The European Research Journal 2022;8(6):851-858 Original Article

DOI: 10.18621/eurj.1132682 *Public Health*

Post-COVID-19 vaccine SARS-CoV-2 antibody investigation in healthcare professionals

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ABSTRACT

Objectives: Main purpose of this study was evaluating inactive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine subsequent anti-S1 IgG feedback and the aspects involved in such reactions for professionals in healthcare (HCP) as the dominant risk group.

Methods: Thirty-six HCPs with previous COVID-19 infection and 164 with no priors, 200 in total, who was working in the Ankara Public Health Molecular Diagnosis Laboratory were included. Main tool of identifying humoral immune response quantifably in serum samples which were obtained 28 days after administering each of two doses of vaccine was Roche Elecsys SARS-CoV-2 kit.

Results: Average antibody levels of 164 negative HCPs were 15.82 ± 8.59 IU/mL and 26.042 ± 10.73 IU/mL while 36 positive HCPs demonstrated antibody responses as 66.083 ± 33.927 IU/mL and 90 ± 27.012 IU/mL 28 days after each of two doses of vaccine for both individual groups respectively. A statistically meaningful difference was found in antibody levels after two vaccine doses in both groups ($p < 0.0001$). The authors observed statistically higher average antibody levels after initial vaccine dosage in HCPs with infection than the antibody levels of naive individuals after second dose ($p < 0.0001$). Age, gender and vaccination feedback did not have a statistically meaningful disparity ($p > 0.05$).

Conclusions: It was concluded that the average antibody level achieved after inital dose n HCPs with COVID-19 infection was surpassing the average antibody level obtained after the second dose in naive HCPs. The authors recommend further clinical researches on antibody levels and the extent of protection to prohibit COVID-19.

Keywords: SARS-COV-2, anti-S1 IgG response, health care professionals, COVID-19

New severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is an enveloped and single-stranded RNA virus that belongs to Coronaviridae family that causes the infectious respiratory disease Coronavirus disease 2019 (COVID-19) [1]. More than 430 million confirmed cases of COVID-19 have been reported worldwide with more than five and a half million deaths by the end of February 2022 according to World Health Organization (WHO) data [2] for coronavirus disease which was declared a pandemic by the WHO on March 11, 2020 [3]. Pandemic lead to an increased danger of vocational liability

Received: ***June 18, 2022;*** *Accepted:* ***August 17, 2022;*** *Published Online:* ***October 19, 2022***

How to cite this article: *Gürer Giray B, Güven Açık G, Baş SM, Bulut YE, Kotanoğlu MS. Post-COVID-19 vaccine SARS-CoV-2 antibody investigation in healthcare professionals. Eur Res J 2022;8(6):851-858. DOI: 10.18621/eurj.1132682*

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e-ISSN: 2149-3189

against a novel and rapidly advancing infection for health and care workers (HCPs) worldwide and thus establishing a set of requirements to accommodate new obligations and aspects for a spacious scope of duties and professional services [4]. Research carried out earlier demonstrate the escalation of infection rates in symptomatic and asymptomatic HCPs up to 14% and 7.1% respectively which surpass the percentages reported by the prevailing demographic studies to date and proposes a professional hazard [5, 6]. Preventing COVID-19 infections in hospitals for HCPs and their families is significant but surging numbers of HCP demise nationally and internationally indicate this premise is being disregarded [7].

Steep movement of proinflammatory immune cells induces acute respiratory distress syndrome, septic shock, bleeding and coagulation dysfunction in intense conditions [8]. 16 nonstructural proteins four structural proteins as of spike (S), envelope (E), membrane (M), and nucleocapsid (N) are encoded by Sars-CoV-2 genome [9]. Viral spike (S) protein engagement with host angiotensin-converting enzyme 2 (ACE2) receptor commences host cell infections by SARS-CoV-2 [10]. The S glycoprotein weighs 180 kDa and consists of two subunits as S1 and S2 [11]. The S1 subunit is one of the best immunological targets for antibodies that neutralize SARS-CoV-2 due to its neutralizing antibody induction capacity and species-specific antigenic specificity. while containing the receptor-binding domain (RBD) responsible for virus entry into the host cell via the ACE2 receptor [12, 13].

The humoral immune response can hinder contagion by subduing antibodies that restricts the virus in a way that inhibits host cell infection [2]. This condition can be fulfilled by obstructing spike-ACE2 receptor interaction or by disturbing fusion system the virus fancies to infiltrate host cell cytoplasm for SARS-CoV-2 [14]. Antibodies targeting the spike (S) glycoprotein and the nucleocapsid (N) protein play a role in the humoral immune response against SARS-CoV-2. Such antibodies neutralize viral infection of human cells and tissues that express angiotensin converting enzyme 2 (ACE2) [12, 15]. Efforts to develop vaccines to control the pandemic started early and today vaccines based on different principles such as mRNA vaccines, adenoviral vector-based vaccines and inactivated virus vaccines are being utilized after phase studies [16, 17].

SARS-CoV-2 vaccines depend on a strategy that induces humoral and cellular immune response and neutralizes antibodies against the virus' S protein which plays an important role in infecting cells or RBD based on its strategy [18, 19]. CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences Co., Ltd. (Beijing, China). CoronaVac vaccine phase 1/2 studies were initiated in China and the vaccine was demonstrated inducing neutralizing antibodies after it was shown to be safe and immunogenic in different animal models such as rodents and non-human primates [20, 21].

SARS-CoV-2 vaccine administration have been initiated after phase 3 with HCPs priority and then to high-risk groups on January 11, 2021 in Turkey. This program was composed of two intramuscular doses of CoronaVac 600 U/0.5 mL (Sinovac Life Science Co, Ltd, Beijing, China) vaccine 28 days in between each dose. The BNT162b2 vaccine (Pfizer-BioNTech) was included in the immunization program with two doses administed with four-week intervals. 52,798,119 people in our country were vaccinated with two doses of SARS-CoV-2 vaccine as of February 28, September 2022 [22]. In this study, it was aimed to determine the antibody responses that occur after two doses of inactivated SARS-CoV-2 vaccine (CoronaVac) administration in HCPs in the COVID-19 risk group and to assess factors leading to this response.

METHODS

Study Design and Ethics

This study was performed with the approval of the TR Ministry of Health COVID-19 Scientific Research Evaluation Commission (Decision No: 2021-12-07T01_19_42) and the approval of the TR Ministry of Health Sciences University Ankara Training and Research Hospital Clinical Research Ethics Committee (Decision No: E-21-859). Samples were obtained after written informed consent had been obtained, and all procedures were performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Study Population and Samples

200 HCPs working in Ankara Provincial Health Directorate Public Health Molecular Diagnosis

COVID-19 Laboratory were included in the study after obtaining informed consent. Blood samples were collected 28 days after both initial and follow-up vaccine doses administered to HCPs. Age, gender, smoking and COVID-19 infection status were recorded to determine the factors that may affect the SARS-CoV-2 antibody response.

Antibody Measurements

Four to five ml blood samples of health worked included in the study were taken into ethylenediamine tetra acetic acid (EDTA) tubes, centrifuged at 4000 rpm for 10 minutes and serum samples were separated. Serum samples were stored at -80°C until they were included in the study. SARS-CoV-2 total antibodies (IgM and IgG) were quantitatively identified by the electrochemiluminescence immunological (ECLIA) process and the Elecsys® Anti-SARS-CoV-2 kit (Roche Diagnostics GmbH, Germany) involving recombinant protein representing the receptor-binding site (RBD) of S1 antigen. The assessment scope of the kit is between 0.40-250 U/mL and values above 0.80 U/mL are acknowledged as positive in result details as recommended by the manufacturer Roche. Results are automatically calculated in the form of a cut-off index (COI) [23].

Statistical Analysis

Percentage and frequencies were used for categorical variables in statistical analysis. Normality assumption was carried out with Shapiro-Wilk and Kolmogorov-Smirnov tests. Independent t test was used to compare independent variables and paired sample t-test was used to compare dependent variables. One-way variance analysis and bonferroni post-hoc analyses were applied in cases where there were more than two groups. The statistical significance level (*p* value) was determined as 0.05 in all analysis, and they were performed with the R software version 3.6.0.

RESULTS

One hundred twenty-two (62%) of the 200 HCPs included in the study were female and 76 (38%) were male with a mean age of 43.69 ± 1.17 years (range: 24 to 65 years) (Table 1). The occurrence of having pre-

Table 1. Demographic characteristics of healthcare professionals

	Total (n = 200)	COVID-19 negative (n = 164)	COVID-19 positive (n = 36)	*p value*
Age (years), n (%)				0.71
Mean ± SD (range)	43.69 ± 1.17 (24-65)	43.78 ± 1.34 (24-64)	43.17 ± 2.27 (28-57)	
24-35	40 (20)	34 (20.7)	6 (16.7)	
36-45	74 (37)	60 (36.6)	14 (38.9)	
≥ 46	86 (43)	70 (42.7)	16 (44.4)	
Gender, n (%)				**0.004**
Female	124 (62)	104 (63.4)	20 (55.6)	
Male	76 (38)	60 (36.6)	16 (44.4)	
Smoking status, n (%)				0.97
No	146 (73)	130 (79.3)	16 (44.4)	
Yes	54 (27)	34 (20.7)	20 (55.6)	
Adverse effect, n (%)				0.36
First post-dose	54 (27)	32 (19.5)	22 (61.1)	
Second post-dose	68 (34)	44 (26.8)	24 (66.7)	

SD = standard deviation

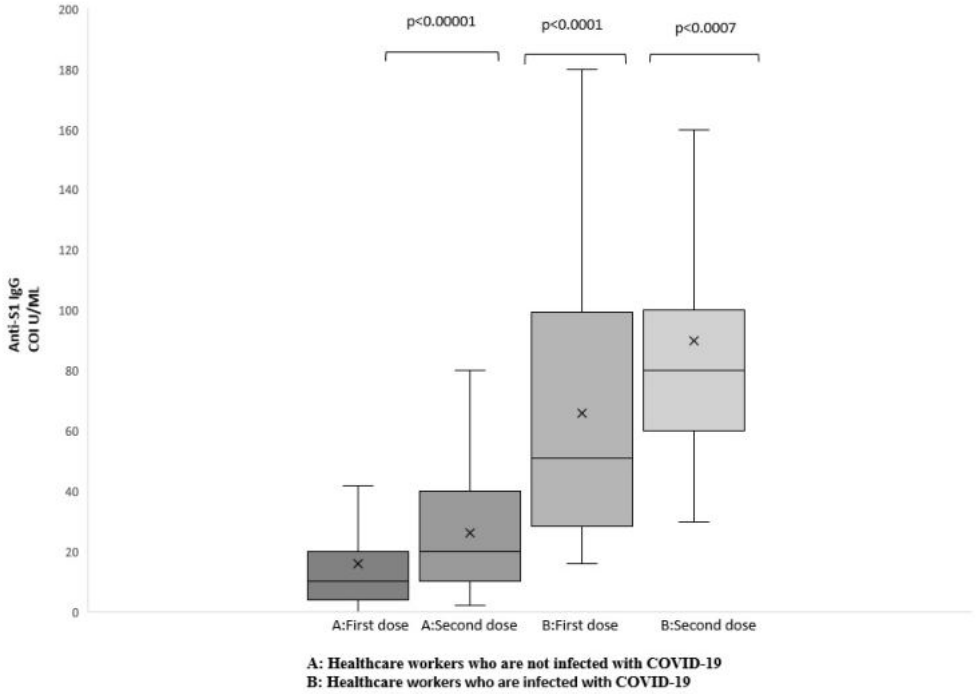

Fig. 1. Antibody response after first and second doses of vaccine.

vious COVID-19 infection confirmed with real-time reverse transcriptase polymerase chain reaction (rT-PCR) was determined as 18% (n = 36). There was no significant difference between the groups with and without COVID-19 infection in terms of age ($p = 0.71$) and smoking ($p = 0.97$) except for gender ($p = 0.004$) according to the data collected to identify the factors affecting the antibody response to the inactivated SARS-CoV-2 vaccine (Table 1). It was found out that 36 HCPs who had COVID-19 infection 65 days (day = 15-150) ago on average had 100% antibody response after the first and second doses of vaccine and the average antibody levels were 66.083 ± 33.927 and 90 ± 27.012. The antibody responses of 164 (82%)

Table 2. Factors affecting inactivated SARS-CoV-2 vaccine response

	Individuals without COVID-19 infection (n = 164)					Individuals with COVID-19 infection (n = 36)				
	n	First dose PVAE, COI (mean + SD)	*p value*	Second dose PVAE, COI (mean + SD)	*p value*	n	First Dose PVAE, COI (mean + SD)	*p value*	Second Dose PVAE, COI (mean + SD)	*p value*
Age (years)										
24-35	34	18.35 ± 8.011	0.49	28.38 ± 9.03	0.74	6	54.5 ± 20.32	0.76	73.33 ± 9.65	0.22
36-45	60	16.13 ± 8.59		25.83 ± 11.39		14	66.07 ± 32.19		85 ± 24.74	
≥ 46	70	14.32 ± 8.78		25.08 ± 11.09		16	70.43 ± 38.72		100.62 ± 31.05	
Gender										
Female	104	14.62 ± 7.55	0.24	24.74 ± 10.23	0.27	20	72.25 ± 29.95	0.35	92 ± 25.66	0.7
Male	60	17.97± 10.50		28.3 ± 11.54		16	58.375± 35.49		87.5 ± 25.04	
Smoking status										
Yes	34	21.32 ± 12.13	0.08	34.55 ± 11.32	**0.03**	20	67 ± 38.57	0.89	90 ± 29.73	1
No	130	14.38 ± 7.36		18.84 ± 10.23		16	64.937 ± 27.72		90 ± 23.31	

COI = cut-off index, PVAE = post-vaccination adverse effect

HCPs who did not have COVID-19 infection were 97.56% (n = 160) and 100% (n = 164) 28 days after each of the two vaccine doses while average antibody levels were determined as 15.82 ± 8.59 and 26.042 ± 10.73 respectively (Table 2). Moreover, it was determined that the average antibody level of HCPs with COVID-19 infection after the first dose of vaccination was higher than the average antibody levels of HCPs who did not have COVID-19 infection after the second vaccine dose and there was a statistically meaningful variance (Fig. 1). ($p < 0.001$).

A statistically important discrepancy was detected between the antibody levels of initial and following vaccine dose in both groups (Fig. 1). Average antibody levels of HCPs aged 24-35, 36-45 years and ≥ 46 years old who were not infected with COVID-19 were determined as 28.38 ± 9.03 IU/mL 25.83 ± 11.39 IU/mL, 25.08 ± 11.09 IU/mL respectively after second vaccine dose. There was no statistically compelling difference between average antibody level and age (Table 2) ($p > 0.05$). 20 (55.6%) of the HCPs with COVID-19 infection were female and 16 (44.4%) were male. The average antibody levels after the first dose of vaccination were 72.25 ± 29.95 and 58.375 ± 35.48 IU/mL while the antibody levels were determined as 92 ± 25.66 IU/mL and 87.5 ± 25.04 IU/mL respectively after the second dose of vaccination. It was found out determined that there was no statistically significant difference in the antibody response after the first and second doses of vaccine (Table 2) ($p > 0.05$).

Post-vaccination adverse effect (PVAE) was observed in 27% (n = 54) and 34% (n = 68) of the patients after two doses (Table 2). It was observed that there was no statistically significant difference in terms of PVAE after the first and second doses of inactivated SARS-CoV-2 vaccine in all HCPs with respect to PVAE ($p > 0.05$). The distribution of PVAE observed after the first and second vaccine doses is given in Fig. 2. The average post-dose antibody levels of smoking HCPs with and without COVID-19 infection were 34.55 ± 11.32 IU/mL and 90 ± 29.73 IU/mL while non-smokers were determined as 18.84 ± 10.23 IU/mL and 90 ± 23.312 IU/mL respectively. A statistically convincing divergence was determined between smoking and antibody feedback in HCPs who did not have COVID-19 infection (Table 2) ($p = 0.03$).

DISCUSSION

Investigation of definitive antibodies ensuing active immunization in managing COVID-19 pandemic has an important place both in the vaccine development and approval process and in the follow-up of vaccinated individuals [24]. In this study, it was determined that 95.12% (n = 156) and 100% (n = 164) antibody response was achieved 28 days after the first and second dose of inactivated SARS-CoV-2 vaccine administration in HCPs who did not have COVID-19 infection respectively while 100% antibody response was obtained after initial vaccine dose in HCPs with previous COVID-19 infection. 100% anti-RBD IgG seroconversion was reported after the second vaccine in the 18-59 age cluster in the phase 1 and phase 2

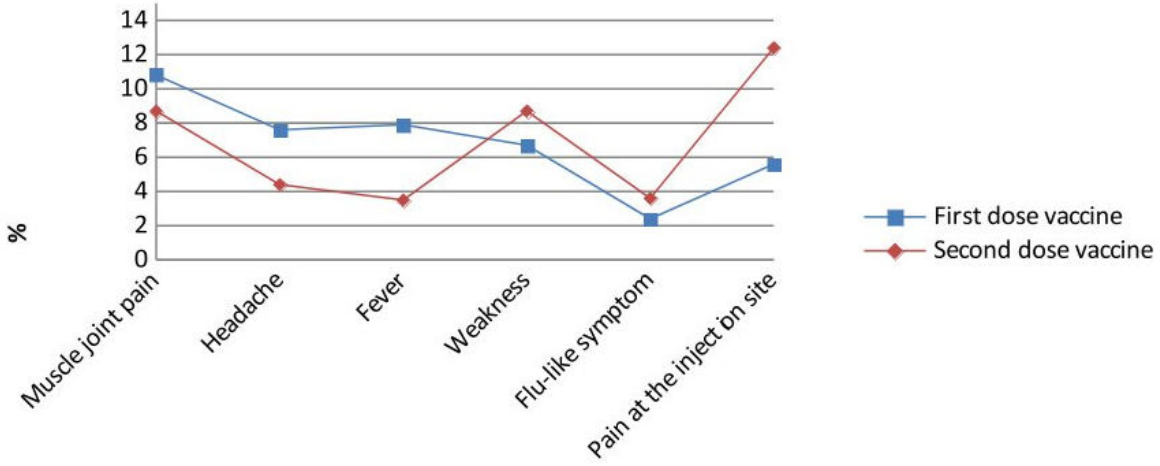

Fig. 2. The distribution of post-vaccination adverse effect (PVAE) (%) after the first and iconic dose of vaccine administration.

clinical trials of the inactivated SARS-CoV-2 vaccine [25].

Antibody responses were found as %92 for BNT162b2/Pfizer-BioNTech and %100 for 1273/Moderna as SARS-CoV-2 mRNA vaccines; 92.9% AstraZeneca and %100 for Sputnik V (rAd26-S and rAd5-S) as viral vector vaccines while 96% and %100 for BBIBP-CorV/Sinopharm as inactivated virus vaccines used worldwide [26-29].

The fact that SARS-CoV-2 vaccines provide different levels of seroconversion shows that the technology used in vaccine production and target antigens affect the antibody response. Antibody level variation after the initial vaccine dose can be explained by the rapid and strong antibody response of individuals with COVID-19 infection due to the secondary immune response. HCPs without previous SARS-CoV-2 infection demonstrated substantially less anti-S antibodies levels at the second (mean 73.2 vs 55.2 U/mL; $p < 0.05$) and third (mean 73.2 vs 55.9 U/mL; $P < 0.01$) measurements when compared with a first-time measurement in another study performed with a similar method to our study. HCPs with prior SARS-CoV-2 infection yielded higher anti-S antibody concentration levels at different measurements. Similar to the results of our study, the outcome of this study proposes that vaccines may promote the memory immune cells that flourish post-infection those are achieving more antibody response which is possibly more vigilant and durable against SARS-CoV-2 infection [30].

In this study, the authors resolved that the average antibody level obtained after first vaccine dose in HCPs with COVID-19 infection was statistically significantly greater than the average antibody level achieved after the second vaccine dose in naïve HCPs. Secondary immune reaction in individuals with COVID-19 infection due to memory B cells activated after vaccination leads to higher antibody response compared to naive individuals. Similar to our study, only one dose of inactivated SARS CoV-2 vaccine was determined to provide rapid and high humoral response because of secondary immune activity in individuals with COVID-19 infection and antibody levels after a single dose vaccine was higher than the second vaccine of naïve individuals [31].

Most of the vaccine studies adopts neutralizing antibody activation approach. Plaque reduction neutralization and microneutralization tests based on the use of live virus particles are virological fundamental methods of showing distinct SARS-CoV-2 neutralizing antibodies. 5-7 days long incubation duration and biosafety level III laboratory obligation of these tests highly limits their routine use [32, 33]. Therefore, it may be an alternative to use serological SARS-CoV-2 tests which do not require an equipped infrastructure, have high efficiency and are cheaper than neutralization tests as a marker to show neutralizing antibody presence [32]. IgM, IgG, and IgA response can be demonstrated by using varying antigenic targets such as C and N proteins, S1 subunit of protein S and RBD in serological tests [34].

In a meta-analysis [35], it was reported that antibodies against N protein do not have a neutralizing effect on SARS-CoV-2 since this antigen is in the envelope structure. Therefore, serological tests seeking surface structures such as SARS-CoV-2 S1 antigen and RBD are recommended if it is not possible to carry out neutralization tests. It was found that the humoral immune response was statistically significantly higher in women and individuals under 37 years of age in a study using mRNA vaccine [36].

In another study using mRNA-based vaccine [26] it was reported that there was a statistically significant relationship between antibody response and age, and the highest antibody levels were found in the cluster below 30 years of age like our study. Twenty (37.03%) smokers were SARS-CoV-2 positive in our study and it has been determined that smokers who have not had COVID-19 infection previously have a higher antibody response to the inactive SARS-CoV-2 vaccine. In other studies smoking is correlated with lower ab titres after COVID-19 vaccination contrary to our findings [37, 38].

CONCLUSION

The effect of various factors such as race, ethnicity, age, gender and smoking status on the antibody response to vaccines based on different principles needs to be investigated in SARS-CoV-2 vaccine studies. The most important limitation of this study is that the SARS-CoV-2 antibody levels of the vaccinated individuals were not identified before the vaccine administration. However, high anti-S IgG levels detected 28 days after the first dose of vaccine in individuals di-

agnosed with COVID-19 infection with RT-PCR positivity can be explained by secondary immune response which distinguishes the naive individuals. Administration of a single dose of subdued SARS-CoV-2 vaccine in COVID-19 positive individuals accomplished higher antibody levels achieved with two doses in naive individuals. However, antibody level that provides protection in COVID-19 infection or the duration of protection has not yet been fully explained. Consequently, there is a need for prospective studies on how long the immunity provided by SARS-CoV-2 vaccines will continue.

Authors' Contribution

Study Conception: BGG, GGA; Study Design: BGG, MSK; Supervision: GGA, YEB; Funding: N/A; Materials: GGA, SMB; Data Collection and/or Processing: BGG; Statistical Analysis and/or Data Interpretation: BGG, YEB; Literature Review: GGA, SMB, YEB; Manuscript Preparation: BGG and Critical Review: MSK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgment

We would like to thank to our colleagues who have not spared their days and nights, who have been away from their children, homes and loved ones since the pandemic started, who did not leave the laboratory for months and all the healthcare workers in our country who struggled under the same conditions.

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