SHORT COMMUNICATION

Long-term antibody response after COVID-19 vaccination in health care workers: A single centre study from Pakistan

Fatima Kanani[1], Javeria Aijaz [2], Sabiha Anis[3], Mamoona Mushtaq[4]

Abstract

The retrospective cohort study was planned to determine long-term anti-spike immunoglobulin G levels after receiving coronavirus disease-2019 vaccination by healthcare workers. The study took place between June and July 2022 at the Indus hospital in Karachi. Healthcare workers who had previously screened negative to pre-vaccination Severe Acute Respiratory Syndrome Coronavirus 2 nucleocapsid antibodies were tested for post-vaccination Severe Acute Respiratory Syndrome Coronavirus 2 anti-spike immunoglobulin G levels using a quantitative assay. The test was also performed on the stored pre-vaccination samples of the subjects collected up to 18 months previously. Antibody levels in subjects without infection, with infection and with booster administration were compared. The median post-vaccination anti-spike immunoglobulin G in infected only, infected with routine vaccination and infected with booster values were 1,725.6 IU/mL (interquartile range: 684.80-4,708.9 IU/mL), 2,067.15 IU/mL (interquartile range: 705.33-4,670.4 IU/mL) and 6,139.15 IU/mL (interquartile range: 2,426.05-10,623.40 IU/mL). There was a doubling of antibody titers, from 1,744 IU/mL to 3,829 IU/mL, in those who received a booster versus routine vaccination (p>0.05). The antibodies remained positive more than a year following vaccination.

Keywords: Healthcare workers, Anti-spike IgG, Sinopharm, CanSino-Biologics, Pfizer, Booster.

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Introduction

As the acute phase of the coronavirus disease-2019 (COVID-19) pandemic subsided, numerous studies confirmed the efficacy of vaccines in limiting the virus's spread and severity.[1-3] In a large study on 35,768 asymptomatic healthcare workers (HCWs), of whom more than 95% had received BNT162b2 (Pfizer) vaccine, it was seen that two doses of the vaccine were associated with high protection against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, which decreased over a period of 6 months.[4] Another study demonstrated that immunity acquired after natural infection and boosted with vaccination remained high more than 18 months after the infection compared to those who were unvaccinated in whom the immunity tapered down in one year.[5] Others demonstrated that boosters increased waning antibody titres.[6] Studies on long-term antibody response are useful for targetted strategies for further vaccination or booster drives. Various types of antibody assays are in use. Nucleocapsid antibodies indicate SARS-CoV-2 infection, while antibodies to spike (S) protein gauge vaccine efficacy. Neutralising antibody assays assess the functional immune status, but, owing to their cumbersome nature, in vitro diagnostic (IVD) binding antibody assays were explored as efficient surrogates.[7,8]

The current study was planned to evaluate the presence of long-term antibodies to SARS-CoV-2 in HCWs following COVID-19 vaccine administration.

Methods, Results and Discussion

The retrospective cohort study was conducted at a tertiary care hospital in Karachi from June to July 2022 after approval from the institutional ethics review board of Indus Hospital and Health Network. HCWs who had been previously tested for pre-vaccination antibodies to SARS-CoV-2 nucleocapsid (NC) antigen by a qualitative assay (Elecsys Anti SARS CoV 2 assay, Roche Diagnostics, GmbH, Germany) as part of regular screening service were approached. Consent to participate in the study was taken from those screening negative and thus assumed uninfected by SARS-CoV-2. They were then tested for post-vaccination anti-Spike immunoglobulin G (anti-S IgG) levels using SARS-CoV-2 IgG II quantitative (Abbott Ireland, Diagnostics Division). Anti-S IgG test was also performed on the pre-vaccination samples of the subjects archived and stored up to 18 months previously. Clinical details including polymerase chain reaction (PCR) test results, dates, type of routine COVID-19 vaccinations, histories of

[1]Department of Chemical Pathology, Indus Hospital and Health Network, Karachi, Pakistan; [2]Department of Molecular Biology, Indus Hospital and Health Network, Karachi, Pakistan; [3]Department of Immunology, Indus Hospital and Health Network, Karachi, Pakistan; [4]Indus Hospital Research Center, Indus Hospital and Health Network, Karachi, Pakistan.

Correspondence: Fatima Kanani. e-mail: fatima.kanani@tih.org.pk

ORCID ID: 0000-0001-6486-8886

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acquired natural infections and boosters were collected retrospectively from electronic medical records.

The SARS-CoV-2 IgG II Quant assay is a chemiluminescent microparticle immunoassay (CMIA) which specifically detects IgG against the receptor-binding domain (RBD) of the S1 subunit of the S protein of SARS-CoV-2 in serum and plasma. This is a quantitative assay and the amount of antibodies are measured in relative light unit (RLU). There is a direct relationship between the quantity of IgG antibodies to SARS-CoV-2 in the sample, and the RLU is obtained, and expressed in AU/mL. The cut-off for positivity is 50AU/mL. The reportable interval of the assay is from 6.8AU/mL to 40,000AU/mL without dilution, and the extended range goes up to 80,000AU/mL with dilution.

For analysis, the participants were categorized into three groups: no documented COVID-19 infection group A, documented infection group B, and documented infection with vaccine booster group C. Rise in antibodies across the groups was compared, and the association of antibody levels with time since vaccination was determined. Data was analysed using Microsoft Excel and SPSS 24. Since the distribution of antibody titers was non-normal, as assessed using the Shapiro-Wilk test, therefore continuous variables were expressed as median with interquartile range (IQR) and compared using the Kruskal-Wallis test. The association between antibody titers and the duration of time since immunisation was evaluated using Spearman's rank correlation. When applicable, pairwise comparisons were carried out, with a significance threshold of $p<0.05$. To investigate the impact of booster dosages and various vaccine types on antibody responses, subgroup analyses were also conducted.

Of the 184 HCWs tested prior to their routine COVID-19 vaccination, there were 57(31%) who were seronegative and willing to participate in the study. The median age of these participants was 31 years (IQR: 28-39 years), ranging 22-60 years. There were 32(56.1%) males and 25(43.9%) females. Overall, 55(96.5%) HCWs eventually received complete vaccine course, while 2(3.5%) received partial dosage. Sinovac was administered to 35(61.4%) participants, Sinopharm to 17(29.8%) and CanSino

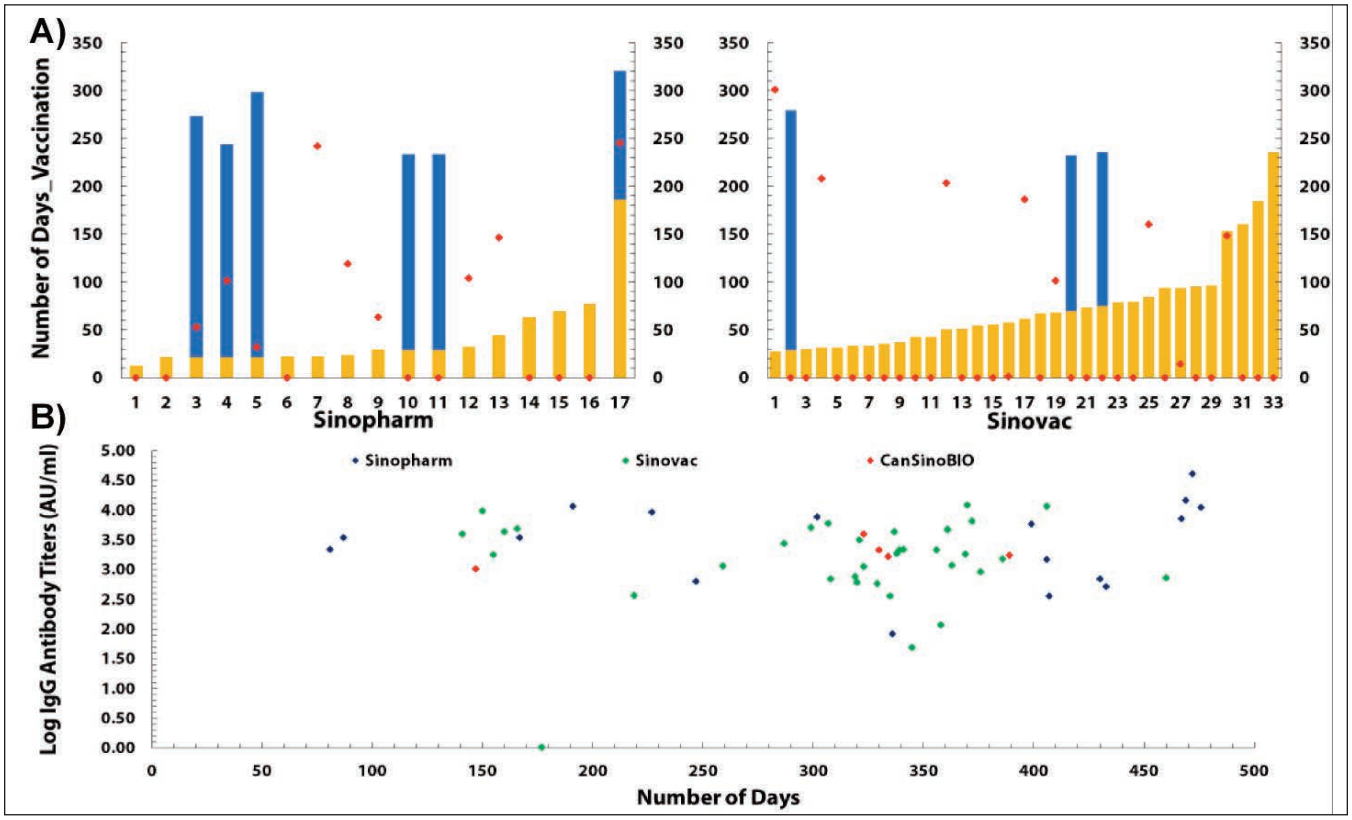

Figure-1: (A) Time difference in days between vaccine doses and post-vaccination infection for individual patients. The first panel shows the time intervals for Sinopharm (yellow bars) and booster doses (blue bars), with red dots representing the days of post-vaccination infection. The second panel displays the same for Sinovac (yellow bars) and booster doses (blue bars). The length of each bar represents the time interval between vaccination doses, while the red dots indicate the exact day of post-vaccination infection. Each bar or dot represents a single patient. Data for Cansino Biologics is not included.
(B) Scatter plot depicting the time interval in days since the last vaccination against the log of anti-spike immunoglobulin G (IgG) antibody titers. Each dot represents a single participant, with colours differentiating vaccine types.

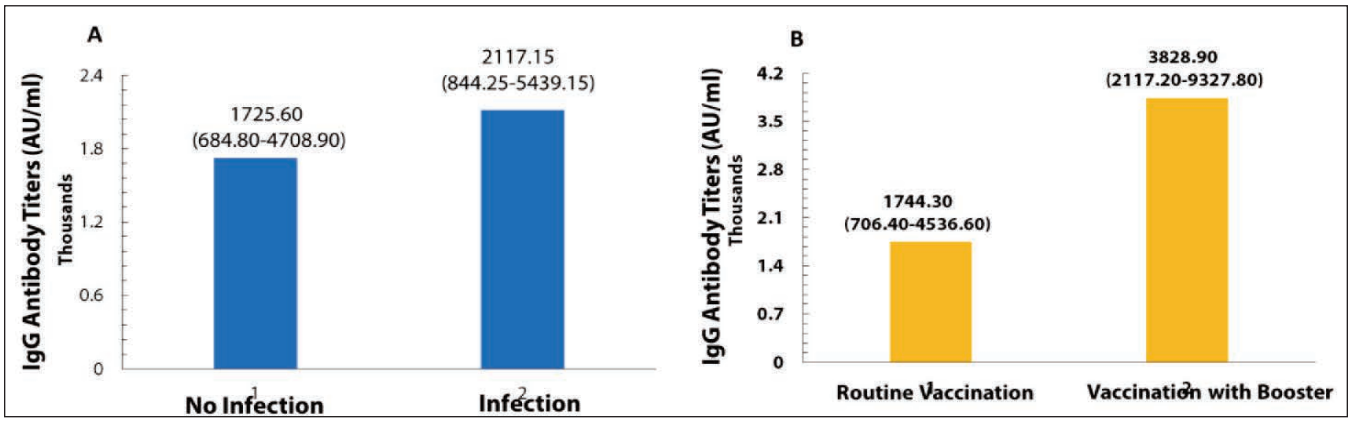

Figure-2: Difference in anti-spike immunoglobulin G (IgG) titer in participants with and without infection (A), and with and without booster dose (B).

Biologics to 5(8.8%). Besides, 11(19.30%) of these HCWs received a booster dose, with 10(91%) of them opting for BNT162b2 (Pfizer/BioNTech) vaccine.

The median gap between Sinopharm doses was 29 days (IQR: 21-53), and for Sinovac, it was 61 days (IQR: 36-88), while CanSino Biologics was a single-dose vaccine. Sampling for post-vaccination antibody levels occurred at a median of 341 days (IQR: 319-407 days) since the last vaccination, and for those receiving a booster, the median difference was 177 days (IQR: 114-237 days). The median time for infection post-vaccination was 176 days (IQR: 108-286 days), with unavailable booster dates for two HCWs. The median time from last COVID-19 infection to specimen draw was 209 days (IQR: 162.50-332.50 days). No association was found between days since last vaccination and antibody titer (Spearman correlation coefficient 0.036) (Figure 1).

The baseline anti-S IgG levels were negative in all but 5(%) participants, with median values being 0 or non-measurable, while post-vaccination median level was 2071.20 AU/mL (IQR: 725.3-4829.6 AU/mL). There were 31(54.4%) HCWs in group A with median anti-S IgG value of 1725.6 AU/mL (IQR: 684.80-4708.9 AU/mL) ranging 47.9-11809.4 AU/mL, 22(38.6%) in group B with median value 2067.15 (IQR: 705.33-4670.4 AU/mL) ranging 80.5-> 40,000 AU/mL, and 4(7%) in group C with median value 6139.15 AU/mL (IQR: 2426.05-10623.40 AU/mL) ranging 2117.2-11189.3 AU/mL. In group B, 4(18.18%) HCWs had asymptomatic infection, 17(77.27%) had mild, and 1(4.55%) had severe disease. All the 4(100%) group C participants had mild disease. There was no association between antibody levels and disease severity in the studied groups (p>0.050. There was a sequential rise in antibody levels across the groups, but no significant association was found (p=0.206). Breakthrough infections, meaning infection after the completion of vaccination, was seen in 18(31.6%) cases, while 3(5.3%) participants got infected after the first shot of vaccine.

Groups B and C were then merged into group D having 26(45.6%) HCWs who were infected at some point with COVID-19. Besides, the rise in antibody titer among those who had had booster dose compared to those with routine vaccination was also noted (Figure 2).

The current study found no decline in antibody titer with increasing time since vaccination, contradicting earlier reports of decreasing immune response after 6 months.[4,9]

The current study covered the time zones of both Delta and Omicron as well as other earlier variants of concern (VOCs), but demonstrates a lower frequency of breakthrough infections than reported in literature.[10,11] The overall resilience and immune resistance of the study population reflects the trend seen in the rest of the country even though HCWs were at relatively higher risk of disease contraction. An element of cross-reactivity with other human coronaviruses may have contributed to stronger immunity, potentially explaining lower infection rates than in some middle and low-income countries (LIMCs).[12]

The limitations of the current study include small sample size, lack of sequencing for variant determination, non-interventional design, variable exposure of HCWs to the virus, and the use of a combination of vaccines. It is significant to mention that the studied cohort included participants who received different vaccine types, including Sinovac, Sinopharm and CanSino Biologics. Previous studies[2,3] suggest that various degrees of immunogenicity could result from the vaccines. As this study shows, aggregating different vaccinations for analysis could conceal specific patterns on the efficacy of specific immunizations.

Future studies should stratify data by vaccination type to have a deeper understanding of long-term antibody responses. Especially, messenger ribonucleic acid (mRNA)

vaccines, like Pfizer-BioNTech, used for boosters could generate immunological response more drastically than inactivated vaccines, like Sinopharm or Sinovac, thereby affecting the interpretation when combined.

Conclusion

Antibody levels were the highest in the vaccinated HCWs who had natural infection and had booster shots, compared to those who were not infected, or were infected and had received only routine vaccination. Antibody levels did not decline with time even up to one year post-vaccination. Natural infection post-vaccination significantly enhanced immune responses. Interestingly, routine vaccination alone prevented infections in approximately half of the participants, underscoring its effectiveness.

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Conflict of Interest: None.

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FK: Design, drafting, critical review and final approval.
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MM: Data collection, statistical analysis and final approval.