Original Article

Immunity Status of Health Care Workers Post-Recovery from COVID-19: Natural Adaptive Immunity Persists at Nine Months Post-Infection : An Online Longitudinal Panel Survey

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Background : Various studies have pinned longevity of protective Immunoglobulin-G (IgG) titres at 2-5 months. The robustness and longevity of the IgG antibody response to COVID-19 infection has been gauged in a cohort of 214 single institutional health care workers by serial quantitative immunometric tests. Currently no separate guidelines exist for vaccination of COVID-survivors and this study provides data to fill this lacuna in knowledge.

Methodology : Prospective longitudinal panel survey administered to the same cohort of Health Care Workers (HCW) till such time they got vaccinated under Indian Government's free vaccination drive for HCW. Depending upon the date of contraction of infection the HCW could be longitudinally monitored for variable periods (2-9 months). The survey questionnaire comprising multiple-choice, dichotomous, matrix and Likert-scale questions was deployed to the respondents online via email/WhatsApp. Data was expressed as box-whisker plots, trendlines and trend areas. A p-value<0.05 was considered statistically significant. The composite index of 'Effective Immunity' was calculated.

Results : The mean IgG antibody titre was 11.13±8.6AU at 1-2m, 9.68±8.9AU at 3-4m, 8.35±5.9 AU at 6-7m and 7.87±4.4 AU at 8-9m after first symptom, respectively. The lowest titre at all time points was 0 while the highest titres were 46.8 AU, 56.5 AU, 23.4 AU and 17.4 AU at 1-2m, 3-4m, 6-7m and 8-9m, respectively.

Conclusion : Adaptive active immunity acquired through natural infection may last for at least 9 months post-initial exposure and lies in the moderate protection range in 77% HCW, which can be extrapolated to vaccination and immunity passports. Separate vaccination guidelines are required for COVID-survivors. The first shot of vaccine serves as a booster second exposure/booster dose in all COVID-survivors.HCW with low IgG-titre may suffer from a false sense of security. Periodic quantitative IgG-titre based serological tests can help guide timing of second shot of vaccination and predict likelihood of re-infection.

[*J Indian Med Assoc* 2022; **120(12):** 33-8]

Key words **: Antibody, COVID-19, Humoral immunity, Immunoglobulin-G.**

The corona virus disease (COVID-19) pandemic with associated lockdowns had mercilessly brought life to a grinding halt. People have now adjusted with remarkable resilience to the new normal of social distancing, repeated hand-washing, personal protective equipment and the concept of work/study from home. The latest official sero-survey (28000 sample size; Februry, 2021) results have divulged that 56% of Delhi inhabitants are seropositive[1]. Herd immunity development is the Holy grail of the COVID-pandemic and duration for which seropositivity lasts is an important determinant. The free, state-sponsored vaccination drive exclusively for HCW has started on a priority basis since 16th January, 2021 after emergency use authorization of two vaccines[2]. 214 Health Care Workers (HCW) of a premier tertiary-care onco-hospital who are COVID-survivors periodically got their IgG-titres tested. On follow-up of this cohort until

Editor's Comment :

- Immunity acquired through SARS-CoV-2 infection may last at least 9 months.
- IgG-titres are inmoderate protection range in 77% convalescent individuals.
- First vaccine shot serves as a second exposure/booster dose in all COVID-survivors.
- Periodic quantitative IgG-based serological tests can guide spacing of second vaccination-shot and predict susceptibility to re-infection.
- Requirement of separate vaccination guidelines for COVID-survivors.

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Received on : 06/07/2021
Accepted on : 09/02/2022

the date they got vaccinated we could collect data for a maximum of 9 months from the date of symptom-onset (index/first case at our institution was diagnosed on 1st of May, 2020 and the last HCW in the survey was enrolled in December, 2020). It is important to gauge the existence, extent and duration of immunity in COVID-survivors, as this would be a predictor of the likely duration of protective effect conferred by the available vaccines and this is the research question we seek to answer. Our primary objective is to find out if IgG antibody levels decline with time and by what amount and the time duration for which they last.

Material and Method

Our prospective longitudinal panel survey was conducted after prior written informed consent from all HCW and approval from the Scientific Committee and Institutional Review Board. The survey was administered to the same cohort of HCW till such time they got vaccinated (15th January to 28th February, 2021) under Indian Government's free vaccination drive for HCW. Depending upon the date of getting infected the HCW could be longitudinally monitored for variable periods of time ranging from 2-9 months. The survey questionnaire comprising multiple-choice, dichotomous, matrix and Likert-scale questions was deployed to the respondents online via email/WhatsApp.

An online survey software (Google forms), was utilized to create the survey questions and get analyzed data on a dashboard which keeps updating real-time as respondents partake the online survey. Data presentation on this dashboard comprises charts and graphs for the ease of statistical analysis.

Initial three steps of the survey (defining the population and sample,deciding the type of survey, designing the survey-questionnaire) were completed before and the remaining three steps (distribution of survey and response-collection, survey-result analysis, penning the survey results) were conducted after ethics committee approval.

All HCW, employed at Rajiv Gandhi Cancer Institute and Research Centre (RGCIRC) with a history of being a laboratory confirmed COVID-positive patient and who underwent antibody tests were included in the study. Non-HCW and HCW without Reverse Transcription Polymerase Chain Reaction (RT-PCR)/Gene Xpert reports were excluded from the survey.

Antibodies binding to the receptor binding domain (RBD) of the surface glycoprotein/spike (S) protein of SARS-CoV-2 can neutralize the virus[3-5]. The antibody test kit utilized at RGCIRC (VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG) is based on the high throughput automated Chemiluminescence Immunoassay (CLIA) technology and the antibodies tested are those produced against the S-protein of SARS-CoV-2. It is an immunometric test utilizing ECi/ECiQ, 3600, 5600/XT 7600 system with incubation time 37mins, time to first result 48mins and an intravenous serum sample of 20 µL tested at 37°C. Positive Percent Agreement to PCR of 90.0% and 100% clinical specificity (95% CI: 99.1–100.0%) are additional features[6].

It describes values<1AU as non-reactive, those between 1-1.46AU as providing low/inadequate levels of immunity, those between 1.46-18.45AU as moderate levels of protection and values above 18.45AU as providing high levels of protection.

Data was collected at three time points. T1, T2 and T3 at 1-2 months, 3-4 months and 6-7 months Post-development of first COVID-19 symptom/positive RTPCR test whichever was earlier, from the same cohort of HCW. IgG tests were repeated prior to vaccination at 8-9 months (T4) in the small subset of HCW who had contracted the disease in May/June 2020. The HCW then partook the nationwide free vaccination drive for HCW initiated on 15 January, 2021 (beginning 8.5 months after our index case) and their antibody levels could be tested for variable periods of time depending on the time elapsed from development of first symptom to first dose of vaccination.

Statistical Analysis : All **c**ontinuous/quantitative variables are expressed as mean ± Standard deviation while categorical/qualitative variables are expressed as numbers and percentage. Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) was utilized for Descriptive statistics and MedCalc software for Box-whisker plots, trendlines and trend-areas. P<0.05 was considered statistically significant.

Observations

Demographic parameters: Out of the 214 respondents,164 (76.64%) belonged to 20-40 years age group, 45(21.03%) in the 40-60 years age bracket, 3 (1.40%) in more than 60y bracket and 2 (0.94%) in <20 years bracket.129 (60.28%) of the COVID-19 infected HCW are females and 85 (39.72%) are male.

Mean IgG antibody titres with standard deviation at 4 time-points have been tabulated (Table 1).

We collected 304 readings from 214 HCW. 137 HCW had their titres measured at one time point only, 52 HCW had their titres examined at only 2 time points. 21 HCW underwent serological test at only 3 time points (18 HCW got their IgG titres measured at T1, T2 as well as T3 (Fig 1), another 3 HCW at T2, T3 and T4) and only 6 HCW had their IgG-titres tested four times in 9 months. None of the surveyed HCW had any symptoms suggestive of re-infection in the

Statistical Variable	T1	T2	T3	T4
Sample size	117	125	41	22
Lowest value	0.0000	0.0000	0.0000	0.0000
Highest value	46.8000	56.5000	23.4000	17.4000
Arithmetic mean	11.13	9.6797	8.35	7.87
95% CI for the mean	9.55 to 12.71	8.10 to 11.26	6.49 to 10.21	5.90 to 9.84
Median	9.19	6.6200	7.84	7.49
95% CI for the median	7.81 to 10.56	5.52 to 8.36	5.46 to 10.12	5.02 to 9.76
Variance	74.4090	79.4770	34.7668	19.7318
Standard deviation	8.6261	8.9150	5.8963	4.4421
Relative standard deviation	0.7748(77.48%)	0.9210(92.10%)	0.7062(70.62%)	0.5645(56.45%)
Standard error of the mean	0.7975	0.7974	0.9209	0.9470
Coefficient of Skewness	1.5793(P<0.0001)	1.9812(P<0.0001)	0.4493(P=0.2118)	0.3829(P=0.4132)
Coefficient of Kurtosis	3.6212(P=0.0001)	6.2236(P<0.0001)	-0.4191(P=0.6139)	-0.3718(P=0.8119)
Kolmogorov-Smirnov test for Normal distribution (with Lilliofer's correction)	D=0.1243 reject Normality (P=0.0001)	D=0.1571 reject Normality (P<0.0001)	D=0.0840 accept Normality (P>0.10)	D=0.1079 accept Normality (P>0.10)

Table 1 — Summary statistics for Health Care Workers at 4 time points
(CI=Confidence Interval; T1: 1-2 months; T2: 3-4 months; T3:6-7 months; T4:8-9 months)

entire study period.

117/214 HCW got their IgG antibody titre tested at 1-2m. 3 months had already elapsed since the institutional index case when the study commenced in August 2020 and hence, 97 HCW missed the T1 time slot of 1-2m. The mean IgG antibody titre was 11.13±8.6AU

125/214 HCW got their IgG tested at 3-4m.5HCW resigned and 85 HCW got vaccinated before they could complete 3-4 m. The mean IgG-titre was 9.68±8.9AU

41/214 HCW got their IgG antibody levels tested at 6-7m post infection. Another 2 HCW resigned between T2 and T3 (total 7 resignations out of 214 at 6-7m post infection) while 166 HCW got vaccinated before they could complete 6-7 months postinfection. The mean IgG-titre was 8.35±5.9 AU.

Only 22 HCW completed 8-9 months Post-Infection before they got vaccinated. Their antibody levels tested at 8-9m Post-Infection had a mean titre of 7.87±4.4 AU.

The lowest titre at all time points was 0 while the highest titres were 46.8 AU, 56.5 AU, 23.4AUand 17.4AU at 1-2m, 3-4m, 6-7m and 8-9m, respectively.

The box plots depict the median (middle line) and first and third quartiles (boxes), while the whiskers show 1.5 times the Inter Quartile Range above and below the box. There were 3 outside values/inner fences (values smaller than the lower quartile minus 1.5 times the interquartile range or larger than the upper quartile plus 1.5 times the interquartile range) at T1, one at T2 and none at T3 and T4. There was one far out value/ outer fence (value smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range) at both T1 and T2 but none at T3 and T4 (Fig 2).

The Standard Deviation at 1-2m and 3-4m was much higher (accompanied by skewed distribution and kurtosis)than that at 6-7m and 8-9m (bell-shaped Gaussian data-distribution).

Discussion

When time, resources and patient-compliance are of exponential essence, selecting the right medical diagnostic test is of utmost importance. Out of diverse antibody isotopes with differential neutralization capacity we chose to focus on IgG directed against RBD-spike protein because these are not just binding but also neutralizing in nature depending upon their plasma levels and a simple, reliable, quantitative immunometric test is available to gauge IgG-titres[7]. Although it is known that time to seroconversion ranges from 11-22 days depending on severity of illness and IgG-titres peak at 21-40 days post appearance of first symptom and thereafter decline[8,9], it is unknown for how long protective IgG-titres last. Long, *et al* have reported that the IgG levels in 93.3% of asymptomatic and 96.8% of symptomatic COVID-survivors declined during the early convalescent phase by 71.1% and 76.2% respectively compared to acute stage levels (3.4 and 20.5 units respectively) and that 40% of asymptomatic and 12.9% of symptomatic individuals became seronegative for IgG in the early convalescent phase[10]. Their study ends in the early convalescent phase (2months post first symptom) while we followed up our HCW (all of whom were symptomatic) for maximum 9 months into the convalescent phase. The

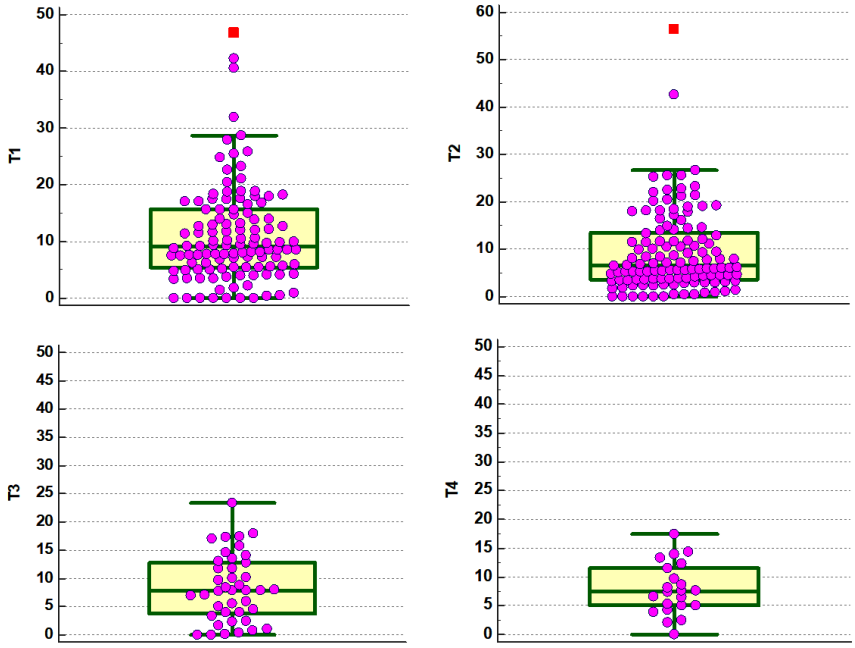

Fig 1 — Box-whisker plotsdepicting distribution of IgG-titres at four different time points

SIREN study, steered by Public Health England (PHE), reported that corona-survivors develop antibodies that provide 83% protection for at least five months duration[11]. Another two studies report detectable IgG-titres at 3 and 5 months post-exposure, respectively[12,13]. We have observed moderate IgG antibody titres in 17/22 (77.3%) HCW even after 9months of developing the first symptom/ positive RT-PCR test.

Immunity against SARS-CoV-2 is not binary, albeit it is graded. Although the mean IgG-titres progressively declined over 9 months (from 11.1 to 7.9AU) the values were still in the moderate immunity range (4.62-18AU) in our patients. On the face value,clinical implications of this decline for the concerned HCWs are insignificant as they still enjoy moderate levels of protection at the end of 9months. Of concern is the large Standard Deviation at T1 and T2, indicating that individual HCW have nil to low levels of protection (<4.62AU) making them vulnerable although the subset as a whole has moderate levels of protection. 20.5% HCW at 1-2months (IgG titre<1=10/171 HCW; IgG-titre 1-4.62 AU= 14/171 HCW), 34.7% of HCW at 3-4 months, 31.7%HCW at 6-7m(4/41 IgG-titre<1; 9/41 with IgG-titre 1-4.62 AU) and 22.73% HCW at 8-9m (IgG-titre<1=1/22; IgG-titre 1-4.62AU=4/22HCW) failed to develop protective levels of IgG.This underscores the importance of serological testing to discover and pinpoint those 1/3rd-1/5th patients with low IgG-titres who may suffer from antibody dependent enhancement[15] and concomitantly may lower their protective measures due to a false sense of security (Peltzman effect)[16].

The detailed sequential IgG-titres in 18 HCW have been plotted as trendlines (Fig 1).

5 HCW displayed a falling trend over the 3 time points with decay in IgG-titres as expected. But the fall in IgG-titres was too steep (18.2<5.52<4) and cannot be accounted for only by exponential decay and may be attributable to convalescent plasma donation by this HCW

4 HCW showed a rise at T2 followed by a fall at T3 (rhomboid pattern) attributable to a delayed IgG-peak at 3-4m instead of 1-2m.

7 HCW showed a fall at T2 followed by a rise at T3 (bowtie pattern). Fall at T2 is expected as per the exponential decay model. But the rise at T3 maybe explained by subclinical infection/anamnestic response

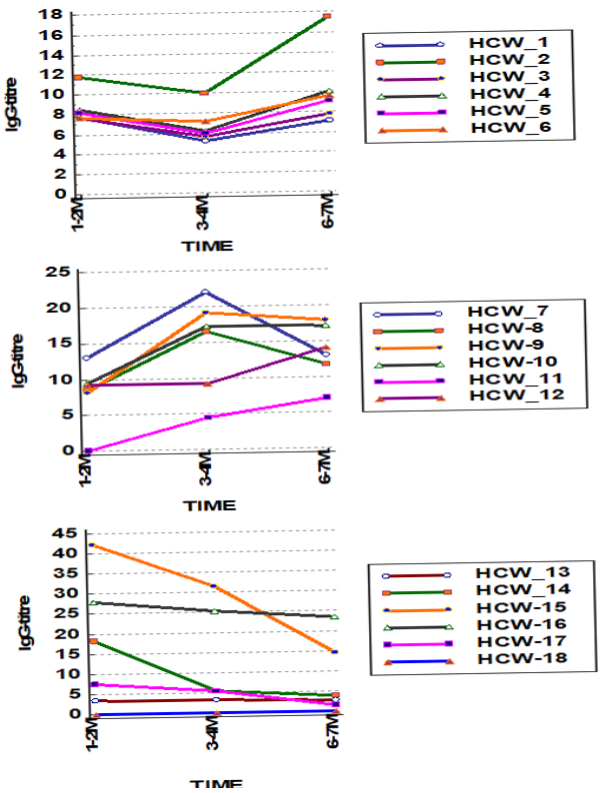

Fig 2 — Trendlines depicting IgG-titres over time

1 HCW failed to develop any antibodies at all three time points. This maybe due to a humoral immune system deficiency, accompanied by compensatory heightened T-cell immunity which enabled this individual to recover from COVID-19[17].

1 HCW showed a rising trend in antibodies at all three time points. Multiple subclinical exposures maybe responsible for this paradoxical rising IgG-titre trendline.

Declining IgG-titres in HCW signify the natural course of this disease. Rising/nearly constant IgG-titres at successive time-points can be explained by re-exposure to SARS-CoV-2 with subclinical infection, akin to a booster dose of vaccination.

An upslope between points T1 andT2 in one HCW may be countered by a downslope between points TI and T2 in another HCW. The vector sum of these individual undulating vectors may hence be a straight line. To demonstrate this we divided the 18 HCW into 3 strata, first strata was rhomboid (low-high-low IgG-titres at T1-T2-T3), the second was bow-shaped (high-low-high IgG-titres at T1-T2-T3) and the third was a right-angled triangle; hypotenuse sloping down from left to right; steadily declining IgG-titres). Stacking would give a false impression of antibody levels remaining fairly constant with elapsed time (Fig 3). Hence, the product of "IgG-titre numerical value" and the "time duration in months for which those titres lasted" is a superior measure of antibody levels in a particular HCW since it also takes into consideration the upslopes and down-slopes in the IgG-titre curves plotted against time. We shall denote this by the term "Effective Immunity" (EI) which is a composite figure facilitating comparisons between different individuals (Table 2).

The fact that 28/41 respondents still had moderate/high IgG-titres 6-7 months Post-Infection indicates that immunity triggered by natural infection to COVID-19 is more robust than imagined earlier. The fact that 22 out of these declined to take the free vaccines being provided to them and had their antibody titres tested at 8-9months indicates that they strongly believe that their IgG-titres would remain maintained at moderate levels in a gently undulating fashion till such time the pandemic lasts/herd immunity is produced. A wait and watch policy has been adopted by many HCW amidst apprehensions of adverse reactions to the vaccine. Some desire to derive full benefit from their pre-existing immunity till it lasts, as indicated by periodic IgG-titres and receive the vaccine shot once the titres fall below 4.62AU.

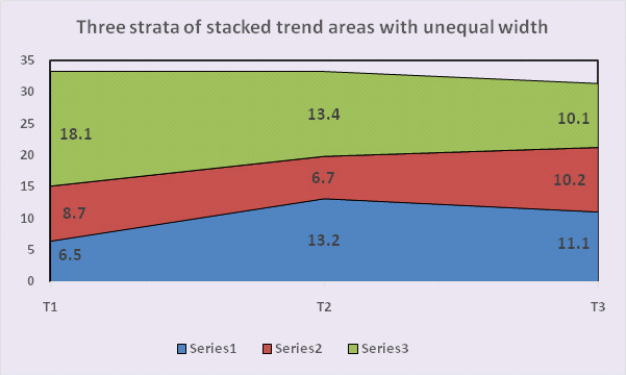

Fig 3 — Stacked area chart with IgG-titres clustered into three strata based on similar time-trends

No vaccination guidelines exist for COVID-survivors. We recommend that the initial dose/ first shot must be taken by all individuals irrespective of history of previous infection/ antibody status. It is unclear whether the second dose should be administered to HCW who have recovered from COVID-19. Their naturally acquired active immunity is at par or even more robust than the artificially acquired active immunity from the first dose of vaccination. The first dose of vaccination in COVID-survivors is akin to the second/booster dose of vaccination prescribed for exposure naïve people. Hence bimonthly serological tests gauging IgG directed at the RBD-antigen are required before the second dose to postpone it till a drop in IgG-titre corresponding to mild levels of protection is observed.

UK-based investigators utilized the Gamma Exponential Decay Model (GEDM) and gamma plateau model (GPM) for predicting longevity of antibody

HCW	IgG-1	IgG-2	IgG-3	Computation of EI	EI	IgG-4
1	0	4.42	7	0+13.26+14	27.26	Vac
2	13	22	13	26+66+26	118	Vac
3	9.19	9.15	14.1	18.38+27.45+28.2	74.03	13.9
4	7.73	5.23	7.12	15.46+15.69+14.24	45.39	4.29
5	11.8	9.98	17.5	23.6+29.94+35	88.54	Vac
6	8.5	16.5	11.7	17+49.5+23.4	89.9	14.3
7	7.69	5.69	7.82	15.38+17.07+15.64	48.09	Vac
8	3.46	3.28	2.91	6.92+9.84+5.82	22.58	2.13
9	8.5	6.2	10.1	17+18.6+20.2	55.8	8.2
10	9.41	17.2	17.1	18.82+51.6+34.2	104.62	Vac
11	8.1	19.1	17.9	16.2+57.3+35.8	109.3	Vac
12	8.2	5.97	8.77	16.4+17.91+17.54	51.85	7.68
13	18.2	5.52	4	36.4+16.56+8	42.76	Vac
14	0	0	0	0	0	0
15	7.77	7.17	9.65	15.54+21.51+19.3	56.35	Vac
16	42.2	31.4	14.6	84.4+94.2+29.2	207.8	Vac
17	27.9	25.4	23.4	55.8+76.2+46.8	178.8	Vac
18	7.53	5.45	1.63	15.06+16.35+3.26	34.67	Vac

Table 2 — Trends in IgG-titres over time and Effective Immunity (EI=Effective immunity; IgG-1=IgG-titre at 1-2months post first symptom; IgG-2= IgG-titre at 3-4months post first symptom; IgG-3= IgG-titre at 6-7months post first symptom; IgG-4= IgG-titre at 8-9 months post first symptom; Vac=Vaccinated)

response to SARS-CoV-2 and reported that the half-lives for the nucleoprotein, RBD and spike protein antibodies were 60 days, 102 days and 126 days, respectively under GEDM[18]. The half-life of RBD antibodies was 110 days while that of spike protein antibodies was projected as 364 days under the GPM, which assumes long-lived antibodies.This implies that at 126 days post infection the IgG-titres should have reduced to half the original values as per GEDM and halved at 364 days post infection as per the GPM. The results of our study demonstrate that at 274 days post first-symptom/RTPCR positive result, the mean IgG-titre was 7.87AU which falls in the moderate protection range. This is not half of the mean titres recorded at 1-2 months post infection (11.13AU) which implies that the GPM is a better predictor of IgG longevity while the GEDM under estimates the half-life of IgG.

The main strength of our survey is its conduction on HCW in a hospital setting who bear the brunt of SARS-CoV-2 exposure as an occupational hazard and would benefit from results and transmit the benefit to the society as a whole in terms of better-organized deployment of healthcare workforce in operation theatres, emergency wards and COVID-intensive care units based on their IgG-titres. Also, the results are reproducible since blood-samples have been preserved in the institutional biorepository for future reference. The main limitation of our study is that all HCW could not be followed for 6-7 months after first symptom as initially planned, owing to the nationwide vaccination drive.

Conclusion

Adaptive active immunity acquired through natural infection may last for at least 9 months postinitial exposure and lies in the moderate protection range in 77% HCW. Moderate levels of protection were observed by our immunometric test at 9 months which can be extrapolated to vaccination and immunity passports. Vaccine can be used as a booster dose/second exposure in all COVID-survivors especially those with low IgG-titre. Periodic quantitative IgG-titre based serological tests can help guide timing of second shot of vaccination.

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