution followed the IFCC guidelines on clinical laboratory testing for COVID-19 diagnosis [15].

Statistical Analysis

The continuous variable results are expressed in mean with range format. For all experiments, two tailed P value was calculated and $P < 0.05$ was considered as significant. The mean differences between independent variables were analyzed using unpaired t-test inferential statistical tool in GraphPad Prism 9.3.1 (471). Unpaired t-test with Welch's correction was used which did not assume equal standard deviations among the independent variables.

Results

Neutralizing antibody expression in naturally infected COVID-19 patients with 1st dose vaccination

To evaluate the primary response to 1st dose vaccination, all subjects were tested for neutralizing antibody levels in serum at 45th day. The subjects previously infected with COVID-19 before 1st dose vaccination (n = 39) were compared with the uninfected control group (n = 129). Based

on the results obtained from eCL 8000, all samples demonstrated high neutralizing antibody level (> 10AU/ml) following COVID-19 infection & 1st dose vaccine. All of these values were above the baseline, reporting very high protection after the infection (Fig. 3).

The neutralizing antibody level in previously infected subjects along with the first dose Covishield ranges from 42.98 AU/mL to 720.7 AU/mL with a mean value of 278.726 AU/mL. Correspondingly the control group (1st dose vaccination alone) neutralizing antibody level ranges from 1.34 AU/mL to 572.4 AU/mL with a mean value of 48.619 AU/mL.

Protective level of antibodies in uninfected subjects

To ascertain the association of antibody and vaccination, all uninfected subjects were tested for neutralizing antibody in three stages to the following schedule; 45th day after the first dose, 85th day after the first dose and 15th day after the second dose of vaccination. We observed that in the first two stages, neutralizing antibody was found to be subsequently less when compared to the incline seen in stage 3. However, a gradual increase in antibody titre was observed after the second dose, indicating a protective response to the body by vaccination. (Fig. 4).

The mean value for neutralizing antibody in uninfected subjects at stage 1 (45th day after 1st dose) was 48.619 AU/mL (range; 1.34 to 572.4 AU/mL), at stage 2 (85th day after 1st dose) was 38.828 AU/mL (range; 1.111 to 567 AU/mL) and at stage 3 was 94.801 AU/mL (range; 1.724 to 583.2 AU/mL).

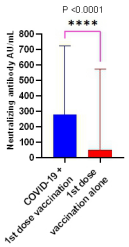

Fig. 3 Difference between Neutralizing antibody titre in COVID-19 infected and uninfected participants. Neutralizing antibodies in uninfected participants after the first dose of vaccination were considered as control

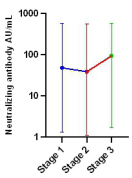

Fig. 4 Plot shows neutralizing antibody titre after each stage in COVID-19 uninfected subjects. Stage 1 - neutralizing antibody titre at 45th day after the first dose (n = 129), Stage 2 – neutralizing antibody titre 85th day after the first vaccination (n = 116) and Stage 3- neutralizing antibody titre 15th day after the second vaccination (n = 116)

COVID-19 infection after 1st dose vaccination: Neutralizing antibody Surge!

The neutralizing antibody expression in participants who were infected with SARS CoV-2 between 1st and 2nd dose vaccination (n = 4) was estimated to understand the neutralizing antibody surge. Based on the measurements all 4 samples showed a sudden surge in NAb after COVID-19 infection; samples S1, S2, S3 and S4 showed titres from 9.19 to 589.9AU/ml, 40.89 to 271.5AU/ml, 10.18 to 626.7AU/ml and 11.57 to 610 AU/ml respectively. In total, although the first dose of vaccination produced responses, the level of neutralizing antibody in serum was not adequate to combat with the virus and prevent the infection. It is also evident that the natural COVID-19 infection triggers a rapid shoot up in the neutralizing level (Fig. 5 A).

COVID-19 infection after 2nd dose vaccination: Insufficient neutralizing antibody levels!

Even after 2nd dose vaccination, 8 participants (sample 5 to 13) in the study group got infected with SARS CoV-2. Although all these subjects showed high neutralizing antibody concentration after the second vaccination, all of them were affected with COVID-19 later. It is observed that the time gap between the second dose vaccination and the infection was around 2–3 months only. Interestingly, there was no protection from COVID-19 even with a high neutralizing antibody level of 188.5 AU/mL (S8) by the complete vaccination (Fig. 5B).

Assessments of protective level in unvaccinated COVID-19 positive samples

Additionally, the study estimated the neutralizing antibody levels in 4 more subjects who were infected with COVID-19 and not vaccinated during the study period. Similar to the interim analysis, all samples showed neutralizing antibody concentration above the baseline value of 10AU/ml. Neutralizing antibody concentration were as follows; sample 13–22.11AU/ml, sample 14–48.45AU/ml, sample 15–42.73 and sample 16–39.88 AU/ml (Fig. 5 C). Antibody concentrations were checked after 3–5 months of infection. This supports all the previous data that the natural infection itself plays a major role in protecting the body by creating specific neutralizing antibodies against the virus. Although later

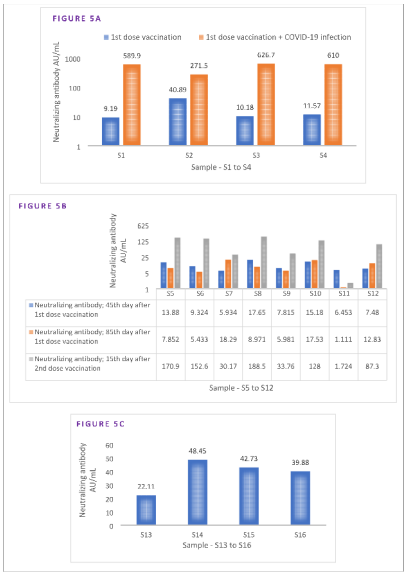

Fig. 5 **A)** Comparison of neutralizing antibody concentration after the first vaccination and COVID-19 infection. **B)** Comparison of neutralizing antibody concentration after both vaccinations. Stage 1 represents neutralizing antibody concentration at 45th day after 1st vaccination, Stage 2 represents neutralizing antibody concentration at 85th day after 1st vaccination and Stage 3 represents neutralizing antibody concentration after complete vaccination. **C)** Level of neutralizing antibody concentration in COVID-19 infected subjects after 3–5 months

responses were not measured, protection from the disease should be largely retained.

Comparison of NAB and SARS CoV-2 IgG in eCL-8000 and using LFIA assay

To further support the efficacy of the neutralizing antibody test, we performed SARS CoV-2 IgG analysis using lateral flow immunoassay. Here, all patients who turned positive before vaccination and taken 1st dose of vaccine were undergone SARS CoV-2 IgG test to measure total anti-SARS CoV-2 Immunoglobulin G presence in the serum samples (Table 1). Similar to neutralizing antibody, SARS CoV-2 IgG was observed to be higher in positive samples (factor 2.5 and above on a scale of 5).

Discussion

All the 39 subjects infected before vaccination showed very high concentration of neutralizing antibody after 1st dose as compared to the control group having 1st dose vaccination alone. None of the previously infected subjects faced reinfection with SARS CoV-2. Even though, reinfection with SARS CoV-2 reported in immunocompromised individuals, this study shows that the natural SARS CoV-2 infection plays a major role in protection from reinfection. Although both memory B and T cells play a major role in immune boosting, neutralizing antibody against SARS CoV-2 acts as an immune correlate and provides a direct correlation between antibody titre and clinical cohort studies. Our study shows that even in the presence of tremendous increase in neutralizing antibody after vaccination, patients were still infected with SARS CoV-2. This analysis is supported by the data from cohorts who were COVID-19 positive after vaccination [16]. However, this model only provides an overall expression of neutralizing antibody thereby predicting vaccine effectiveness. From previous observation, neutralizing antibodies act as protectors from reinfection in animal models and later proved in humans [17]. A strong linear correlation between Immunoglobin antibody titre and

Table 1 Shows correlation between SARS CoV-2 IgG analysis using lateral flow immunoassay and Neutralizing antibody using CLIA method

Sample Number	LFIA IgG factor	Neutralizing antibody (AU/ml)	Sample Number	LFIA IgG factor	Neutralizing antibody (AU/ml)	Sample Number	LFIA IgG factor	Neutralizing antibody (AU/ml)
1	3.5	65.09	**14**	3.5	322.2	**27**	2.5	70.28
2	3.5	151.2	**15**	4	67.34	**28**	3	92.53
3	4	254.1	**16**	4	406.3	**29**	3	316.5
4	4	471.5	**17**	3.5	146.7	**30**	2.5	230
5	3.5	335.2	**18**	4	266.4	**31**	4	620
6	3.5	720.7	**19**	4	572.8	**32**	4	310.9
7	2.5	80.5	**20**	3.5	257.5	**33**	4	186.5
8	3	409.5	**21**	3.5	372	**34**	4.5	383.4
9	4	287.1	**22**	3.5	217.8	**35**	4	186.5
10	3.5	67.46	**23**	3	67.87	**36**	4	615.9
11	3.5	388.3	**24**	4.5	61.85	**37**	4	74.01
12	3.5	292.8	**25**	2.5	230.7	**38**	4	257.3
13	4	546.3	**26**	2.5	424.3	**39**	3.5	42.98

neutralization levels provides greater comparability and relevance for the entire data.

Structural correlation studies of Neutralizing antibodies in complex with SARS-CoV-2 RBD classifies antibodies into different categories. Differences in encoding gene segments in neutralizing antibodies, blocks only certain areas of ACE2 and binds different RBD sites. These differences might lead to decrease in neutralization, therefore evaluating avidity effects and applying combinations against SARS-CoV-2 should be considered in improving vaccine efficacy [18]. Mainly antibodies that neutralise SARS-CoV-2 either target Receptor binding domain (RBD) or N-terminal domain (NTD). NTD directed neutralizing antibodies target a single supersite when compared to RBD directed antibodies that recognise multiple non-overlapping epitopes. This narrows down the chances of utilising combinations of NTD directed neutralizing antibodies [19]. VIR-7831 and VIR-7832 are monoclonal antibodies that target wild-type SARS-CoV-2 in vitro as well as pseudo typed viruses encoding spike protein from the B.1.1.7, B.1.351 and P.1 variants [20]. In variants (B.1.1.7 and B.1.351), mutation positions are within the NTD supersite inducing resistance against most of NTD targeting antibodies. There are studies showing resistance to neutralization in 10 pseudo viruses with mutation in RBD binding domain [21].

It would have been of great interest to track the long term protective response of neutralizing antibody, forming a direct pointer in assisting future deployment of vaccines. The potential lack of study between age groups, immunogenicity, protective efficacy and duration also supports the need for research in further testing and validation of Covishield vaccine efficacy and the need for booster doses against COVID-19.

Based on this study, the efficacy of 2 dose Covishield to prevent the SARS CoV-2 virus infection is not satisfactory. Acquiring COVID-19 infection even after two shots of Covishield implicates the epitope disparity between the vaccine and the viral spike protein. COVID-19 Infection within 2–3 months after the second dose Covishield vaccination questioning the protective capacity of the vaccine. Of course, the vaccination helps in mitigating the symptoms and thereby reducing the severity of COVID-19 infection.

In conclusion, these novel findings of Covishield efficacy in different cohort samples before and after 2 doses of vaccination provide impetus for the improvement or development of next generation vaccines. Along with the findings and observations of this study with recent publications, it is evident that the Covishield vaccination may not prevent SARS CoV-2 infection, but the symptoms and severity of the disease could be decreased to a certain extend.

Acknowledgements Fig. 1 courtesy to Mr. Shine Raghavan, Agappe Diagnostics Limited, Kochi.

Declarations

Conflict of interest All authors declare that there is no conflict of interest.

Compliance with Ethical Standards Informed consent forms were signed by all the participants. Approval from Institutional Review Board has been taken to conduct the study.

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