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Original Research Article

SARS-CoV-2: comparison of IgG levels at 9 months post second dose of vaccination in COVID-survivor and COVID-naïve healthcare workers

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ABSTRACT

Background: Natural (asymptomatic/symptomatic COVID-19 infection) and artificial (vaccination) exposure to the pathogen represent two modes of acquiring active immunity. No definitive guidelines exist regarding whether COVID-survivors (with infection/re-infection/re-re-infection in the three COVID-19 waves) require a modified vaccination schedule. Most countries are offering a third vaccine dose and many are contemplating a fourth dose. Our aim was to gauge the IgG-antibody levels 9m post second vaccination in healthcare workers (HCW) and compare these with IgG-levels 1m post-vaccination in the same cohort for any decline, and to compare the post-vaccination IgG-levels in COVID-survivors and COVID-naïve HCW at 9m.
Methods: This prospective observational single-centric cohort study included 63 HCW of either sex, aged 18-70y who completed 9m post-vaccination. The IgG-titre was tested at 9-10m post second vaccination in COVID-survivors and COVID-naïve HCW.
Results: At 1m and 9m post-vaccination IgG-levels in COVID-survivors (23.097±4.58 and 15.103±4.367 respectively; $p<0.0001$) and COVID-naïve HCW (16.277±6.36 and 9.793±6.928 respectively; $p=0.0013$) had unequal variance (Welsch test; $p=0.0022$ at 9m). 9/31 COVID-naïve HCW but none of the 32 COVID-survivors tested COVID-positive in the second wave post second vaccination. 11/31 and 3/32 HCW belonging to the former and latter groups developed COVID-19 in the third wave consequently deferring their third/precautionary vaccination.
Conclusions: Although HCW with IgG-levels in all brackets developed COVID-19, the severity of symptoms corresponded with the IgG-levels. COVID-19 is here to stay, but in peaceful co-existence in endemic proportions. Considering evidence that immunity acquired by vaccination/natural infection is ephemeral, re-invention of vaccines to match the ever-mutating virus is foreseen.

Keywords: COVID-19, Immunity, Vaccine

INTRODUCTION

The two methods of acquiring active immunity against COVID-19 infection are natural exposure to the pathogen or by vaccination. There exist no guidelines as to whether individuals who have previously been documented as COVID-19 positive by the RT-PCR test would require a modified vaccination schedule. Plasma B-cells rapidly divide when exposed to a second dose of the same virus/vaccine. The process of B-cell maturation is also activated by the booster dose resulting in better targeted antibodies. Hence, a second dose produces antibodies faster than the initial exposure/inoculation (which is known to produce an IgG antibody response only after 1 month of exposure).

Currently, most countries including India have incorporated a third dose of vaccine for vulnerable

elderly and healthcare workers, considering that antibody levels are expected to wane/deteriorate with time and some new variants of concern like the Omicron strain have emerged against which two doses might be ineffective.[1] On 22/9/21, the US Food and Drug Administration amended the emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine to allow for use of a single booster dose to be administered at least six months after completion of the primary series in individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19. India flagged its third vaccine dose programme on 10/1/22 for the elderly, those with co-morbidities and healthcare workers branding the 'third dose' as precautionary dose.[2,3]

Israel, Chile and Cambodia have already begun offering fourth shots of vaccine to priority groups and immunocompromised citizens, while Denmark, Hungary and Sweden have announced similar intentions in the near future.[4] But is this race for booster shots leading us anywhere? The virus is constantly mutating as a survival tactic to escape these antibodies and memory cells. The vaccines developed may already have become ineffective/obsolete because their target has mutated/changed.

The second dose of vaccination in COVID-survivors is akin to a third/booster dose of vaccination in COVID-naïve individuals and each infection is equitable to a vaccine dose.[5] Measuring the IgG levels at 9m post second dose of vaccination in COVID-survivors can provide a snapshot of what IgG levels to expect in COVID-naïve individuals following a third/precautionary dose of vaccination. We already have data pertaining to IgG levels 1 month post first and second dose of vaccination in both COVID-survivor and COVID-naïve HCW.[5] Measuring IgG levels at 9 months in the same cohort of HCW would guide us regarding the utility and timing of third dose of vaccination. Our primary objectives were to find out the IgG antibody levels 9 months post second dose of vaccination in HCW and to compare the post-vaccination IgG antibody levels in COVID-survivors with post vaccination antibody levels in COVID-naïve HCW at 9m. Our secondary objective was to gauge the extent of decline in IgG levels at nine months post second vaccination as compared to IgG levels one month post second vaccination.

METHODS

This prospective observational, two-arm, single-centric cohort study was carried out after obtaining written informed consent from all health care workers, approval from the scientific committee and institutional review board and was prospectively registered with the clinical trial registry, India. 63 adult ASA I-II HCW were included in the study conducted at Rajiv Gandhi Cancer Institute and Research Centre. The four vaccines currently offered by India are locally-manufactured Covishield and Covaxin, the Russian vaccine, Sputnik and Corbevax.[6-8] Since all the HCWs in our institution were vaccinated with Covishield, the vaccine employed in our study was Covishield (ChADOx1 nCoV-19/AZD1222; chimpanzee adenoviral vector vaccine produced by Oxford-AstraZeneca; manufactured by Serum Institute of India).[9]

The IgG antibody test kit employed for serological testing at RGCIRC (VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG), was constructed on the high throughput automated chemiluminescence immunoassay (CLIA) technology. Serum from HCW was tested for antibodies that were IgG isotypes directed against the spike protein of SARS-CoV-2. This immunometric test utilizes ECi/ECiQ, 3600, 5600 /XT 7600 system fed with an intravenous serum sample of 20 µL which is incubated and tested at 37 °C for 37 min. 48 min elapse before the first test-result appears. 90.0% positive percent agreement to PCR along with 100% clinical specificity (95% CI: 99.1-100.0%), were other salient features.[10]

Clinical interpretation classifies IgG titres <1 AU as non-reactive/non-protective, those between 1-1.46AU as conferring low grade immunity, those between 1.46-18.45 AU providing medium levels of protection and values above 18.45 AU bestowing high levels of protection.[10]

The study group (group P; n=32) comprised HCW with a history of being COVID-positive and developing moderate/high antibody titre, while the control group (group N; n=31) comprised those HCW who had negative RT-PCR test reports during the (first and) second wave of the pandemic which coincided with the vaccination drive in India. The COVID-naïve HCW were differentiated from asymptomatic COVID-positive HCW on the basis of the RT-PCR test done prior to vaccination. Antibody response post-vaccination was noted at 9 months after the second dose in the study group and the control group and compared with the pre-existing data at 1 month post second vaccine dose in the same cohort of HCW.

All HCW of either sex, aged 18-70 years who were vaccinated with the recommended two doses, with a history of testing positive for SARS-CoV-2 were included in the study. HCW who did not get vaccinated against COVID-19 and who did not have pre-existing record of IgG level at 1m post second vaccine, were excluded from the study.

Sample size calculation

Keeping type-I/alpha-error at 0.05 and power of the study at 90%, difference in means as 4.2, expected standard deviations as 2.79 and 6.55 respectively, from a study by Shah et al 31 HCW in each group were required.

Allowing for dropouts, we enrolled 35 HCW in the study group and 35 HCW in the control group.[5]

Statistical analysis

Student's t test, intraclass correlation and Pearson's correlation coefficient was used for normally distributed, continuous/quantitative variables (expressed as mean±SD), whereas Chi-square test was performed for categorical/qualitative variables (expressed as numbers and percentage). Mann-Whitney test was utilised for non-Gaussian data (expressed as median and range). IBM SPSS (International Business Machines; Statistical Package for the Social Sciences) statistics for windows (version 23.0; released 2015; Armonk, NY: IBM Corp.) was utilised and $p<0.05$ was considered statistically significant. Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) was utilised for the analysis of descriptive statistics.

RESULTS

Out of 70 potentially eligible HCW vaccinated with both the doses 9 months earlier, all were assessed for eligibility but only 65 were confirmed eligible and included in the study (five HCW developed symptoms and tested COVID-positive by the RTPCR test before they could give their blood samples for the IgG antibody test). Two HCW had resigned and were lost to follow up. Data from 63 HCW was analysed.

Table 1: Descriptive statistics.

Parameter	Group-CN	Group-CP	P value
Age (years)	41.9±10.25	44.3±9.81	0.36
Gender (male:female)	15:16	17:15	
Workplace related exposure to COVID-19	+	+++	

Mean age with standard deviation was 41.9±10.25 and 44.3±9.81 in CN and CP groups respectively (p=0.36). The sex ratios (male: female) were 15:16 in group-CN and 17:15 in group-CP (Table 1).

At 1m and 9m post vaccination in the group-CP, IgG levels were 23.097±4.58 and 15.103±4.367 respectively (p<0.0001). At 1m and 9m post vaccination in the group-CN, IgG levels were 16.277±6.36 and 9.793±6.928 respectively (p=0.0013; Figure 1 and Table 2).

Nine out of 31 HCW in the CN group tested COVID-19 positive in the second wave after receiving both doses of vaccine. None of the 32 patients in the CP group tested COVID-19 positive in the second wave of COVID-19 after receiving both the doses of vaccine.

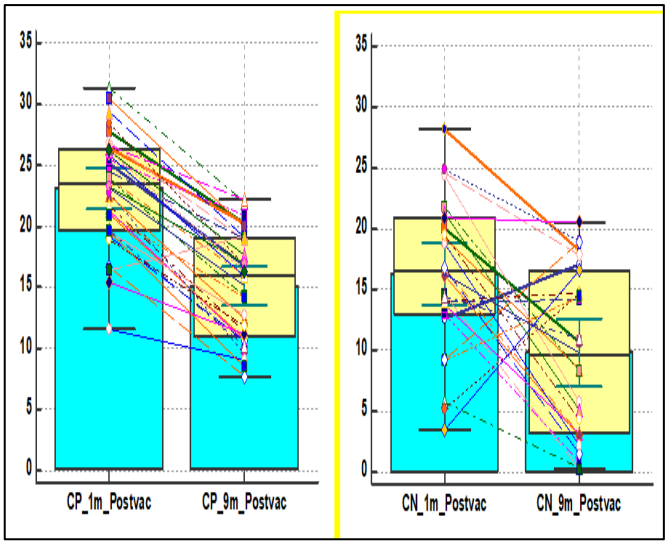

Figure 1: Dotted box-whisker plots comparing IgG levels at 1m and 9m post second dose of vaccination in COVID-positive and COVID-naïve healthcare workers.

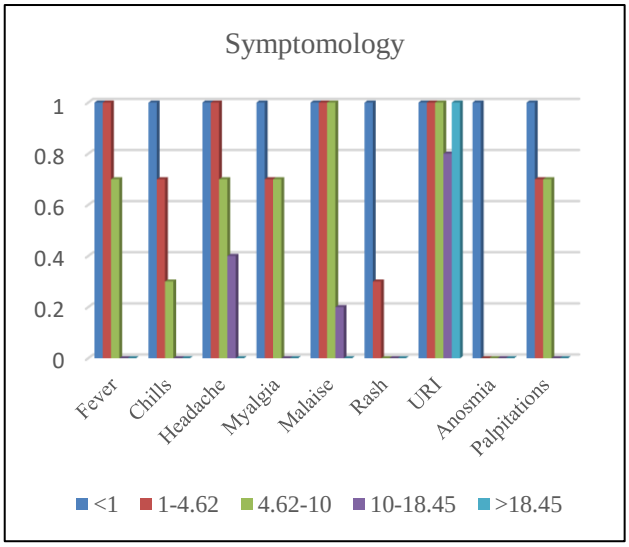

Figure 2: Signs and symptoms pertaining to COVID-19 infection in the third wave stratified by the IgG antibody levels at 9-10m post both doses of Covishield vaccine.

11/31 HCW in CN group developed RT-PCR positive COVID-19 in the third wave (one with IgG level above 18.45 AU, three each had IgG between 10-18.45 AU, between 4.62-10 AU, and between 1-4.62 AU and another one with IgG <1 AU) while 3/32 HCW in CP group developed RT-PCR positive re-infection in the third wave and hence deferred their third dose of vaccine. Although HCW with IgG in all brackets (mild, moderate and high levels of protection) turned RT-PCR COVID-19 positive, the severity of symptoms corresponded with the IgG levels (Figure 2). At 9m post 2nd dose of vaccination IgG levels in both groups had unequal variance (Welsch test; p=0.0022) (Figure 3).

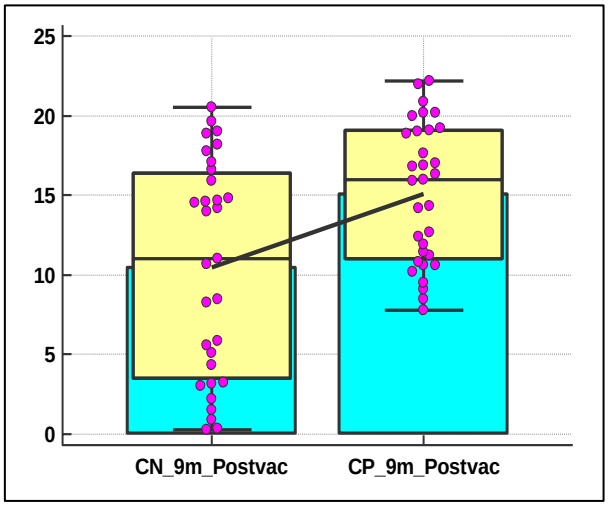

Figure 3: Dotted box-whisker plots depicting comparison of IgG antibody levels developed by COVID-positive and COVID-naïve groups of healthcare workers 9 months after second vaccine.

Table 2: Paired samples t-test statistics for group-CP and group-CN at 1m and 9m post vaccination.

Parameter	CP-1m-Postvac	CP-9m-Postvac	CN-1m-Postvac	CN-9m-Postvac
Arithmetic mean	23.10	15.1031	16.28	9.79
95% CI for the mean	21.45 to 24.75	13.53 to 16.68	13.71 to 18.85	6.10 to 12.59
Variance	20.98	19.07	40.49	47.99
SD	4.58	4.37	6.36	6.93
Stand. error of the mean	0.81	0.77	1.25	1.36
Mean difference	-7.9937		-6.4838	
SD of differences	3.1183		9.1575	
Standard error of meandif	0.5512		1.7959	
95% CI	-9.12 to -6.87		-10.18 to -2.79	
Test statistict	-14.50		-3.610	
Two-tailed probability	p<0.0001		p=0.0013	

DISCUSSION

COVID-19 afflicted India in three waves. The first wave swept India in June to November 2020, the second wave with the Delta variant (B.1.617.2 variant) predominating in March-May 2021 and the current third wave with the Omicron variant (B.1.1.529;11/11/21 in Botswana) from January 2022 onwards.[11] The vaccines were developed against the COVID-19 strain belonging to the first wave and administration began just prior to the second wave in January 2021.

The two groups are comparable in terms of age, sex-ratio but not in workplace-related exposure to the virus. In fact, the CP-group of HCW were preferentially posted to the COVID-wards, COVID-ICUs and during emergency/elective surgery on COVID-positive patients during the first and second waves due to a notion that natural infection had given them a stronger immunity against the virus.

The 32 HCW in CP-group were affected in the first wave and the 31 HCW in the CN-group tested negative by the RT-PCR test before receiving both doses of vaccine. The fact that 9/31 in the CN-group developed COVID-19 in the second wave indicates that Covishield conferred maximum 71% protection to those vaccinated, assuming that all 31 of these HCW were exposed to COVID-19 in the second wave. This was supported by clinical trials on Covishield efficacy.[12] But it was highly likely that some of these HCW were not exposed to COVID-19 at all due to either social distancing, COVID-appropriate behaviour or efficient personal prophylactic equipment (PPE) kits. So, <71% protection can be attributed to Covishield. The fact that none of the 32 HCW in the CP group developed COVID-19 in the second wave indicates that three doses (one of them being the natural infection in this case) offer better protection/immunity. This was also supported by the higher IgG levels in the CP-group 1-month post both doses of vaccination as compared to the CN-group.

The fact that 11/31 HCW in CN-group versus 3/31 HCW in CP-group developed COVID-19 in the third wave was probably because natural infection might have conferred better immunity than vaccination. During the second wave, Covishield showed effectiveness of nearly 90%, while Covaxin an effectiveness of about 80% with

satisfactory efficacy against several mutant variants of SARS-CoV-2. Any dramatic structural change in spike protein, may diminish the efficacy of Covishield as was witnessed with the omicron virus (A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F; these 34 mutations were observed in the spike protein. Many other mutations were located in RBD 319 to 541).[13] In this situation, Covaxin might prove more effective owing to its ability to produce multiple antibodies against various epitopes.[13] Three doses of the Pfizer BioNTech Vaccine prove potent against the Omicron variant. The fact that none of the HCW required hospitalization maybe due to two factors. Firstly, because all the HCW had received 2 doses of vaccination and secondly because the Omicron variant inherently might produce milder symptoms (de-coupling of COVID-19 infection with hospital/oxygen/ICU beds). The three HCW in CP-group developed only cough with expectoration and reported less malaise during re-infection than during their first infection and could resume duties within a week as against 3-4 weeks earlier.

Increased infectivity with milder symptoms maybe attributable to survival tactics of the COVID-19 virus and is in line with the 'natural selection' theory. The virus strain producing lethal symptoms is eliminated with the host's death whereas the strain producing mild/no symptoms is propagated far and wide till it becomes endemic and a stage of peaceful co-existence with the human hosts is reached.

In context of the antibody kit utilized by us brackets of 1-4.62 AU, 4.63-18.45AU and >18.45AU indicate mild, moderate and high levels of immunity. The IgG level at 1m post vaccination in CN-group was just 1AU higher than the IgG level at 9 m post vaccination in CP-group. At 9m, IgG levels were 5 AU higher in the CP-group as compared to CN-group despite the fact that 9 HCW in CN-group had turned COVID-19 positive in the second wave after 2nd dose of vaccination.

Collective IgG levels have fallen from the high level of protection bracket to the moderate protection bracket 9m post vaccination in the 32 HCW of CP-group considered together. Similarly collective IgG levels declined in CN-group by roughly 6AU but still remained in the moderate level of protection bracket.

Only one HCW showed a reverse trend of rise in IgG level in CP-group indicating a missed asymptomatic re-infection. 7 HCW displayed a paradoxical increase in IgG at 9 m post vaccination as compared to the IgG levels at 1m post vaccination in CN-group indicating asymptomatic/mild infection during the third wave. This again points to the fact that the Omicron variant which is the pre-dominant strain in the third wave produces mild to no symptoms in majority of the cases.

The mammoth task of vaccinating 940 million strong Indians is ongoing. 99% have received the first dose and 90% both doses till date.[14]

Since moderately high IgG antibody levels have been attained by the study group at 9 months post vaccination, they may not require the third round of vaccination at this point of time and may postpone it by a few months (since a third dose may not provide any extra benefit by way of immunity, the chances of adverse vaccine-related reactions may be increased and precious resources in a resource-constrained country like ours shall be wasted).[15] This would also prompt future multicentric trials on the utility, durability and impact of the third/fourth dose of vaccination. Non-responders and immunocompromised individuals and even HCW with low IgG levels detected at 9m (owing to heightened risk of exposure), may benefit from a third dose of vaccination.[15]

Updated variant-specific vaccines eg those against the delta virus (synonymous with high morbidity and mortality) are in the pipeline.[16] Polyvalent vaccines with at least three components, one each against the predominant viral strain in each wave (alpha, delta and omicron) would be welcome. The small sample size and a narrow focus of interest (only Covishield vaccine studied) comprise the limitations of our study.

CONCLUSION

COVID-19 is here to stay, but in peaceful co-existence in endemic proportions. Since evidence that immunity developed by vaccination/natural infection barely lasts an year, re-invention of vaccines to match the ever-mutating virus is foreseen.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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