Original Article

Antibody titres in fully vaccinated healthcare workers with and without breakthrough infection during the Delta and Omicron waves

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Abstract

Introduction: Assessment of antibody response to vaccination against SARS CoV2 has clinical, public health, and policy implications during the pandemic and in the context of future waves. **Method:** In this repeated cross-sectional study, we estimated total binding antibody levels to the spike protein of the SARS CoV2 virus post two doses of Covishield vaccine among 133 health care workers (HCWs) (phase 1), followed by antibody levels among a subset ($n = 61$) of this group at 9 months after the second dose (phase 2). The time period of the first and second blood collection corresponds to Delta and Omicron waves, respectively. **Results:** We report 100% seroconversion post 28 days of the second dose of the Covishield vaccine among infection naïve HCWs. In this study, 33% had a breakthrough infection in phase 1 and 24% reported a history of infection in phase 2. The antibody titres were higher in the breakthrough infection group compared to the infection naïve group during both Delta and Omicron waves. **Conclusion:** This shows that there is a good seroconversion with two doses of vaccine, weaning of antibody with time, and a rise of antibody titre if infected with SARS CoV 2 subsequently.

Keywords: Breakthrough infection, delta wave, health care workers (HCWs), omicron wave, post-vaccination antibody titre, SARS COV2

Introduction

Vaccination against SARS CoV2 is one of the most powerful public health tools against SARS CoV2 pandemic. In India, health care workers (HCWs) were the first to receive a vaccine against SARS (AstraZeneca, ChAdOx1 nCoV- 19 Corona Virus recombinant Vaccine under the tradename Covishield) in January 2021, followed by vaccination for the general population from age 18 to 45 years (May 2021).[1] A severe wave of the pandemic with Delta variant of SARS CoV2 (B.1.617.2) happened during April and May 2021, at a time period, where most HCW were vaccinated with two doses of vaccine and the first dose of vaccination for general population was going on.[2] It is estimated that the Delta variant escaped immunity in 34.6% of individuals with prior wildtype infection and caused breakthrough infections after vaccination.[3] Prior vaccination reduced the severity of illness and mortality during the Delta wave among symptomatic

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COVID-19 patients, and full vaccination conferred greater protection than partial vaccination.[4]

The next pandemic wave occurred with Omicron variant of SARS COV2 (B.1.1.529), which was classified as a variant of concern by the WHO technical advisory committee on November 26, 2022. At this time, at least 50% of the eligible population in India had received one or two doses of a vaccine and 30.6% were fully vaccinated.[5]

In India, the Omicron variant was reported to be in community transmission by January 2022 and had become dominant in multiple metros, according to the Indian SARS-CoV-2 Genomics Consortium. The first two Omicron cases in India were reported from Bengaluru on December 2, 2021. By January 9, with 333 cases, Bengaluru was reported to account for 92% of Karnataka's Omicron cases.[6] This wave was milder with fewer hospitalizations, which is attributed to the low pathogenicity of the variant and the wider vaccination coverage.

Massive disruption, sheer velocity of pandemic waves, novel pathogen with novel vaccine, urgency of testing, treatment, and vaccination – all posed a significant challenge to health systems the world over. There was limited information regarding antibody response to the vaccine against SARS CoV2, though this knowledge is of critical importance because of the possibility of the emergence of new variants of the same pathogen and the advent of novel respiratory pathogens. Hence, this study was intended to address this gap.

The research questions we explored were – (i) does everybody getting two doses of vaccine to mount an antibody response, (ii) will there be a chance of breakthrough infection if vaccinated with two doses? and (iii) will the antibody rise if challenged later with exposure to another variant of virus? These questions are of critical importance which gives insights about antibody response to the vaccine and subsequent virus exposures. This will contribute to the scientific knowledge and will have clinical, public health, and policy implications in future pandemics.

In this cross-sectional study, we estimated total binding antibody levels to the spike protein of the SARS CoV2 virus after two doses of Covishield vaccine among HCW. We also estimated antibody levels among a subset of this group of HCW at the beginning of the Omicron wave about 9 months after the second dose.

Methodology

We did a cross-sectional study among HCW in a tertiary care hospital in Bangalore in two phases, phase 1 from March to June 2021 (Delta wave time period) and phase 2 from December 2021 to March 2022 (Omicron wave time period).

In phase 1, HCW vaccinated with two doses of Covishield vaccine under the existing guideline (4 weeks interval between doses) with no reported SARS CoV 2 infection before the second dose of vaccination were eligible to participate in the study. The blood samples were collected after 30 days and within 100 days of the second dose of vaccine. Among those who consented for the study, demography, vaccination details, and history of breakthrough infection were collected. Breakthrough infection was defined as a history of COVID19 infection in an individual who is vaccinated with either a primary series or a primary series plus a booster dose as per the CDC guidelines.[7]

In phase 2, invitations to participate in phase 2 were sent out to those who participated in phase 1 study. History of SARS-CoV-2 infection was recorded, and the blood sample was collected from those who were willing to participate in this phase.

In both phases, four milliliter of blood was collected, and the serum separated and tested using the Elecsys Anti-SARS CoV 2 S assay (Roche Diagnostics), measuring predominantly anti-SARS CoV2 IgG, as well as IgA and IgM using a recombinant protein representing the receptor-binding domain of the S1 subunit of the spike antigen.[8]

The measurement range of the assay is from 0.40 to 250 U/mL, and dilutions up to 1 in 50 were done. According to the manufacturer's recommendations, levels of <0.80 and ≥0.80 U/mL were considered negative and positive. The assay is reported to have its highest sensitivity of 84.0%% (95% CI: 73.8–94.2) and specificity of 100% at 15 to 30 days post testing positive by polymerase chain reaction (PCR) positivity.[9]

The data was analyzed using Statistical Package for Social Sciences version 20. In both phases, the prevalence of breakthrough infection was calculated. Antibody titres of infected and noninfected groups were reported as mean with SD and percentage and interquartile range (IQR). For statistical calculations, titre values of >12,500 U/mL were considered as 12,501 U/mL.

The study was approved by the Ethics Committee of Bangalore Baptist Hospital on the following dates: BBH/IRB/2020/007 dated 28/08/2020 and BBH/IRB/2021/42 dated 19/04/2021.

Results

In Phase 1, 133 HCWs participated in the study. More than half of them (58.6%) were females and the mean age was 39.6 ± 8.8 years among women and 40.7 ± 10.3 years among men. The median time between vaccination doses was 37 days, ranging between 25 and 69 days. Almost half (49.6%) of blood samples were between 81 and 93 days post second dose. All the participants tested positive for antibodies (100% seroconversion).

About one-third of the participants, 43 (32.3%), had a breakthrough COVID19 infection confirmed by RT-PCR and/or Immunochromatography. Among those who had a breakthrough infection, the blood sample was collected within a week of infection (early sampling group) in 69.8% (30) of HCW. In the

remaining 13 people, the blood sample was obtained after two weeks (late sampling group) of breakthrough infection due to the prevailing quarantine rules.

Antibody titres were less than 100 U/mL in 22% of HCW among the noninfected group. The mean antibody titre was lesser (373 U/mL, IQR 471) in the noninfected group than in the breakthrough infection group (5857 U/mL, IQR 11737) [Table 1]. Among those with breakthrough infection, all except one with breakthrough infection had antibody levels above 100 U/mL, and most (81.3%) had titre more than 500 U/mL.

The mean antibody titre was higher in the late sampling group as compared to the early sampling group (3844 IU/ml vs 10501 IU/ml) [Figure 1]. Among the early sampling group, 66.6% had antibody titres less than 5000 U/mL, whereas 100% of the late sampling group had antibody titres above 5000 U/mL.

In Phase 2, 61 (45.9%) HCWs participated in the study. Among them, 15 (24.5%) had a breakthrough infection. The median antibody titres were higher (4682 U/ml vs 886.8 U/ml) among those who had a breakthrough infection as compared to those who did not have breakthrough infection [Table 2]. All among the breakthrough infection group had values above 100 U/mL; the lowest value is 637 U/mL.

When the antibody titre was compared between phase 1 and phase 2, the median antibody titre at 9 months was lower in phase 2 than phase 1 (89.4 vs 245.9) in the absence of breakthrough infection. Median antibody titre was higher among the breakthrough infection group in both phase 1 and phase 2 as compared to the nonbreakthrough infection group [Figure 2].

Discussion

The study reports 100 per cent seroconversion among HCW post 28 days of the second dose of Covishield vaccine. Many studies report a high rate of seroconversion after two doses of Covishield vaccination.[10-15] Our results were similar to what was reported in phase 3 clinical trial of Covishield vaccine.[12]

In our study, 33% had a breakthrough infection in phase 1 and 24% reported a history of infection in phase 2. The prevalence of breakthrough infection varied from 5 to 23.5% in various studies during the delta wave.[16-20] The proportion of breakthrough infection varied based on the time of the wave in the particular place, time period of recruitment (early, during or after wave), and exposure of the HCW to COVID 19 wards. Omicron variant was more infectious than delta, and studies have reported a breakthrough infection rate of 71–83%.[21-23] The proportion of breakthrough infection is much less (24%) because our sample collection corresponded to the early phase of the Omicron wave.

The mean antibody titres among the breakthrough infection group were higher than the nonbreakthrough infection group in both phase 1 and phase 2. An increase in antibody titre following a viral challenge after vaccination is reported, and this is an expected response of the immune system.[24] The same is seen 9–10 months after the second dose as well in phase

Table 1: Phase 1 (March to June 2021) binding S - antibody levels (total samples=133) among HCW with and without breakthrough infection

Parameter	Breakthrough infection absent (U/mL)	Breakthrough infection present (U/mL)
No of samples	90	43
Prevalence	67.7%	32.3%
Mean (SD)	373.12 (345.24)	5857.21 (5100.87)
Median (IQR)	245.85 (471.42)	5529. (11737.2)

Table 2: Phase 2 (January 2022) binding S - antibody levels (total samples=61) among HCW with and without breakthrough infection

Parameter	Breakthrough infection absent U/mL	Breakthrough infection present U/mL
No of samples	46 (75.4%)	15 (24.6%)
Mean (SD)	886.8 (2664.2)	6473.7 (5243.7)
Median (IQR)	89.43 (130)	4682 (11523)

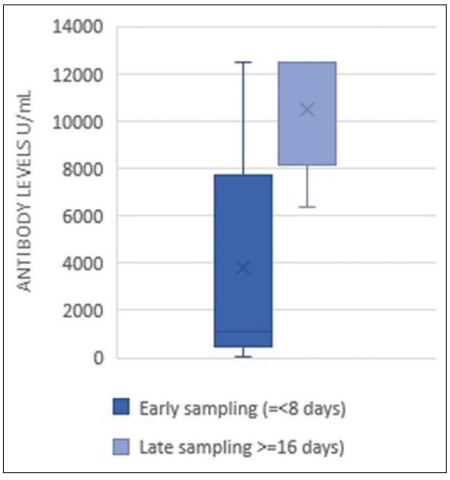

Figure 1: Comparison of antibody titres among HCW with breakthrough infection based on the time period of sample collection during phase 1 of the study (*n* = 43)

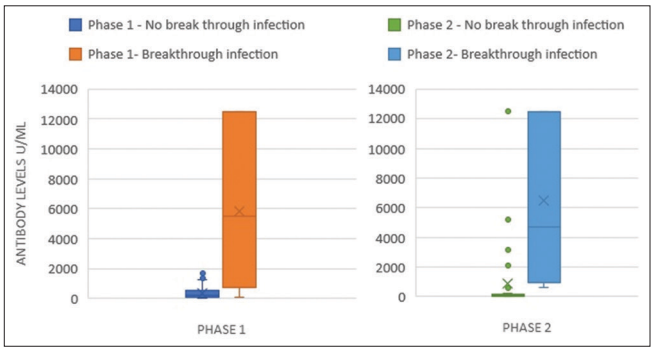

Figure 2: Comparison of median antibody level over phase 1 and phase 2 among HCW with and without breakthrough infection

2, when the predominant variant was Omicron, showing that the binding antibody has risen to the viral challenge. This is in keeping with results from studies which showed boosting of humoral immunity after breakthrough infection, even if it was predominantly a mild disease.[25,26] Other studies have shown neutralizing antibody titres as predictors of protection, and some have suggested the monitoring of binding antibodies as well to assess the level of protection.[27-29]

This study is a repeated cross-sectional study of antibody levels of HCW following two doses of vaccination during Delta and Omicron wave in India. This study answers few critical questions. Firstly, the study reports seroconversion in all HCW post two doses of vaccination in this small sample. There is a chance of breakthrough infection post vaccination, based on the exposure and the infectivity of the virus lineage. The study reports that antibody titre decays over time in the absence of viral exposure. However, we only measured binding antibody response, though neutralizing antibodies and T cell response are a critical part of immune response to SARS COV 2 vaccines. Recent studies have shown that there is a modest correlation between binding antibodies and, hence, would not have affected the conclusion.[30,31] Another limitation is that we did not ask the history of reinfection. Lastly, we did not establish the antibody values after a maximum of 12,500 U/mL due to cost implications.

The breakthrough infections reported are based on testing when symptomatic, but this might have introduced a proportion of misclassification bias in the context of the asymptomatic profile of the disease. However, we have addressed it statistically by removing the outliers in Phase 1 among the noninfected group. We do not know the actual strain which caused the infection in these HCW as we did not do genome sequencing, but we have considered that they may have been infected by the dominant strain at the time.

Antibody response to COVID-19 vaccine is an essential knowledge domain with significant knowledge gaps to be filled even now.[32] This study contributes to building evidence regarding binding antibody response to vaccination post second dose within 28–100 days and after 9 months among noninfected and breakthrough infection groups.

Conclusion

We report 100% seroconversion post 28 days of the second dose of the Covishield vaccine among infection naïve HCWs with an interval of 4 weeks between the first and second doses. The antibody titres were higher in the breakthrough infection group compared to the infection naïve group during both Delta and Omicron wave.

The information on the possibility of breakthrough infections and subsequent rise of antibody levels during viral challenge post vaccination is of both clinical and public health importance, especially in the context of novel mutations leading to new variants of concern and related respiratory pandemics in future.

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Authors' contributions

Sindhulina Chandrasingh contributed to the conception and design of work, data acquisition, supervision, and validation of the blood analysis, and participated in analysis and interpretation, contributed to the writing of the article. Carolin Elizabeth George contributed to the conception, study design, developed the study tool, supervised data collection, participated in analysis and interpretation, and contributed to the writing of the article. Tatarao Maddipati participated in developing the study tool and statistical analysis. Leeberk Raja Inbaraj contributed to the conception, statistical analysis, interpretation of the data, and contributed to the writing of the manuscript. All authors revised the work for important intellectual content and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ministry of Health and Family Welfare, Govt of India. COVID-19 vaccination. Frequently asked questions 2021[homepage on the Interne]. [Last accessed on 2022 Sep 08]. Available from: https://www.mohfw.gov.in/covid_vaccination/vaccination/faqs.html#who-will-get-the-vaccine.
2. Singh UB, Rophina M, Chaudhry R, Senthivel V, Bala K, Bhoyar RC, *et al.* Variants of concern responsible for SARS-CoV-2 vaccine breakthrough infections from India. J Med Virol 2022;94:1696-700.
3. Yang W, Shaman J. COVID-19 pandemic dynamics in India, the SARS-CoV-2 Delta variant and implications for vaccination. J R Soc Interface 2022;19:20210900. doi: 10.1098/rsif. 2021.0900.
4. Abhilash KPP, Mathiyalagan P, Krishnaraj VRK, Selvan S, Kanagarajan R, Reddy NP, *et al.* Impact of prior vaccination with CovishieldTM and Covaxin® on mortality among symptomatic COVID-19 patients during the second wave of the pandemic in South India during April and May 2021: A cohort study. Vaccine 2022;40:2107-13.
5. COVID-19 Data Explorer. One world in Data. Available from: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true and time=2020-03-01. [Last accessed on 2022 Sep 08].
6. Bengaluru accounts for 92% of Karnataka's Omicron cases. Times of India. Available from: http://timesofindia.

indiatimes.com/articleshow/88784513.cms?utm_source=content of interest and utm_medium=text and utm_campaign=cppst. [Last accessed on 2022 Sep 08].

7. COVID-19 after Vaccination: Possible Breakthrough Infection. [Updated on 2022 Jun 23]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html. [Lastaccessed on 2022 Sep 08].
8. Elecsys® Anti-SARS-CoV-2 Immunoassay for the qualitative detection of antibodies against SARS-CoV-2. 2020. Available from: https://diagnostics.roche.com/in/en_gb/products/params/elecsys-anti-sars-cov-2.html. [Last accessed on 2022 Sep 08].
9. Higgins V, Fabros A, Kulasingam V. Quantitative measurement of Anti-SARS-CoV-2 antibodies: Analytical and clinical evaluation. J Clin Microbiol 2021;59:e03149-20.
10. Mishra SK, Pradhan SK, Pati S, Panda BK, Bhattacharya D, Sahu SK, *et al*. Anti-SARS-CoV-2 antibodies among vaccinated healthcare workers: Repeated cross-sectional study. J Family Med Prim Care 2022;11:1883-9.
11. Varghese SM, Mateethra GC, George G, Chandran VS, John GM, Varghese LT, *et al*. A study on seroconversion following First and second doses of ChAdOx1 nCoV-19 vaccine in Central Kerala. Indian J Med Res 2022. doi: 10.4103/ijmr.ijmr_1917_21.
12. Kulkarni PS, Padmapriyadarsini C, Vekemans J, Bavdekar A, Gupta M, Kulkarni P, *et al*. A phase 2/3, participant-blind, observer-blind, randomised, controlled study to assess the safety and immunogenicity of SII-ChAdOx1 nCoV-19 (COVID-19 vaccine) in adults in India. EClinicalMedicine 2021;42:101218. doi: 10.1016/j.eclinm.2021.101218.
13. Tsundue T, Namdon T, Tsewang T, Topgyal S, Dolma T, Lhadon D, *et al*. First and second doses of Covishield vaccine provided high level of protection against SARS-CoV-2 infection in highly transmissible settings: Results from a prospective cohort of participants residing in congregate facilities in India. BMJ Glob Health 2022;7:e008271. doi: 10.1136/bmjgh-2021-008271.
14. Devi LS, Sardar M, Sharma M, Khandait M. Impact of ChAdOx1 nCoV-19 (Covishield™) vaccination: How long will it persist? Int J Microbiol 2022;2022:4729844. doi: 10.1155/2022/4729844.
15. Bhuiyan TR, Akhtar M, Khaton F, Rahman SIA, Ferdous J, Alamgir ASM, *et al*. Covishield vaccine induces robust immune responses in Bangladeshi adults. IJID Reg 2022;3:211-7.
16. Tyagi K, Ghosh A, Nair D, Dutta K, Singh Bhandari P, Ahmed Ansari I, *et al*. Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India. Diabetes Metab Syndr 2021;15:1007-8.
17. Thangaraj JWV, Yadav P, Kumar CG, Shete A, Nyayanit DA, Rani DS, *et al*. Predominance of delta variant among the COVID-19 vaccinated and unvaccinated individuals, India, May 2021. J Infect 2021;504:9-11.
18. Vaishya R, Sibal A, Malani A, Prasad K. SARS-CoV-2 infection after COVID-19 immunization in healthcare workers: A retrospective, pilot study. Indian J Med Res 2021;153:550-4.
19. Krishna B, Gupta A, Meena K, Gaba A, Krishna S, Jyoti R, *et al*. Prevalence, severity, and risk factor of breakthrough infection after vaccination with either the Covaxin or the Covishield among healthcare workers: A nationwide cross-sectional study. J Anaesthesiol Clin Pharmacol 2022;38(Suppl 1):S66-78.
20. Victor PJ, Mathews KP, Paul H, Mammen JJ, Murugesan M. Protective effect of COVID-19 vaccine among health care workers during the second wave of the pandemic in India. Mayo Clin Proc 2021;96:2493-4.
21. Khan K, Karim F, Cele S, San JE, Lustig G, Tegally H, *et al*. Omicron infection of vaccinated individuals enhances neutralizing immunity against the Delta variant. medRxiv 2022. doi: 10.1101/2021.12.27.21268439.
22. Espenhain L, Funk T, Overvad M, Edslev SM, Fonager J, Ingham AC, *et al*. Epidemiological characterisation of the first 785 SARS-CoV-2 Omicron variant cases in Denmark, December 2021. Eurosurveillance 2021;26:2101146. doi: 10.2807/1560-7917.ES.2021.26.50.2101146.
23. Kared H, Wolf A-S, Alirezaylavasani A, Ravussin A, Solum G, Tran TT, *et al*. Immune responses in Omicron SARS-CoV-2 breakthrough infection in vaccinated adults. Nat Commun 2022;13:1-12. doi: 10.1038/s41467-022-31888-y.
24. Terreri S, Piano Mortari E, Vinci MR, Russo C, Alteri C, Albano C, *et al*. Persistent B cell memory after SARS-CoV-2 vaccination is functional during breakthrough infections. Cell Host Microbe 2022;30:400-8.e4.
25. Bates TA, McBride SK, Winders B, Schoen D, Trautmann L, Curlin ME, *et al*. Antibody response and variant cross-neutralization after SARS-CoV-2 breakthrough infection. JAMA 2022;327:179-81.
26. Callaway E. Breakthrough COVID powers up immune response to variants-including Omicron. Nature 2022. doi: 10.1038/d41586-022-00328-8.
27. Cromer D, Steain M, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, *et al*. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: A meta-analysis. Lancet Microbe 2022;3:e52-61.
28. Dimeglio C, Herin F, Martin-Blondel G, Miedougé M, Izopet J. Antibody titers and protection against a SARS-CoV-2 infection. J Infect 2022;84:248-88.
29. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, *et al*. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine 2021;39:4423-8.
30. Favresse J, Gillot C, Bayart JL, David C, Simon G, Wauthier L, *et al*. Vaccine-induced binding and neutralizing antibodies against Omicron 6 months after a homologous BNT162b2 booster. J Med Virol 2023;95:e28164. doi: 10.1002/jmv.28164.
31. Dolscheid-Pommerich R, Bartok E, Renn M, Kümmerer BM, Schulte B, Schmithausen RM, *et al*. Correlation between a quantitative anti-SARS-CoV-2 IgG ELISA and neutralization activity. J Med Virol 2022;94:388-92.
32. Krammer F. A correlate of protection for SARS-CoV-2 vaccines is urgently needed. Nat Med 2021;27:1147-8.