COVID-19 Vaccines Portray the Bright Side of Human Creativity, But It Means Nothing until They Prove Their Worth: A Study on Seroconversion after the first Dose of Covishield Vaccine in Central Kerala

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Abstract

Background: COVID-19 vaccines, we believe, have come to rescue us from the clutches of the dreaded severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With rapid ongoing mutations, it is difficult to predict the effectiveness of seroconversion following vaccination. This study aims to find out the proportion of people with seroconversion following first dose of Covishield vaccine. Methods: Randomly selected health-care workers were followed up for SARS-CoV-2 immunoglobulin G (IgG) antibodies between 28 and 42 days after receiving their first vaccine dose. The VITROS SARS-CoV-2 IgG test (Ortho-Clinical Diagnostics, USA) with 100% specificity and >90% sensitivity was used to assess seroconversion. Results: The first dose of vaccine induced seroconversion in 91.7% of beneficiaries. Nearly one-third (30.2%) of them had high antibody titers, and it showed a significant association with female gender (9.6 ± 5.5 vs. 7.6 ± 5.6) and younger age (P = 0.008). In addition, those with previous COVID infection showed a more robust immune response when compared to others (P = 0.001). Conclusion: Seroconversion rate of more than 90% offers a promising hope toward successful pandemic control. In the current scenario, the inability to attain the targeted coverage due to an upsurge in vaccine hesitancy, compounded with only lower proportion of seroconversion in elderly, faster rollout of the vaccines without any age limit, will help achieve the herd threshold more rapidly.

Keywords: Covishield vaccine, first dose, Oxford–AstraZeneca vaccine, seroconversion

Introduction

COVID-19 pandemic caused the world to be at a standstill for the past 1 year. Many countries were feverishly trying to contain the pandemic, and at the end of a troublesome year, amid all uncertainties, finally vaccines, we believe, have come to our rescue. Heavy investment in the field of vaccine development has come out with some promising results. However, every disease is an immunological problem in itself, and COVID-19 is no different. Moreover, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) being an RNA virus with a generally high mutation rate, the challenge to produce effective vaccines is even greater. It is difficult to predict what kind of vaccine can be truly effective.

Vaccine efficacy is the percentage reduction in disease incidence attributable to vaccination.[1] Vaccine efficacy is dependent on individual factors such as the immunologic competence of the vaccine recipient, dose, and strain of the vaccine virus. If an immunological correlate of protection is known, then the protective efficacy of a vaccine can be assessed by measuring the proportion of vaccinees who generate a particular immune response such as neutralizing antibody titers without having to measure clinical outcomes. Antibody titers against spike (S) proteins are suitable biomarkers for

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assessing the protective efficacy after vaccination.[2] We do not yet know the antibody titer that would be needed for protection, and sufficient evidence regarding seroconversion lacks in our population.[3] Herd immunity also plays its role in contributing to vaccine efficacy. It occurs when most of a population becomes immune to a disease, breaking the chain of transmission from one person to another, preventing or slowing down the spread of the disease.

With apprehensions, people with chronic diseases may not seroconvert effectively and the crude prevalence of diabetes in India is 7.5%, and hypertension is 25.3%.[4] It is important to understand whether factors, such as immunosenescence associated with increasing age, weight, smoking, exercises, alcoholism, hypertension, or diabetes, might influence immune responses after vaccination.

It is also a common belief that systemic symptoms after vaccination (reactogenicity) are predictive signs of a desirable vaccine response (immunogenicity), favoring the “no pain, no gain” concept.[5] However, data supporting or refuting this concept are limited. Antipyretic analgesics are widely used to ameliorate vaccine adverse reactions, but their use has been associated with blunting of immune responses.[6] Consequently, the WHO advised against the administration of prophylactic oral analgesics during vaccination.[7] This study along with assessing seroconversion following the first dose of Covishield vaccine also assessed whether paracetamol intake after vaccination affected seroconversion.

Affirmations are our mental vitamins. We must be ready to counter the barrage of negative events we face daily with facts and evidence. Otherwise, we may have to pay the price – a costly price which may be a massive setback to the nationwide COVID-19 vaccination drive. Hence, this study was undertaken to assess the seroconversion rate following vaccination and thereby establish their worth during the pandemic.

**Methods**

The study was conducted in a tertiary care center in Central Kerala after obtaining clearance from the institutional ethics committee (IEC 2021/04/203). The study participants were health-care workers who were randomly selected by the district authorities from the entire list of hospital staff handed over to them by the HR department of the hospital, during the first 3 days of the first phase of the COVID-19 vaccination drive. The beneficiaries were contacted between the 29th day and the 42nd day of receiving their first dose but before their second dose. Antibody test was performed using the VITROS® anti-SARS-CoV-2 immunoglobulin G (IgG) (Ortho-Clinical Diagnostics, Rochester, NY, USA), a highly accurate test for the detection of serum IgG antibodies to SARS-CoV-2, having a sensitivity of >90% and specificity of 100%.[8] The test is approved for use under the Food and Drug Administration’s Emergency Use Authorization.

Interpretation of results is as follows: a signal-to-cutoff ratio ≥1 indicates a positive result indicating seroconversion. A value <1 is negative for seroconversion. Antibody titer 12 or greater qualifies as a high titer for anti-SARS-CoV-2 antibodies.[9] Persons with a positive IgG antibody test prior to vaccinations and those who were pregnant, lactating, on immunosuppressants, and who contracted COVID after the first dose were excluded. Prevaccination antibody status was tested by an immunochromatographic card test (Sensit Rapid COVID-19 IgG/IgM, UBIO Biotech, Cochin). Those with prior COVID infection were excluded from primary analysis to assess seroconversion solely due to vaccination but were included in the study to evaluate the impact of COVID on seroconversion following vaccination.

Assuming the seroconversion rate to be at least 50%, the required sample size was 100, but we decided to include all beneficiaries of the first 3 days of the vaccination drive who were willing to participate to ensure adequate sample size for subgroup analysis also.

Statistical analysis was done on SPSS v. 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Chi-square was used to test for associations. Mean antibody titers across different age groups were compared using ANOVA and t-test.

**Results**

The study was conducted on 240 vaccine recipients. Of them, 23 had previous documented COVID-19 infection. Therefore, seroconversion solely due to the first dose of Covishield vaccine was studied in 217 beneficiaries.

Majority of the study participants belonged to the age group of 30–50 years (64.1%) and were female (59.4%). The first dose of vaccine induced reactogenicity (fever and body pain) in 82.9% of the participants. However, only 34.6% reported using paracetamol for symptom relief [Table 1].

**Seroconversion after vaccination**

The first dose of Covishield vaccine induced seroconversion in (199/217) 91.7% (confidence interval [CI] – 88.04%–95.37%) of the recipients. Of them, nearly one-third (66/217) (30.4%) (CI – 24.37%–37%) had a high antibody titer (>12).

**Factors influencing seroconversion**

Seroconversion was found to have a significant association with gender. Among those with a high titer value, females outnumbered males (P = 0.008). The mean antibody titer in females (9.6 ± 5.5) was significantly higher compared to males (7.6 ± 5.6) [Table 2].

The proportion of people with postvaccination symptoms decreased as age advanced. The mean antibody titers also showed a declining trend with increasing age. This association was found to be statistically significant (ANOVA F = 4.022, P = 0.008) [Figure 1]. The mean antibody titer in people above
Factors such as the presence of comorbidities, medications for chronic diseases, perceived stress, exercise (≥3 times/week), poor sleep (sleep <6 h), alcohol consumption, or paracetamol intake were not found to have a significant effect on antibody titers.

Previous COVID infection induced better seroconversion with a high mean antibody titer (18.29 ± 5.8) compared to those without prior COVID infection (8.80 ± 5.6, \( P = 0.001 \)).

**DISCUSSION**

No vaccine is 100% effective. A small percentage of people are not protected even after vaccination, and, for others, the protection may wane over time. However, the first dose of the Covishield vaccine inducing seroconversion in more than 90% of the recipients has come as a good hope, precisely in line with the findings of the Phase ½ trial by Folegatti et al.\(^\text{[10]}\) and Logunov et al.\(^\text{[11]}\) The variation is possibly due to the difference in the validity of the assays used. However, there has been no information on the cutoff of antibody titer to date, which can confidently offer protection against COVID-19. Furthermore, the association of protection cannot be attributed to neutralizing antibodies alone, as other forms of immunity such as T-cell immunity and nonneutralizing antibody may contribute to protection.

We expect to bring about herd immunity through vaccination. Most estimates had placed the threshold at 60%–70% of the population, gaining immunity either through vaccination or previous infection.\(^\text{[12]}\) The demographic structure of India reveals that 24% of the Indian population is below 18 years of age\(^\text{[13]}\) and so far, vaccine has not been administered for this age group. This implies that the rest of the entire population should be covered for achieving the herd threshold. It is generally achievable only with high vaccination rates. During the interim period, COVID control precautions should be in place with universal masking and social distancing – not allowing the pandemic to explore its full potential. However, the current situation is looking a little grim with an upsurge in vaccine hesitancy and emergence of new variants.

We see that seroconversion and mean antibody titer values decrease as age advances, which could be a little worrisome when we are aiming to rapidly enhance herd immunity. It is particularly noteworthy that giving the elderly preference was a good gesture, but unfortunately, they may not be able to achieve expected levels of seroconversion when compared to younger people. Hence, for rapidly enhancing herd immunity, especially in the midst of vaccine hesitancy, vaccine delivery without imposing age limits could have been a better option.

Moreover, the elderly are mostly confined to homes while the younger people are more mobile, contributing to the spread of COVID-19 in a major way. However, we do expect higher seroconversion after two doses of vaccine.

To our relief, seroconversion is not affected by the presence of comorbidities – hypertension and diabetes, medications for chronic illnesses, nor by factors such as alcoholism,
sleep disturbances, exercise, and stress. With a high burden of people with hypertension and diabetes in India, it would have been quite worrisome if seroconversion was affected by these factors.

Covishield has induced a robust immune response in people who were seropositive at baseline. This finding supports the theory that those who were seropositive at baseline respond faster and reach higher antibody levels compared to those without previous COVID infection.\cite{14} However, after the course of natural COVID infection, there is rapid waning of antibody titers due to apoptosis of the initial pool of antigen-specific B-cells, followed by slow waning of antibody titers thereafter, with the antibody levels being maintained by antigen-specific long-lived plasma cells in the bone marrow.\cite{15} Hence, even if antibody titers after vaccination may drop as time passes, there is hope as we may be able to expect a similar immunological memory after vaccination.

Investigating the effect of paracetamol intake on seroconversion would provide insight into the potential impact on public health. The first dose of Covishield vaccine induced side effects such as fever, fatigue, and headache in a majority of its recipients (82.9%). This led to paracetamol consumption in more than 30% of the recipients. Although febrile reactions would reduce significantly, routine administration of antipyretics at the time of vaccination is not recommended as studies showed that paracetamol could reduce antibody responses to several vaccine antigens.\cite{6} However, the present study did not find any significant association between paracetamol consumption and low antibody titer.

Vaccine hesitancy is on the rise with governments unable to reach the intended vaccination coverage, and the problem is compounded by the emergence of mutant strains exhibiting immune escape. Although the vaccine is new and we do not have data on how long its protection might last and its effect on mutant strains of the virus, there is a glimmer of hope with the possibility that memory B- and T-cells may wake up to mount an immune response which prevents serious/severe illnesses and death among those vaccinated.\cite{16}

**Conclusion**

Covishield vaccine has induced seroconversion in more than 90% of beneficiaries after the first dose, offering promising hope toward successful control of the COVID-19 pandemic, and has proved their worth. This is expected to be even higher after the second dose, but we would have to wait until more evidence is gathered. In the current scenario, where

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**Table 2: Factors associated with postvaccination antibody titer**

| Factors                        | Antibody titer after the first dose of Covishield vaccine | Total | P (Chi-square test) |
|--------------------------------|----------------------------------------------------------|-------|---------------------|
|                                | High titer ($n=66$), $n$ (%)                              | Low titer ($n=151$), $n$ (%) |       |
| Gender ($n=217$)               |                                                          |       |                     |
| Male                           | 18 (20.5)                                                | 70 (79.5) | 88 | 0.008 |
| Female                        | 48 (37.2)                                                | 81 (62.8) | 129 |       |
| Age (years) ($n=217$)          |                                                          |       |                     |
| $\geq50$                       | 5 (13.9)                                                 | 31 (86.1) | 36 | 0.018 |
| $<50$                         | 61 (33.7)                                                | 120 (66.3) | 181 |       |
| Postvaccination symptoms ($n=217$) |                                                          |       |                     |
| Present                       | 60 (33.3)                                                | 120 (66.7) | 180 | 0.039 |
| Absent                        | 6 (16.2)                                                 | 31 (83.8) | 37 |       |
| Comorbidities ($n=217$)        |                                                          |       |                     |
| Present                       | 10 (22.7)                                                | 34 (77.3) | 44 | 0.214 |
| Absent                        | 56 (32.4)                                                | 117 (67.6) | 173 |       |
| Regular exercise ($n=217$)     |                                                          |       |                     |
| Yes                           | 35 (34.7)                                                | 66 (65.3) | 101 | 0.205 |
| No                            | 31 (26.7)                                                | 85 (73.3) | 116 |       |
| Stress ($n=217$)               |                                                          |       |                     |
| Yes                           | 24 (32.9)                                                | 49 (67.1) | 73 | 0.575 |
| No                            | 42 (29.2)                                                | 102 (70.8) | 144 |       |
| Short sleep duration (<6 h) ($n=217$) |                                                          |       |                     |
| Yes                           | 13 (24.5)                                                | 40 (75.5) | 53 | 0.284 |
| No                            | 53 (32.3)                                                | 111 (67.7) | 164 |       |
| Usage of paracetamol for postvaccination symptom relief ($n=217$) |                                                          |       |                     |
| Yes                           | 28 (37.3)                                                | 47 (62.7) | 75 | 0.107 |
| No                            | 38 (26.8)                                                | 104 (73.2) | 142 |       |
| Previous COVID infection ($n=240$) |                                                          |       |                     |
| Present                       | 19 (82.6)                                                | 4 (17.4) | 23 | 0.001 |
| Absent                        | 66 (30.4)                                                | 151 (69.6) | 217 |       |
we cannot attain the targeted coverage due to an upsurge in vaccine hesitancy, compounded with weak seroconversion in the elderly, faster rollout of the vaccines without any age limit and supply constraints could help in breaking the chain of transmission.

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Conflicts of interest
There are no conflicts of interest.

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