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Humoral response to SARS-CoV-2 vaccination after failure to develop adequate humoral immunity post natural exposure to the virus

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Abstract

Background: Active acquired immunity may be induced by natural exposure to a pathogen or via vaccination. Seventeen out of 214 health care workers (HCW) after testing positive by the RT-PCR test failed to develop any specific IgG-antibodies against SARS-CoV-2 even after repeated testing (IgG-titre <1 arbitrary unit). Another 35 HCW displayed a titre < 4.62AU (mild protection). These individuals were symptomatic too and successfully fought off the viral infection as well. We aimed to find out whether the COVID-recovered HCW with IgG titre <1AU develop any detectable antibodies post vaccination, the absolute antibody titre post vaccination in COVID-recovered HCW with pre-vaccination IgG titre <4.62AU, and also the signs/symptoms of any reaction to the vaccination.

Methodology: This prospective observational single-centric cohort study included 36 HCW of either sex, aged 18-70 years with either undetectable (<1AU) or very low (< 4.62 AU) IgG-titre after surviving laboratory confirmed

COVID-19. Non -vaccinated HCW were excluded. The IgG-antibody titre was tested 2weeks post first dose of COVISHIELD-vaccination and again at 28 days post second dose.

Results: All HCW with no (<1AU) to mild (1-4.62AU) IgG protection, post COVID-19 infection, developed high level (>18AU) of protection (13.65±9.63AU and 22.11±1.7AU, respectively),1-2 weeks post first dose of vaccination except 4HCW with a post-COVID-19 titre <1AU which failed to increase post-vaccination. Hence 30.77% of HCW who initially had an IgG titre <1AU continued with a titre<1AU post-vaccination. The mean IgG-titre after second vaccination was 16.4 ±2.9 AU and 22.03 ±1.4AU in HCW with prevaccination titre<1 and 1-4.62AU respectively.

Conclusion: The first dose of vaccine serves as a second exposure/booster dose for corona-survivors imparting protective IgG-titres and second dose/third exposure maybe postponed till such time the titres fall (>6 months later as against the current recommended 28days). COVID-survivors who failed to develop detectable antibodies should get priority-vaccination assuming higher susceptibility to re-infection. Serological testing post-vaccination can pinpoint individuals with persistent low IgG-titre, predicting which individuals are prone to re-infection by the same strain of virus.

Keywords: Corona virus, COVID-survivor, Immunity, Vaccination.

Introduction

Immunity can be categorized as innate or acquired. The former is non-specific/generic and is boosted by several vitamins, minerals and immunity boosting herbs (Indian gooseberry, giloy, forsythia). The latter is against a specific pathogen eg severe acute respiratory syndrome corona virus-2 (SARS-CoV-2). Acquired/adaptive immunity maybe passively acquired either naturally (from convalescent mother via placenta/breast milk) or artificially (convalescent plasma infusion). Active acquired immunity may be induced either by natural exposure to a pathogen by way of contracting a disease or by artificial exposure via vaccination (figure-1).

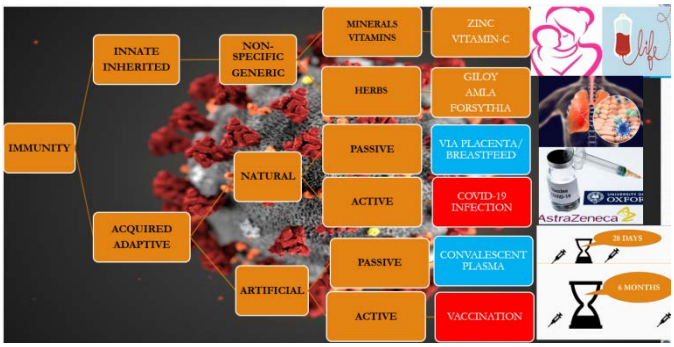

Figure-1: Infographic on immunity against SARS-CoV-2

Humoral (B-cell) immunity is by virtue of B-cells maturing into antibody secreting plasma cells and memory B-cells (pivotal role in secondary infection by same virus) after exposure to SARS-CoV-2. Effector function of antibodies includes neutralization of virus, opsonization and phagocytosis of virus, NK cell mediated antibody dependent cellular toxicity and complement activation (lysis of virus; phagocytosis after opsonization with complement fragment 3b; inflammation). IgG antibodies against the spike-RBD antigen are the last to develop but are long lasting and protective in high titres.[1]

IgG-based serological tests directed against receptor binding domain of spike protien epitope of SARS-CoV-2 are instrumental in diagnostic, seroepidemiologic, and vaccine evaluation studies.[2] Serological test results should not be visualized as binary. Seropositivity can be further quantified into three categories (1-4.62AU = low; 4.63-18AU = moderate; >18AU = high) with immense clinical implications. Low antibody titres provide little or no protection against re-infection and give a false sense of security. This is supported by a study on 3082

convalescent plasma recipients where transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels.[3] What is more alarming is that low antibody titres maybe harmful by triggering antibody dependent enhancement (ADE) in SARS-CoV-2, akin to that observed with other macrophage infecting viruses like dengue-virus. ADE in viral infections manifests via two definite pathways: firstly by augmentation of virus uptake into Fc-gamma-receptor-IIa (FcγRIIa) expressing phagocytes enhancing viral infection and replication, and secondly by disproportionate Fc-mediated antibody effector functions or immune-complex formation culminating in inflammation and immunopathology. Both ADE mechanisms are activated when non-neutralizing antibodies or sub-neutralizing/low titres of antibodies bind to viral antigens without stalling or clearing infection.[4]

Seventeen out of 214 health care workers (HCW) of Rajiv Gandhi Cancer Institute and Research Centre (RGCI) who had voluntarily got their IgG antibody titres tested 1-2months after testing positive by the reverse transcriptase polymerase chain reaction (RT-PCR; gold standard) failed to develop any specific IgG antibodies against SARS-CoV-2. Their IgG-titre was less than 1 arbitrary unit. Another 35 HCW displayed a titre < 4.62AU corresponding to mild protection.[5] Paradoxically, despite absent/low IgG titres, these individuals were symptomatic and they successfully fought off the viral infection as well. Fortunately, the Indian government has issued emergency use authorization (EUA) to three vaccines against COVID-19 (Covishield; Covaxin; Sputnik).[6] The vaccine may either produce no response in these HCW just like there was no response to natural infection or may serve as a booster dose leading to high titres of IgG corresponding to high levels of protection. This study aims to ascertain whether the above two subsets of HCW develop a protective IgG-antibody titre post COVID-19 vaccination. Our primary objective was to find out whether the COVID-recovered HCW with IgG titre <1AU develop any detectable antibodies post vaccination and to find out the absolute antibody titre post vaccination in COVID-recovered HCW with pre-vaccination IgG titre <4.62AU. Our secondary objective was to note the signs and symptoms of any reaction to the vaccination and any medication instituted for the same.

Methodology

This prospective, observational, single-centric, cohort study was conducted in accordance with the Helsinki Protocol after obtaining written informed consent from participating HCW, approval from the scientific committee and institutional review board and CTRI registration (CTRI/2021/04/032572). Thirty-six adult ASA I/II HCW were included in the study conducted at Rajiv Gandhi Cancer Institute and Research Centre (RGCI). The IgG antibody titre was tested at 1-2weeks post first dose of vaccination and again at 1 month post second dose of vaccination. Antibodies binding to the receptor binding domain (RBD) of the spike(S) protein of SARS-CoV-2 have neutralizing potential.[7-9] VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG, the IgG-test kit employed for serological tests at RGCIRC, is based on the high throughput automated chemiluminescence immunoassay (CLIA) technology. Antibodies tested are IgG isotypes produced against the spike protein of SARS-CoV-2. It is an immunometric test utilizing ECi/ECiQ, 3600, 5600/XT 7600 system requiring an intravenous serum sample of 20 µL tested at 37 °C with incubation time 37mins and time to first result 48mins. 90.0% Positive Percent Agreement to PCR and 100%

clinical specificity (95% CI: 99.1–100.0%), are additional characteristics.[10]

IgG titres <1AU are considered non-reactive, those between 1-1.46AU provide low level of immunity, those between 1.46-18.45AU confer medium levels of protection and values above 18.45AU provide high levels of protection.

The vaccine employed was COVISHIELD (ChADOx1 nCoV-19/AZD1222; chimpanzee adenoviral vector vaccine produced by Oxford-AstraZeneca; manufactured by Serum Institute of India)[11]

All HCW of RGCI, of either sex, aged 18-70 years with a history of testing positive for SARS-CoV-2 and having either undetectable (<1AU) or very low (< 4.62 AU) IgG antibody titre, were included in the study. HCW who did not get vaccinated against COVID-19 were excluded from the study

Sample size calculation

Sample size was limited by the HCW in the cohort who got vaccinated. Myriad reasons for non-vaccination include name missing from Government Registry for vaccination (8HCW), pregnancy(1HCW), apprehension about side effects (4HCW), notion that vaccine is ineffective (2HCW) or vaccine is not required (2HCW) and resignation from job (4HCW).

13 HCW with an antibody titre <1AU post COVID-19 infection and another 23 HCW with an IgG titre between 1-4.62 AU underwent voluntary vaccination.

Statistical Analysis

Continuous/quantitative variables were expressed as mean ± Standard Deviation whereas categorical/qualitative variables were expressed as numbers and percentage. Medcalc statistical software (version 15; MedCalc Software Ltd; Ostend, Belgium) was utilized for summary statistics, box-whisker plots, correlation scatter diagrams and deriving the regression equation. $P < 0.05$ was considered statistically significant. Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) was utilised for the analysis of descriptive statistics.

Results

The mean age with standard deviation was 38.3 ±7.6 years for HCW with IgG-titres<1AU and 33.6±9.4 years for HCW with IgG titres 1-4.62AU. 7/13 (53.85%) were female HCW and 6/13 (46.15%) were male HCW out of 13 HCW with IgG-titre<1AU whereas 16/23 (69.56%) and 7/23 (30.44%) belonged to the female and male gender respectively, amongst 23 HCW who had IgG-titres between 1-4.62AU (Table-1).

Table 1: Summary statistics and demographic profile

Category	IgG<1AU		IgG 1-4.62AU	
Age (years)	38.3 ±7.6		33.6±9.4	
Gender(M/F)	6(46.15%)/7(53.85%)		7(30.44%)/16(69.56%)	
Timepoint	Pre-Vac	Post-Vac	Pre-Vac	Post-Vac
Sample size (n)	13	13	23	23
Lowest value (AU)	0.0000	0.0000	1.4500	18.3000
Highest value (AU)	0.9400	23.4000	4.6200	25.4000
Arithmetic mean (AU)	0.2854	13.6454	3.3191	22.1087
95% CI for the mean	0.058 to 0.51	7.83 to 19.46	2.93 to 3.71	21.38 to 22.84
Median	0.01000	18.6000	3.5800	22.1000
95% CI for the median	0.0053 to 0.6722	0.04784 to 20.5405	3.0191 to3.7795	21.7000 to 22.6651
Variance	0.1421	92.7269	0.8185	2.8708
Standard deviation	0.3770	9.6295	0.9047	1.6944
Relative standard deviation	1.3210 (132.10%)	0.7057 (70.57%)	0.2726 (27.26%)	0.07664 (7.66%)
Standard error of the mean	0.1046	2.6707	0.1886	0.3533
Coefficient of Skewness	0.7145 (P=0.2334)	-0.819 (P=0.175)	-0.7703 (P=0.1062)	-0.3047 (P=0.5046)
Coefficient of Kurtosis	-1.4785 (P=0.0872)	-1.388 (P=0.123)	-0.3376 (P=0.8421)	0.3376 (P=0.5517)
Kolmogorov-Smirnov test for Normal distribution	D=0.3828 reject Normality (P<0.0001)	D=0.2973 reject Normality (P=0.0026)	D=0.1746 accept Normality (P=0.0671)	D=0.1438 accept Normality (P>0.10)

The mean IgG-titre in the cohort of 13 HCW who failed to develop any IgG antibodies post recovery from COVID-19 was 13.65±9.63AU, 1-2 weeks post first dose of vaccination. The cohort of 23 HCW with mean IgG 3.32±0.9AU (mild protection/1-4.62AU subset) 1-

2months post natural infection with coronavirus, developed a mean IgG-titre of 22.11±1.7AU (lowest 18.3AU; highest 25.4AU) 1-2weeks post-vaccination (Table-1). Box-whisker plots with boxes depicting the median (middle line) and first and third quartiles and the whiskers showing 1.5 times the Inter Quartile Range above and below the box(figure-2) show no outliers.

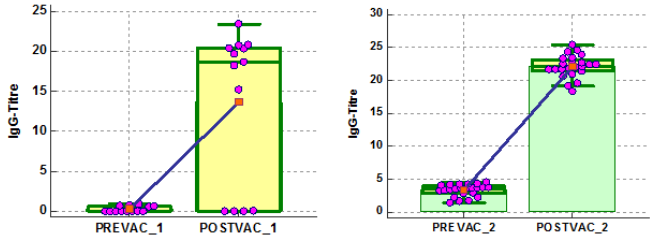

Figure 2: Box-whisker plots with boxes depicting the median (middle line) and first and third quartiles and the whiskers showing 1.5 times the Inter Quartile Range above and below the box

All HCW with no (<1AU) to mild (1-4.62AU) IgG protection, post COVID-19 infection, developed high level (>18AU) of protection 1-2 weeks post first dose of vaccination except four HCW all of whom had a post-COVID-19 titre <1AU which failed to increase post-vaccination. Hence 30.77% of HCW who initially had an IgG titre <1AU continued to have a titre <1AU post-vaccination as well.

A statistically significant positive corelation was observed between pre-vaccination IgG titres(x) and the IgG titres post first dose of vaccination(y) (r=0.58; p=0.038) in HCW with IgG-titre <1AU (Figure-3).

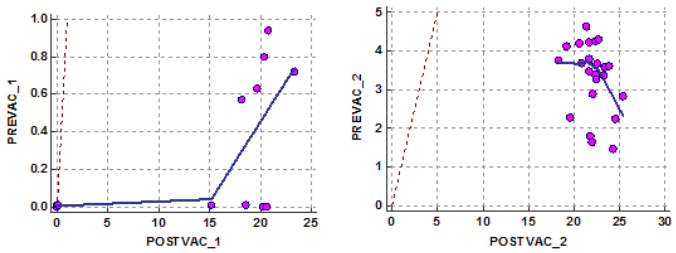

Figure 3: Scatter diagrams showing corelation between pre and post vaccination IgG-titres (PREVAC_1= Pre-vaccination IgG titres in the cohort of health care workers with post-COVID IgG-titres<1AU; POSTVAC_1= IgG titres after first dose of vaccine in the cohort of health care workers with post-COVID IgG-titres<1AU; PREVAC_2= Pre-vaccination IgG titres in the cohort of health care workers with post-COVID IgG-titres1-4.62AU; POSTVAC_2= IgG titres after first dose of vaccine in the cohort of health care workers with post-COVID IgG-titres 1-4.62AU).

The regression equation obtained (y = 9.43 + 14.8 x) has a coefficient of determination(r^2) equalling 0.34. A weak and statistically insignificant negative corelation was observed between pre-vaccination IgG titres and the IgG-titres post first dose of vaccination (r=-0.31; p=0.14) in HCW with IgG between 1-4.62AU. No clinically significant corelation was seen between the pre-vaccination IgG titres and the IgG titres post first dose of vaccination in the latter subset. There was no significant difference between IgG titres obtained 7-14days after first dose and those obtained 28days after second dose where the second dose was injected 28 days after the first dose in 14 of our HCW cohort except in two HCW with post-vaccination IgG of 0AU whose IgG-titre rose to 15.4 AU and 11.6AU respectively, 28 days after the second dose of vaccination. The mean IgG titre was 16.4 ±2.9 AU and 22.03 ±1.4AU in HCW with prevaccination titre<1 and 1-4.62AU respectively. The remaining HCW decided

against taking the second dose at 28 days gap and postponed it indefinately, depending on results of serial IgG-titres recorded every 2 months.

Adverse reactions post-vaccination and medication required

No correlation was observed between pre-vaccination IgG-titre and vaccine reactions. Pain at injection site was observed in 9 HCW followed by fever, myalgia, malaise, headache in 8 HCW each. 2HCW each developed chills and rash respectively and only 5HCW were completely asymptomatic (Figure-4).

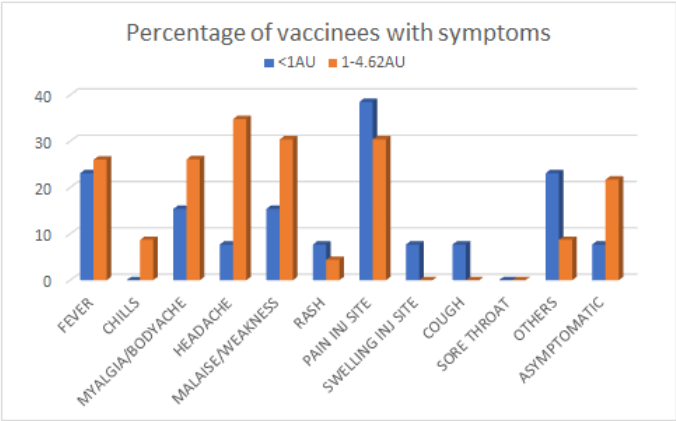

Figure 4: Percentage of vaccines with different symptoms until 1-week post-vaccination

Some HCW developed other symptoms like light headedness (2HCW), tingling and twitching sensation in the upper limb with injection site lasting 3days (amenable to crocin and allegra), pain abdomen lasting 4 days (requiring secnidazole and norfloxacin), aphonia lasting a week (treated with levocetrizine, azithromycin, voice rest) and calf pain lasting one day (figure-4). Twelve patients required paracetamol (Dolo-650, crocin, combiflam)

No corelation was observed between sign and symptoms developed post-vaccination and post vaccination IgG titre. In fact, 2 out of four patients with persistent <1AU IgG titre post-vaccination developed vaccine related reactions (malaise and headache for 4days and impaired taste for salt on 3rd day in one HCW and abdominal pain for 4 days plus injection site pain for a day in the other). Incidentally, these two patients have a Kashmiri lineage and this lack of humoral immunity maybe a yet unrecognized/undocumented phenomenon, like Kashmiri thrombocytopenia.[12] The third developed pain at injection site for 2days while the 4th HCW was asymptomatic.

Discussion

The average age of HCW with IgG titres<1AU was 5 years higher than that for HCW with IgG between 1-4.62AU even in this narrow age group of HCW aged 20-45years. Hence, age might be a contributary factor towards a weaker humoral response. An association between aging and compromised adaptive immune response to SARS-CoV-2 has been reported.[13] The same maybe applicable to adaptive immune response post-vaccination as well.

Percentage of males with an IgG titre<1AU was higher than males with IgG titre between 1-4.62AU implying that male gender too might influence IgG titre. This poorer adaptive immune response in males in our study corroborates with other studies reporting male bias in COVID-19 mortality, with the average male case fatality rate being1.7 times higher than that for females across 38 countries.[14]

Exposure to the virus is quintessential for development of active adaptive immunity against it. It takes 1-2 months for the IgG titres to peak after first exposure. Humoral response is quicker in onset (1-2weeks) after subsequent exposures to the same virus due to pre-existing memory B-cells. In COVID-survivors, the first exposure comprises contracting COVID-19, the second exposure comprises the first dose of vaccine while the second dose of vaccine is like a third exposure. Covishield vaccine gives a

consistent IgG titre between 20-25AU in most COVID-survivors with IgG-titre<4.62AU, just 1-2 weeks post first dose. The first vaccine shot serves as a booster dose for individuals already exposed to the virus by contracting COVID-19 infection, and results in protective, neutralizing, antibody production.

A small standard deviation in the mean IgG-titre post-vaccination is explained by the fact that vaccine shots comprise a fixed quantum of virus as against natural exposure with variable viral loads corresponding with different cycle threshold (CT) values in the gold standard RT-PCR test. A negative correlation has been observed between CT-value and viral load (17-24=high viral load; >31=low viral load).

From our study it can be seen that a fixed viral load translates into a narrow range of post-exposure IgG-titres.The post vaccination titres (after first dose) are predictable (20-25AU), high and protective (>18AU). Health ministry GOI has granted emergency use authorization to two vaccines (covaxin and Covishield) and recommends two doses of vaccine 28 days apart for all individuals since second dose increases vaccine-effectivity.[6,15] A week back the window period has been increased to 6-8 weeks for COVISHIELD but not for covaxin.There exist no separate guidelines for vaccination of individuals with prior exposure to the virus (COVID-survivors). Pre-vaccination serological testing for IgG-titres has an important role in determining whether and when to give the second shot of vaccination. There is no significant difference between IgG-titres obtained 7-14days after first dose and those obtained 28days after second dose when the second dose is injected 28 days after the first dose in our HCW cohort. The increment in IgG titre after second vaccine dose in our study was roughly “22 minus vaccination titre after first vaccine dose”, where 22.11AU was the mean IgG titre after first dose. Hence, the second dose acts like a third exposure and may not even be required in COVID-survivors. Second dose maybe safely postponed in these individuals till such time their titres fall below 4.62AU. This gives a window period of at least 6-7months as against the current recommended 28days gap.

Individuals who failed to develop detectable antibodies post-recovery from natural COVID-19 infection should get vaccinated on a priority basis since they have the highest chance of re-infection. If they fail to develop IgG titres above 1AU post first dose/ second exposure, they may still develop an adequate IgG-titre, a month after the second dose. This can be extrapolated to COVID-naïve individuals undergoing vaccination. A third dose of vaccine/third exposure may be the solution in that subset of individuals who fail to develop any protective titres of IgG after the first two doses of vaccine akin to development of moderate levels of antibodies in two of our HCW who failed to develop IgG-titres after first (COVID-infection) and second (first dose of vaccine) exposures but developed moderate levels after the third-exposure (second vaccine-shot)

Serological testing post-vaccination can pinpoint individuals with persistent low IgG-titre and hence predict which individuals are prone to re-infection by the same strain of virus even post vaccination. Otherwise these individuals may be harmed by a false sense of security and may refrain from face-mask usage, social distancing and repeated handwashing akin to the Peltzman effect that describes how a perception of safety increases the risk.[16]

All HCW with no (<1AU) to mild (1-4.62AU) IgG protection, post COVID-19 infection, developed high level (>18AU) of protection 1-2 weeks post first dose of vaccination except four HCW all of whom had a post-

COVID-19 titre <1AU which failed to increase post-vaccination. 36.4% of HCW who initially had an IgG titre <1AU continued to have a titre <1AU post first dose of vaccination.

This phenomenon of non-development of IgG antibody response can be explained in at least five ways. Firstly, lets scrutinize the possibility that the RT-PCR test was false positive. This does not account for their typical COVID-19 symptoms and moreover RT-PCR is considered the gold standard with no false positives. This points towards some clerical error in printing the antibody-titre report or a mix-up of blood samples, or the antibodies might not have developed at 1-2months post exposure (outliers). To rule out these possibilities two successive antibody tests, at 1-2months and again at 3-4 months post infection (positive RTPCR/ first symptom) were performed with same results. The probability of two successive reports in the same individual having some clerical error is negligible and 3-4 months is more than sufficient time required to develop IgG antibodies.

The IgG antibodies might have peaked early and disappeared by the time the blood sample was taken. In this subset of outliers, even a repeat test is futile.

A second possibility is that IgG antibodies (or even IgA or IgM subtypes) directed against antigens other than spike RBD may have neutralized the natural infection in these HCW.[17] A valid apprehension stems that Covishield vaccine contains only the spike RBD antigen of SARS-CoV-2 and the ungauged/invisible subset of IgG antibodies against other epitopes/antigens may not have been boosted by vaccination.

A third possibility is that, although these HCW did not develop any humoral immunity, they developed cell mediated immunity (CMI; Helper T-cells for phagocytosing the viruses via macrophages; Cytotoxic T-cells for lysis of virus-laden body cells) which played a dominant role in their recovery. Since no tests were carried for T-cell immunity we do not know for sure the status of CMI.

A fourth possibility is that their body lacks the resources to form antibodies or the repertoire of molecules in their HLA-haplotype makes them more susceptible to SARS-Co-V-2 infection.[18] If this is true, then these HCW should not have developed antibodies after vaccine inoculation as well, which seems to be the case with the 4 HCW whose pre-vaccination IgG-titres were <1AU and which continued to remain <1AU post-vaccination. Conversely, in remaining 9 HCW with IgG-titres <1AU, 1-2m post first symptom of COVID-19, the first dose of vaccine acted like a booster dose and high titres of IgG were actually detectable post-vaccination.

Disease severity is also reported to have a direct relationship with antibody titres. But three out of four of these HCW had more severe symptoms than HCW with higher IgG titres.

Lastly, current trials report a Covishield vaccine efficacy ranging from 70-76% (100% efficacy in preventing severe/critical disease and hospitalization).[10,19] So, the vaccine might have been ineffective in generating IgG in these HCW as expected in 1/4th of COVID-naïve individuals who receive it, but nevertheless, despite working in the hospital milieu with constant exposure to COVID-19 patients none of the HCW became symptomatic again.

R-squared is the proportion of the variance in the response variable (y/IgG post first vaccination) that can be explained by the predictor variable (x/pre-vaccination IgG) and in our study x explains one third of variance in y.

None of the HCW developed serious vaccine related adverse effects. A German study reports an incidence of 1

in 90000 vaccinations for vaccine induced prothrombotic immune thrombocytopenia although COVISHIELD was found to be generally safe.[20]

Conclusion

The first dose of vaccine serves as a booster dose for individuals already exposed to the virus by contracting COVID-19 infection and results in protective antibody production. Second dose of COVISHIELD vaccine maybe postponed in these individuals for at least 6-7 months, as against the current recommended 28days. Individuals who failed to develop detectable antibodies post-recovery from natural COVID-19 infection should get vaccinated on a priority basis since they have the highest chance of re-infection. Serological testing post-vaccination can pinpoint individuals with persistent low IgG-titre and hence predict which individuals are prone to re-infection by the same strain of virus.

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