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# Association of Robust Anti-SARS-CoV-2 Trajectories among Communities with and without COVID-19 Infection

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## Abstract

**Globally, 767 million people have been affected by SARS-CoV-2 infection and nearly a population of 6.94 million were deceased as per the World Health Organization (WHO) as of June 7, 2023. In India, the spreading of infections is now being restricted by the use of BBV-152 (Covaxin™) and ChAdOx1-nCOV (Covishield™) vaccines. The present study comprises 327 candidates and Chemiluminescent microparticle immunoassay (CMIA) was used as a quantitative analytical tool to detect IgG and IgM antibodies. Out of 327 candidates, 177 (54.1%) were vaccinated and 150 (45.9%) were non-vaccinated. Among vaccinated and non-vaccinated candidates, 49 (27.7%%) and 44 (29.3%) had a history of infection, respectively; meanwhile, most of the study participants were immunized with Covishield™ (n=145, 81.9%) and 18.1% (n=32) were immunized with Covaxin™. There were insignificant differences observed among immunized as well as non-immunized study participants in considering median age, gender, age categories, IgM levels, or IgM seropositivity. Predictably, there was an important variation in IgG median values and IgG positivity noticed among the immunized and non-immunized categories as well as between populations with and without preceding infections. Our research is hence coherent with prospective requirements for booster shots to assist in controlling the rate of infections and fatality rates together throughout the pandemic conditions.**

**Keywords:** SARS-CoV-2, Chemiluminescent Microparticle Immunoassay, IgG Antibody, Covaxin, Covishield, Vaccine, COVID-19

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## INTRODUCTION

In the Chinese territory of Wuhan, a suspicious viral infection with a range of acute pneumonia cases emerged by December 2019. This was then determined in the name of the novel coronavirus which has started to spread very quickly thus emerging as a worldwide pandemic.[1] World Health Organization (WHO) by February 2020, indicated novel coronavirus on account of its large resemblance towards severe acute respiratory syndrome (SARS-CoV), and it is known to be coronavirus infectious disease 2019 (COVID-19). Globally, 767 million people have been affected by SARS-CoV-2 infection as of June 7, 2023, and nearly a population of 6.94 million were deceased as per WHO.[2] SARS-CoV-2 emerged as an RNA virus that is positively stranded with a single envelope and it also has less than 30,000 nucleotides that code for 29 recognized viral proteins approximately.[3] There are four significant structural proteins encoded at the 3'-end of its genome: membrane protein (M), nucleocapsid protein (N), spike protein (S), and envelope glycoprotein (E). The protein N develops a capsid as it protects RNA and the viral envelope is formed by Protein E, Protein M, and Protein S.[4] The protein N and S protein are mostly related to causing infections by SARS-CoV-2. Perhaps, protein S has been divided by proteases into S1 and S2 subunits similar to other coronaviruses.[5] Angiotensin-converting enzyme-2 (ACE2) which is a receptor for host cells is identified as well as linked by the S1 protein. Integration of the envelope of the virus and the cell membrane of the host has been facilitated by the following conformational modifications in S2 proteins.[6]

Epidemiological statistics show that nearly 85% of SARS-CoV-2 infected patients have mild to moderate symptoms; hospitalization is needed for 15%, and of them, almost 5% of the people acquire serious diseases that require organ support and intensive care therapy.[7] Since a higher viral transmission rate eventually results in an increased incidence of subjects looking for care in hospitals, determines a significant charge among national health systems as most of them have deceased in the pandemic.[8] Children and young adults infected with severe SARS-CoV-2 infections have an increased titer of antibodies despite periodic coronaviruses.[9] Meanwhile, the reduced inflammation condition has been maintained by facilitating the infection by expressing high ACE2.[10] Ultimately, indefinite defensive impacts followed by taking live vaccinations and T-cell repertoire among children and younger individuals that are additionally varied may present with compassionate manifestations. Children having inflammatory or systemic conditions may be further shielded with the overcoming of immune evasion SARS-CoV-2 mechanism and a few therapies may also defend against cytokine storm syndrome development that is present within subsequent disease course.[11] Severe infections have been strongly related to weak innate immunological responses and then robust inflammatory reactions contributing to the cytokine storm, finally giving rise to organ failure. To diminish the pandemic and also to manage infections, understanding SARS-CoV-2 immunological responses are very much essential.[12]

Both the presentation of distinct antibodies that are conducted to the spiral proteins of the virus and T cell-dependent immunity have been associated with the protection of consecutive infections.[13] Numerous types of research have already shown that SARS-CoV-2-infected individuals turn out to be seropositive in 10 to 15 days following infections which can be prolonged if there are moderate infections. Nonetheless, there is a decline in the antibody response just as stated by multiple studies.[14-16] Although the infected individuals sustained higher neutralizing IgG levels for an extended period, neutralizing IgG levels decreased by 40% only after 5 months. Moreover, subjects who are asymptomatic and presenting with moderate diseases produce weaker antibody responses, and inconsistent over long-lasting immune responses. Such outcomes enhance the significance of vaccination to hinder infections and perhaps attain population-level immunity.[17] Multiple vaccinated subjects versus SARS-CoV-2 became available and accredited by the European Union (EU) as well as by different regulators only a year following the very first COVID-19 case reported. They used various immunization policies by December 2020: a vaccine that is adenoviral-vectored (ChAdOx1 nCoV-19 by University of Oxford/Covishield™) and BBV-152 (Covaxin™).[18,19]

As per WHO (5th June 2023), 13.39 billion population have been administered the SARS-CoV-2 vaccination globally. In India, as of 12th June 2023, 2.2 billion population are immunized.[2] However, all these vaccines vary in their efficacy to impede the viral infections which are symptomatic.[20] On the other hand, the efficacy of the vaccine might be affected by increased rates of infection and discrepancies in producing long-lasting defensive immune responses by the affected individuals. Therefore, to appraise immunization protection as well as the need for precautionary doses, neutralizing IgM and IgG levels follow-up would be of maximum significance among vaccinated subjects.[21] The present study intended to appraise the dynamics regarding humoral immunity towards the vaccine of SARS-CoV-2 by estimating levels of IgM and IgG among vaccinated individuals with and without a history of SARS-CoV-2 infection.

## MATERIALS AND METHODS

### Study cohort and sample selection

This cross-sectional study was carried out between January 2022 to December 2022. The Ethical Review Committee (2923/IEC/2021) of SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu reviewed and accepted. This study comprises three hundred and twenty-seven candidates (n=327) study participants and all the candidates were asked to fill out an informed consent form. Also, a patient proforma containing a history of infections of SARS-CoV-2 and contact history, along with immunization date (administration date and vaccination types) were completed by the study participants.

### Sample processing

After obtaining consent, a skilled phlebotomist performed venipuncture under aseptic conditions to draw blood. The blood was subsequently centrifuged after clot formation to separate serum. The serum samples were then aliquoted and stored at -80°C until the tests were conducted.

### Assay principle

Employing chemiluminescent microparticle immunoassay (CMIA) technology, this automated, two-step immunoassay is crafted for the qualitative identification of IgG and IgM antibodies to SARS-CoV-2 in human serum. Paramagnetic microparticles coated with SARS-CoV-2 antigen, sample, and assay diluent are mixed and subjected to incubation. The SARS-CoV-2 antigen-coated microparticles bind with the IgG and IgM antibodies to SARS-CoV-2 found in the sample. After washing the mixture, anti-human IgG and IgM acridinium-labeled conjugates are introduced to form a reaction mixture, which is then incubated. Subsequently, Pre-Trigger and Trigger Solutions are added following another washing step.

The system optics detect the resulting chemiluminescent reaction as a relative light unit (RLU). A direct correlation exists between the quantity of IgG and IgM antibodies to SARS-CoV-2 in the sample and the RLU measured. The calculated Index (S/C) reflects this correlation. By comparing the chemiluminescent RLU in the reaction to the calibrator RLU, the presence or absence of IgG and IgM antibodies to SARS-CoV-2 in the sample is determined.[22]

### Calibration

Every assay control underwent testing to assess the calibration of the assay. Once calibration was deemed acceptable and stored, all subsequent samples could be tested without requiring further calibration unless a reagent kit bearing a new lot number was utilized.

### Antibody analysis

The medium value of 3 replicates from the chemiluminescence calibrator was calculated using ARCHITECT iSystem by saving the results. Division of sample (S) by the calibrator will give the results of the samples. IgM and IgG antibodies against the S1 subunit of S were measured using the Abbott kit which is commercially available. The results of IgG were reactive ≥ 50.0 AU/mL (arbitrary units by milliliter) and the results of IgM were reported as reactive when the index factor was ≥ 1.1 AU/mL.

## RESULTS

The majority of the candidates were middle-aged over 18-30 years and just a few

**Table 1.** Clinical characterization of the study participants (n=327)

| Variables | Total sample n (%) |
|---|---|
| Gender (n=327) | |
| Women | 226 (69.1%) |
| Men | 101 (30.9%) |
| Age in years (n=327) | 45 (35.0-58.0), med (IQR) |
| Age groups in years (n=327) | |
| 18–30 | 121 (37.0%) |
| 31–45 | 145 (44.3%) |
| 46-60 | 56 (17.1%) |
| 61-65 | 5 (1.6%) |
| SARS-CoV-2 infection (n=327) | |
| With infection | 93 (28.4%) |
| Without infection | 187 (57.2%) |
| Unknown | 47 (14.4%) |
| Vulnerable to positive SARS-CoV-2 cases (n=327) | |
| With exposure | 88 (26.9%) |
| Without exposure | 219 (66.9%) |
| Unknown | 20 (6.2%) |
| SARS-CoV-2 immunization (n=327) | |
| Vaccinated | 177 (54.1%) |
| Non-vaccinated | 150 (45.9%) |
| Type of SARS-CoV-2 immunization (n=177) | |
| ChAdOx1 nCoV-19 (Covishield™) | 145 (81.9%) |
| BBV-152 (Covaxin™) | 32 (18.1%) |

participants were under 65 years. Out of 327 study participants, 177 (54.1%) were administered their 2 doses of immunization for SARS-CoV-2 infections and 150 (45.9%) were non-immunized participants. Table 1 represents the clinical characterization of the study participants (n=327). In this cohort study, the predominant gender was reported as female (69.1%, n=226). Following the response from the patient proforma, 93 (28.4%) subjects were reported with past diagnosis upon SARS-CoV-2 infections, whereas reports of prior exposure to positive cases were found to be 88 (26.9%) (Table 1).

During the study, vaccinated individuals were resulted as 54.1% (n=177), while most of the study participants were immunized with ChAdOx1 nCoV-19 (Covishield™) (n=145, 81.9%) and 18.1% (n=32) were immunized with BBV-152 (Covaxin™). The vaccination interval for BBV-152 (Covaxin™) and ChAdOx1 nCoV-19 (Covishield™) is 84.5 days.

As compared to non-immunized candidates, the maximum incidence of specific IgG-positive individuals was reported among vaccinated candidates (97.1% vs 61.5%) and showed greater IgG median values (7220.6 vs 163.0 AU/ml) (Table 2). There was an increased rate of prior exposure to positive cases. Of the unvaccinated participants, we noticed that there was an increased incidence of past SARS-CoV-2 infections (29.3%, n=44) respectively. Assessing the history of immunized prior exposure to the positive case, it has been reported that there was a higher incidence of 31.6% (n=56) compared to 21.3% (n=32) for non-immunized study participants. There were insignificant differences observed among immunized as well as non-immunized study participants in considering median age, seropositivity of IgM, gender, IgM levels, and age categories (Table 2).

Every SARS-CoV-2 immunized individual who was infected prior was IgG positive during the study period, irrespective of age category, gender, elapsed time from vaccination, and type of vaccination. Insignificant lower positivity for IgG resulted among the vaccinated individuals without prior SARS-CoV-2 infection; however, it is not substantially varied from the previous one. Significantly, there was an increased seropositivity incidence and an increased IgG median value between women participants in equal comparison to male subjects. Furthermore, ChAdOx1 nCoV-19 (Covishield™) was noticed to develop substantially reduced seropositivity for IgG levels and lesser median values of IgG over BBV-152 (Covaxin™).

Of the vaccinated groups with or without prior infections of SARS-CoV-2, there was no considerable variation among IgG median values and IgG positivity, while considering vaccine age and gender. Increased median IgG values were demonstrated by the immunized study candidates above 65 years when infected previously with SARS-CoV-2 infections, although it is not significant statistically over other age categories.

**Table 2.** Clinical characterization based on the SARS-CoV-2 vaccination (n=327)

| Variables | SARS-CoV-2 vaccinated | |
|---|---|---|
| | Vaccinated | Non-vaccinated |
| Total sample (n=327) | 177 (54.1%) | 150 (45.9%) |
| Gender (n=327), n (%) | | |
| Female | 127 (71.8%) | 99 (66%) |
| Male | 50 (28.2%) | 51 (44%) |
| Age in years (n=327), med (IQR) | 42 (36.0-58.0) | 45 (34.0-56.6) |
| Age groups in years (n=327) | | |
| 18-30 | 70 (39.5%) | 51 (34%) |
| 31-45 | 75 (42.1%) | 70 (46.7%) |
| 46-60 | 30 (17.2%) | 26 (17.3%) |
| 61-65 | 2 (1.2%) | 3 (2%) |
| SARS-CoV-2 infection (n=327), n (%) | | |
| With infection | 49 (27.7%) | 44 (29.3%) |
| Without infection | 95 (53.6%) | 92 (61.3%) |
| Unknown | 33 (18.7%) | 14 (9.4%) |
| Vulnerability to positive SARS-CoV-2 case (n=327) | | |
| With exposure | 56 (31.6% ) | 32 (21.3%) |
| Without exposure | 101 (57%) | 118 (78.7%) |
| Unknown | 20 (11.4%) | 0 |
| IgM AU/mL (n=327), med (IQR) | 0.54 (0.20-1.26) | 0.50 (0.06-1.60) |
| IgG AU/mL (n=327), med (IQR) | 7220.6 (3094.0-14760.8) | 163.0 (6.5-637.2) |
| IgM positive with > 1.0 UA/mL (n=327) | | |
| IgM positive | 48 (27.5%) | 47 (31.7%) |
| IgM negative | 129 (72.5%) | 103 (68.3%) |
| IgG positive with ≥ 50 UA/mL (n=327) | | |
| IgG positive | 172 (97.1%) | 92 (61.5%) |
| IgG negative | 5 (2.9%) | 58 (38.5%) |

## DISCUSSION

The SARS-CoV-2 vaccines that are at hand are stated as extremely efficacious in preventing infections that are symptomatic and hospitalized in clinical testing. As a result of the quick emergence of novel variants of viruses, effectiveness has been likely to decrease in reality.[21] However, multiple study reports suggest that the production of protein-specific IgG is at higher rates regarding vaccination, while the fluctuation among IgG levels exists in various studies.[23-25]

In the current study, IgG and IgM antibody production was studied in opposition to SARS-CoV-2 spike protein S1 was produced subsequently after vaccination BBV-152 (Covaxin™) as well as (ChAdOx1 nCoV-19) (Covishield™). It was interpreted that there was a rise in the levels of antibodies among the vaccinated and non-vaccinated study candidates and also among those individuals who were presented and not presented with any prehistory of infection. Also, this research work annexes broadening publications in connection with the immune reactions regarding infections over immunization and promotes the necessity of booster shot administration.[26]

Following multiple study results, we noticed a gradual reduction in the values of IgG, even if seropositivity was observed among immunized individuals. Merely an insignificant proportion of negative IgG specific for SARS-CoV-2 immunized study candidates was found, that correlated with study candidates who are not having any past infections.[26-28]

However, various other studies suggest that vaccine-induced seroconversion rates have been reduced as well as are not present among immunosuppressant candidates comprising patients receiving immunosuppressive therapeutics, organ transplantations, and patients

with hematological cancers.[28-30] At the same time, in the present study, it is observed that there is an association between weaker seroconversion to lesser acceptance of the plan of immunization that has been established (administration of a single dose rather than two shots). Remarkably, it was noticed that non-vaccinated candidates who have not been diagnosed previously with infections have 30% of SARS-CoV-2-specific IgG seropositivity, which might result in consequences of former infections that were previously asymptomatic.[30]

This study's results demonstrate that the impacts of immunizations are increased upon the SARS-CoV-2 specific IgG antibodies development against other infections that are natural. We have not evaluated the state of T-cell immunity; our study focuses solely on humoral immune responses. However, the findings signify that immunization produces considerable importance in obtaining subsequent protection from infections and these results were similar to other study results.[30-32]

Interestingly, we found significantly higher levels of vaccine-induced IgG in females compared to males, even though the research participants were not previously exposed to SARS-CoV-2 infections. Our study reports and results by Zimmermann and Curtis were coherent, proposing that the humoral immunological responses upon vaccination were more prone to develop at higher rates, particularly among females.[32] Recent research on humoral reactions towards SARS CoV-2 immunization also exhibited increased levels of IgG response than IgM in women.[33] The decline in neutralizing antibodies and anti-S titers, as well as a rise in age due to illness and vaccination, have all been strongly correlated with a reduction in seroconversion. However, it wasn't established in the present study, despite the reduced levels of IgG that was noticed among earlier immunized non-infected individuals has become a trend over the age as reported by Omran et al., in their study.[34]

The present report of the study was found to correlate with the results reported by Wei *et al*. From this report, it has been noticed that there was no significant variance among seroconversion over age categories following the administration of 2 doses of BBV-152 (Covaxin™) and ChAdOx1 nCoV-19 (Covishield™).[35] On the contrary, from the results of the study conducted by Khoury DS et al., we have seen that there was a rise in the IgG levels in the age categories of subjects with 65 years, regarding the immunized candidate having the earlier SARS-CoV-2 infection history.[36] One possible interpretation is that the infection in this category has had varying effects on the immune system, which is in line with a number of previous studies on the immune system's response to infections that occur naturally.[37]

From the earlier investigations, the efficaciousness of the ChAdOx1 nCoV-19 (Covishield™) vaccine was determined to be lower than the other vaccines that are mRNA-based. Likewise, the current work also demonstrates reduced humoral reactions (IgG levels and seropositivity) which are protective following the administration of ChAdOx1 nCoV-19 (Covishield™) against BBV-152 (Covaxin™). Such outcomes reveal a greater performance of mRNA-based vaccines versus viral-vectored vaccines.[38,39]

Although our research has manifested an effective IgG response for SARS-CoV-2 immunization, as a whole, the titres of antibodies attain half the original value following 2.5 months (reduction of nearly 20% every month on average), validating another report. It was discovered that the immunized study candidates who were diagnosed earlier with SARS-CoV-2 demonstrate a less IgG antibody rates, even if they are significant statistically over earlier non-infected cases.

## CONCLUSION

Amidst the pandemic on COVID-19, an unparalleled universal contribution to the development of vaccination drags significant anticipation in preventing infections that are symptomatic and cause hospital admissions. Despite all these attempts, as we all know, the efficiency of these vaccines has been especially imperiled by the rapid appearance of novel variants of SARS-CoV-2 viruses. From this present investigation, we reported that following the vaccination, there is an increased level of IgG antibody over 1-2 weeks and it has attained peak in 4-6 weeks. Subsequently, the ranges progressively declined even though the maximum number of study candidates continued to show seropositivity during the study time. Moreover, the females were reported to show remarkably greater levels

of IgG which are vaccine induced as compared to males. In contrast to other age groups, immunized candidates who are above 65 years revealed a trend regarding higher values of IgG if infected earlier, yet there were comparably reduced IgG median values in its absence. Moreover, the efficaciousness of the ChAdOx1 nCoV-19 (Covishield™) vaccine was determined to be higher than the other vaccines and these reports demonstrate a greater performance of mRNA-based vaccines versus viral-vectored vaccines. In conclusion, the study results imply a powerful vaccination effect upon the specific IgG antibodies of SARS-CoV-2 against natural infection. However, there is a rapid decline in the titers of antibodies analogous to a reduction of 20% approximately every month. Our research is hence coherent with prospective requirements for booster shots to assist in controlling the rate of infections and fatality rates together in the course of the current pandemic.

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None.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

None.

## DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

## ETHICS STATEMENT

The study was approved by the Institutional Ethical Committee of SRM Medical College Hospital and Research Centre, Chengalpattu, India, with reference number 2923/IEC/2021.

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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