
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 40 (2022) 52–58

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Inactive SARS-CoV-2 vaccine generates high antibody responses in healthcare workers with and without prior infection

Harika Oyku Dinc [a,b], Nese Saltoglu [c,*], Gunay Can [d], Ilker Inanc Balkan [c], Beyhan Budak [c], Dogukan Ozbey [b], Bilge Caglar [c], Rıdvan Karaali [c], Bilgul Mete [c], Yesim Tuyji Tok [b], Yagmur Ersoy [b], Mert Ahmet Kuskucu [b], Kenan Midilli [b], Sevgi Ergin [b], Bekir Sami Kocazeybek [b]

[a] Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Bezmialem Vakıf University Istanbul, Turkey
[b] Department of Medical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul 34098, Turkey
[c] Department of Infectious Diseases and Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul 34098, Turkey
[d] Department of Public Health, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul 34098, Turkey

ARTICLE INFO

*Article history:*
Received 8 June 2021
Received in revised form 9 October 2021
Accepted 17 November 2021
Available online 22 November 2021

*Keywords:*
COVID-19
CoronaVac
Chemiluminescent microparticle immunoassay
Healthcare workers
the anti-spike/RBD antibody

ABSTRACT

*Background and Objectives:* Healthcare workers (HCWs) were among the first groups to be vaccinated in Turkey. The data to be obtained by the vaccination of HCWs would guide wide spread vaccination programs.

*Materials and Methods:* The study included 330 HCWs working at Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Hospital and vaccinated with inactive CoronaVac (Sinovac Life Sciences, China) SARS-CoV-2 vaccine in two doses (28 days apart). Anti-Spike /RBD IgG levels were measured 14 days after the first dose and 28 days after the second dose. Chemiluminescent microparticle immunoassay (CMIA) (ARCHITECT IgG II Quant test, Abbott, USA), which is 100% compatible with plaque reduction neutralization test (PRNT), was used.

*Results:* Of the participants, 211 (63.9%) were female, 119 (36.1%) were male, and mean age was 39.6 ± 7. 7 years. In those without prior COVID-19 history; (n = 255) antibody positivity was detected as 48.2% (95% CI: 42.1–54.3) 14 days after the first dose of vaccine, and 99.2% (95% CI: 98.1–100) at day 28 after the second dose. Antibody titers were significantly lower in patients with hypertension (p = 0.011). In those with prior history of COVID-19 (n = 75); both the antibody positivity rates after the first vaccine (48.2% vs 100%, p = 0.000) and the anti-spike/RBD antibody levels after the second vaccine (with a $\geq$ 1050 AU/mL titer equivalent to PRNT 1/80 dilution) was significant than infection-naive group (25.9% vs. 54.7%, p = 0.000). Antibody positivity after two doses of vaccination for all study group was 99.4% (95% CI: 98.6–100).

*Conclusions:* Two doses CoronaVac produce effective humoral immunity in HCWs. Antibody response is significantly higher in those with prior history of COVID-19 than infection-naive group. Given no significant benefit of the second dose, a single shot of vaccination may be sufficient for those with prior history of COVID-19. Monitoring humoral and cellular immune responses, considering new variants, is required to validate this approach.



## 1. Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to cause high morbidity and mortality worldwide [1]. As of Oct 4, 2021 worldwide, 234.809.103 confirmed cases of SARS-CoV-2 infection had been reported, 4.800.375 of which resulted in death [2]. A total of 7.238.267 people have been infected in Turkey throughout this period, and 64.661 of these have died [3]. Despite these devastating consequences of the Covid-19 pandemic, it is promising that many vaccines are available today.

CoronaVac vaccine, produced by Sinovac Life Sciences (Beijing, China) using the conventional inactivation technique, develops immune response against the entire viral proteins including matrix, envelope, nucleoprotein structures and spike protein of

* Corresponding author at: Department of Infectious Diseases and Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul 34098, Turkey.
*E-mail address:* saltoglu@iuc.edu.tr (N. Saltoglu).

https://doi.org/10.1016/j.vaccine.2021.11.051
0264-410X/

SARS-CoV-2. In phase 2 clinical trial, 97% seroconversion was reported 28 days after CoronaVac (3 μg on day 0 and day 28) administration [4]. In the phase 3 study, efficacy rates remained high, though varying between 51 and 84%, according to the countries [5]. However, the protective efficacy of current vaccines against infection and re-infection and the duration of protection in real life, are still unclear.

In Turkey, the Ministry of Health approved the use of CoronaVac (Sinovac) on 13.01.2021, and vaccination was launched first in the healthcare workers (HCWs). At Cerrahpaşa "COVID-19 Adult Vaccination Center", the first dose of vaccines were administered to 2426 HCWs between January 15 and 25, 2021. The second vaccinations were administered in the following month.

The primary aim of this study is to quantitatively detect IgG antibody levels in blood samples of HCWs, obtained 14 days after the first dose of the vaccine and 28 days after the second dose, and to monitor the time-dependent changes in the antibody levels. HCWs who were administered SARS-CoV-2 inactivated vaccine were divided into two groups as those with prior history of COVID-19 (recovered at least 4 months ago) and those with no evidence of prior infection. The aim here is to determine whether there is a difference between antibody levels in those who have had the disease and those who have not. We also aimed to determine whether there is a difference in antibody levels between those who have had and those who have not comorbidities. The second aim of this study was to reassess antibody levels in the long term (3rd and 6th months) and to determine whether HCWs were infected with SARS-CoV-2 during this time period as an indicator of long-term protection.

## 2. Methods

The study included 346 healthcare professionals who were administered the first dose of CoronaVac (Sinovac Life Sciences, Beijing, China) between 15.01.2021 and 28.01.2021, and the second dose between 18.02.2021 and 05.03.2021. The study population consisted of those who had the first dose of the vaccine between 15 and 25 January 2021. By evaluating the literature data, the sample size was determined to be at least 310 individuals within the 95% confidence interval, when the 75% margin of error of the expected antibody positivity after the second dose was taken into consideration and the 5% design effect as 1.2. The number of samples was increased by 10% due to dropout problems that may be encountered in the follow-up. It was planned to collect peripheral blood samples from the participants 14 days after the first dose and 28 days after the second dose to investigate the presence of SARS-CoV-2 IgG. At various stages of the study, 2 healthcare workers who had COVID-19 and 14 who had not had COVID-19 voluntarily left the study (Fig. 1).

The demographic data of all participants were recorded in the follow-up form (age, gender, blood group type, the symptoms, the presence of comorbidities, etc.). Individuals with prior history of COVID-19 and native for Covid 19 had no respiratory symptoms until 14 days before the study. The antibody responses of 255 healthcare workers with COVID-19 infection-naive group and 75 healthcare workers with prior history of COVID-19 (with clinical symptoms and PCR-confirmed SARS-CoV-2 infection) at least four months ago before the study were evaluated. We also had the pre-vaccine serum samples taken for routine/study purposes from participants with prior history of COVID-19. In addition, the history of infection (diagnosis, clinical presentation, symptoms, etc.) in those who had COVID-19 and also vaccinated was evaluated together with the obtained antibody results. informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. This study was approved by the Republic of Turkey Ministry of Health General Directorate of Health Services Scientific Research Studies Commission (Date: 26.01.2020), Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Scientific Research and Evaluation Commission (Date: 19.02.2021 and Number: 35131) and Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Clinical Research Ethics Committee approval (Date: 03.02.2020 and Decision No: 23461).

In this study, the SARS-CoV-2 IgG test (ARCHITECT IgG II Quant test, Abbott, USA), which can quantitatively detect immunoglobulin G(IgG) antibodies, including neutralizing antibodies against the receptor-binding region (RBD) of the spike protein S1 subunit of SARS-CoV-2 was used by the chemiluminescent microparticle immunoassay (CMIA) method. The antibody results of studied sera were evaluated as Arbitrary Unit/mL (AU/mL). The antibody concentrations obtained in AU/mL were multiplied by the correlation coefficient of 0.142 and converted to the "Binding Antibody Unit (BAU/mL)" in the WHO's International Standard for Anti-SARS-CoV-2 immunoglobulin [6]. Accordingly, 50 AU/mL or 7.1 BAU/mL and above concentrations were considered positive. It was also reported that this test was 100% compatible with the plaque reduction neutralization test (PRNT), and a concentration of 1050 AU/mL was associated with a 1:80 dilution of PRNT [7].

The SARS-CoV-2 IgG test (ARCHITECT IgG test, Abbott, USA), which semi-quantitatively detects IgG antibodies against the Nucleocapsid protein (NCP) of SARS-CoV-2, was used in serum samples taken after both doses of healthcare workers without history of COVID-19. In the previous study conducted in our center for the diagnostic performance of antibody tests, the mean NCP IgG (2.03 S/Co) in the acute period of patients with covid 19 was evaluated as cut-off [8]. The volunteers with a concentration above 2.03 S/Co were considered to be in contact with SARS-CoV-2 and concentrations between 1.4 and 2.03 S/Co were evaluated as vaccine-induced.

### 2.1. Statistical analysis

The IBM SPSS statistic 21 package program was used to evaluate the data. Qualitative data are presented as number and percentage, and quantitative data are presented as median and IQR25-75. Chi-

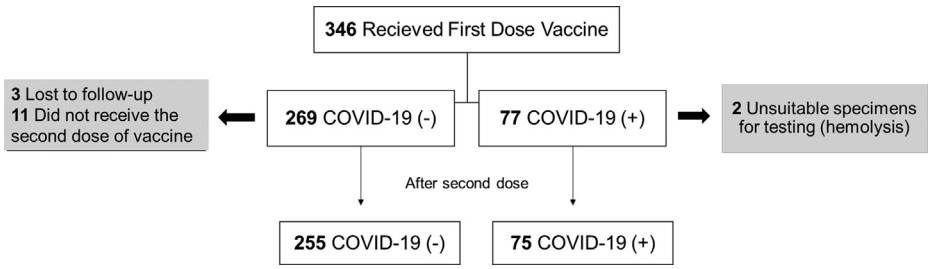


**Fig. 1.** Flowchart of volunteers participating in the Inactive SARS-CoV-2 Vaccine Efficacy Study.

square and Fisher's exact test were used in the evaluation of qualitative data, Student's *t* test, Mann Whitney *U* test and Kruskal Wallis test were used in the comparison of quantitative data. Spearman analysis was used for the correlation analysis. and $p < 0.05$ value was considered significant in all analysis.

This work was supported by IU- Cerrahpaşa Scientific Research Projects Unit (Project ID: 35691).

## 3. Results

The ages of 330 HCWs included in this study are ranged between 19 and 65, with a mean age of 39.6 ± 7.7 years. 211 (63.9%) of the participants were female, and 119 (36.1%) were male. Of the 75 participants with prior history of COVID-19, 38 (50.7%) were male, and 37 (49.3%) were female, with a mean age of 39.53 ± 11.54 years. Of the infection-naive group, 81 (31.8%) were men, 174 (68.2%) were women, and the mean age was 39.5 2 ± 11.06 years.

Of the individuals with a prior history of COVID-19, 5 had asymptomatic COVID-19, 36 had mild, 31 had moderate, and 3 had severe clinical forms of the disease [9]. Fever(53,3%), fatigue (74,6%), arthralgia(57,3%), loss of taste and smell (69,3%) and headache(49,3%) were observed as the most common symptoms in these individuals. Of the 75 participants with a prior history of COVID-19, three had no detectable antibodies in the serum sample obtained before vaccination. The percentage of positive antibodies against the SARS-CoV-2 was 96.0% (95% CI: 91.6–100) in above group. Antibody levels were detected in all cases after the first and second doses of the vaccine. When the antibody response after two doses of vaccination was compared to the severity of COVID-19 in the group with a prior history of COVID-19, no significant difference was found ($p > 0.05$).

In the infection-naive group, the percentage of positive antibodies 14 days after the first dose of vaccine was 48.2% (95% CI: 42.1–54.3). The positive antibody percentage 28 days after the second dose of vaccine was 99.2% (95% CI: 98.1–100), and only two HCWs among this group were negative for antibody against SARS-CoV-2 (Table 1). In the total study group, the antibody positivity for SARS-CoV-2 was 99.4% (95% CI: 98.6–100) after two doses of vaccination

IgG antibody titers of over 1050 AU/mL (which is equivalent to 1:80 dilution in the plaque reduction neutralization test) were detected in 25.9% of the infection-naive group and in 54.7% of those with a prior history of COVID-19, the difference was statistically significant ($p<0.001$) (Table 1). The percentage of antibody positivity was found to be 51.1% and 42.0% in males and females after the first dose vaccination, respectively. On the other hand, the percentage of antibody positivity was found to be 99.5% and 99.2% in males and females after the second dose of vaccination, respectively. The efficacy rate of the CoronaVac vaccine was found as 99.4% in all participants, both under 40 and over 41 years old. No significant difference was detected between antibody responses according to blood groups.

Median antibody titer was 48,4 AU/mL after the first dose of vaccine in the infection-naive group, which increased to 707,1 AU/mL after the second dose, the difference was statistically significant ($p<0.001$). While the median antibody titer was 301.9 AU/mL before vaccination in participants with prior history of COVID-19, it was found to be 1331.2 AU/mL after the first dose of vaccination ($p<0.001$). After the second dose in the above group, the median antibody titer was found as 1090,0 AU/mL (Table.2) (Fig. 2) ($p>0.05$). Median antibody titers in groups with and without a prior history of COVID-19 did not differ significantly in terms of age and gender. There was a very low significant negative correlation between the age and antibody titers after the second dose in

**Table 1**
Evaluation of demographic data and antibody results of participants as a percentage.

| | Infection-naive Group n = 255 (%) | Prior History of COVID-19 n = 75 (%) | p |
|---|---|---|---|
| ***Gender*** | | | |
| *Male* | 81 (31,8) | 38 (50,7) | ,003* |
| *Female* | 174 (68,2) | 37 (49,3) | |
| ***Age*** | | | |
| *<40* | 128 (50,2) | 39 (52,0) | ,784 |
| *≥40* | 127 (49,8) | 36 (48,0) | |
| ***Body-Mass Index*** | | | |
| *Normal* | 120 (49,0) | 34 (45,9) | ,320 |
| *Overweight* | 89 (36,3) | 33 (44,6) | |
| *Obese* | 36 (14,7) | 7 (9,5) | |
| ***Department*** | | | |
| *Basic Medical Sciences* | 9 (4,0) | 7 (9,7) | ,063 |
| *Internal Medical Sciences* | 93 (41,3) | 22 (30,6) | |
| *Surgical Medical Sciences* | 59 (26,2) | 26 (36,1) | |
| *Other Staff* | 64 (28,4) | 17 (23,6) | |
| ***Comorbidity*** | | | |
| *Allergy* | 22 (8,6) | 5 (6,7) | ,586 |
| *Auto-immune Diseases* | 4 (1,6) | 1 (1,3) | 1,000 |
| *Neurological Disorders* | 2 (0,8) | 2 (2,7) | ,223 |
| *Malignity* | 2 (0,8) | 0 (0,0) | ,442 |
| *Diabetes Mellitus* | 9 (3,5) | 3 (4,0) | ,848 |
| *Hypertension* | 15 (5,9) | 3 (4,0) | ,773 |
| *Hypothyroidism* | 15 (5,9) | 4 (5,3) | ,858 |
| *Cronic Heart Diseases* | 2 (0,8) | 2 (2,7) | ,190 |
| *Asthma* | 7 (2,7) | 0 (0,0) | ,357 |
| **Blood Groups** | | | |
| *0+* | 69 (32,1) | 17 (25,4) | ,815 |
| *0-* | 6 (2,8) | 3 (4,5) | |
| *A+* | 86 (40,0) | 27 (40,3) | |
| *A-* | 8 (3,7) | 5 (7,5) | |
| *B+* | 23 (10,7) | 8 (11,9) | |
| *B-* | 4 (1,9) | 1 (1,5) | |
| *AB+* | 18 (8,4) | 5 (7,5) | |
| *AB-* | 1 (0,5) | 1 (1,5) | |
| **Anti-SARS-CoV-2 IgG After first dose (AU/mL)** | | | |
| *Negative (<50 AU/mL)* | 132 (51,8) | 0 (0,0) | ,000 |
| *Positive (≥50 AU/mL)* | 123 (48,2) | 75 (100,0) | |
| **Anti-SARS-CoV-2 IgG After second dose (AU/mL)** | | | |
| *Negative (<50 AU/mL)* | 2 (0,8) | 0 (0,0) | – |
| *Positive (≥50 AU/mL)* | 253 (99,2) | 75 (100,0) | |
| **Anti-SARS-CoV-2 IgG After second dose (AU/mL)** | | | |
| *<1050 AU/mL* | 189 (74,1) | 34 (45,3) | ,000 |
| *≥1050 AU/mL* | 66 (25,9) | 41 (54,7) | |

**Table 2**
SARS-CoV-2 IgG averages in blood samples taken at different times from healthcare workers who have prior history of COVID-19 and who are infection naïve.

| Anti-SARS-CoV-2 IgG | Infection-naive Group | Prior History of COVID-19 | p |
|---|---|---|---|
| | Median (IQR 25–75) | Median (IQR 25–75) | |
| *Before Vaccination (AU/mL)* | – | 301,9 (124,1–854,2) | |
| *After First Dose (AU/mL)* | 48,4 (17,4–109,3) | 1331,2 (900,1–2573,7) | **,000***** |
| *After Second Dose (AU/mL)* | 707,1 (426,4–1083,7) | 1090,0 (612,0–1864,1) | **,000***** |

AU/mL : Antibody Unit / mililiter ; IQR : Inter Quantile Range.

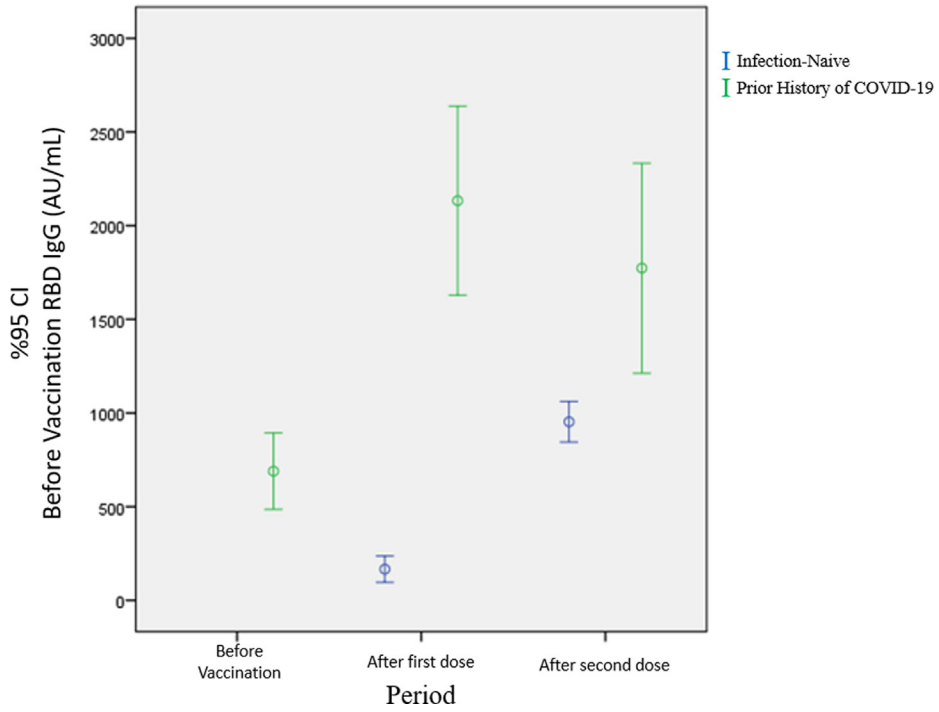


**Fig. 2.** SARS-CoV-2 IgG averages in blood samples taken at different times from healthcare workers who have prior history of COVID-19 and who are infection naïve.

infection-naive group (r = -0.15 p<0.05). When evaluated in terms of comorbid conditions; It was found that COVID-19 infection-naive group had significantly lower antibody titers in the presence of hypertension (p<0.05) (Table 3).

**Table 3**
Evaluation of antibody titers in healthcare workers according to demographic data.

| | **Infection-Naive Group** | | | **Prior History of COVID-19** | | |
|---|---|---|---|---|---|---|
| | n | Median (IQR) | p | n | Median (IQR) | p |
| **Gender** | | | | | | |
| *Male* | 81 | 674,4(447,3–1289,3) | ,923 | 38 | 1114,6(444,5–1873,5) | ,711 |
| *Female* | 174 | 720,1(420,1–1032,8) | | 37 | 1078,1(617,2–1996,9) | |
| **Age** | | | | | | |
| *<40* | 128 | 807,7(482,5–1155,9) | **,024** | 39 | 947,5(454,8–1552,9) | ,071 |
| *≥40* | 127 | 601,9(382,9–1009,4) | | 36 | 1253,2(732,8–2371,9) | |
| **Body-Mass Index** | | | | | | |
| *Normal* | 120 | 764,0(422,7–1028,8) | ,546 | 34 | 806,8(444,5–1441,1) | ,077 |
| *Overweight* | 89 | 626,3(388,5–1132,8) | | 33 | 1413,1(870,2–2204,4) | |
| *Obese* | 36 | 619,0(460,4–1032,5) | | 7 | 1055,5(582,5(1269,7) | |
| **Department** | | | | | | |
| *Basic Medical Sciences* | 9 | 729,1(358,7–1632,5) | ,846 | 7 | 883,6(438,6–1864,1) | ,500 |
| *Internal Medical Sciences* | 93 | 703,0(427,4–1035,7) | | 22 | 974,1(470,7–2375,5) | |
| *Surgical Medical Sciences* | 59 | 767,8(477,4–1241,9) | | 26 | 1266,8(717,0–2039,0) | |
| *Other Staff* | 64 | 735,0(459,6–1124,6) | | 17 | 970,7(419,4–1485,4) | |
| **Allergy** | | | | | | |
| *Absent* | 233 | 705,6(424,0–1087,9) | ,719 | 70 | 1056,7(562,1–1711,0) | – |
| *Present* | 22 | 842,8(466,1–1074,0) | | 5 | 3382,0(1816,4–6631,8) | |
| **Diabetes Mellitus** | | | | | | |
| *Absent* | 246 | 720,1(415,6–1105,5) | ,268 | 72 | 1084,1(589,9–1858,0) | – |
| *Present* | 9 | 488,9(464,9–674,0) | | 3 | 1152,6(738,6 | |
| **Hypertension** | | | | | | |
| *Absent* | 240 | 731,5(445,4–1134,6) | **,011** | 72 | 1068,0(589,9–1820,4) | – |
| *Present* | 15 | 488,9(255,3–674,4) | | 3 | 2374,9(1152,6 | |
| **Hypotroidism** | | | | | | |
| *Absent* | 240 | 706,4(422,8–1089,9) | ,621 | 71 | 1090,0(582,5–1839,8) | – |
| *Present* | 15 | 896,9(450,0–1042,0) | | 4 | 1948,3(708,4–3440,7) | |
| **Comorbidity** | | | | | | |
| *Absent* | 196 | **745,2(435,8–1221,3)** | **0,041** | 62 | 1056,6(495,4–1781,7) | 0,203 |
| *Present* | 59 | 584,6(386,8–989,9) | | 13 | 1152,6(854,6–3153) | |

IQR : Inter Quantile Range.

**Table 4**
Comparison of demographic data and post-vaccine antibody responses by viral exposure in 255 infection-naive participants.

| COVID-19 naive | **NCP IgG Negative(n: 231)** | **NCP IgG Positive(n: 24)** | **p** |
|---|---|---|---|
| *Gender; n (%)* | 162 | 12 | |
| - *Female* | (70,1%)69 | (50%)12 | 0,044 |
| - *Male* | (29,9%) | (50%) | |
| *Age; Mean (SD)* | 39,58 (11,152) | 39,14 (10,631) | 0,828 |
| *After First Dose (AU/mL); Median (IQR25-75)* | 46,7(15,9–96,6) | 98,3(30,9–604,2) | **,000***** |
| *After Second Dose (AU/mL); Median (IQR25-75)* | 672,7(401,2–1012,3) | 1687,1(1013,5–2995,1) | **,000***** |

NCP: Nucleocapside ; SD : Standard Deviation ; AU/mL : Antibody Unit / mililiter ; IQR : Inter Quantile Range.

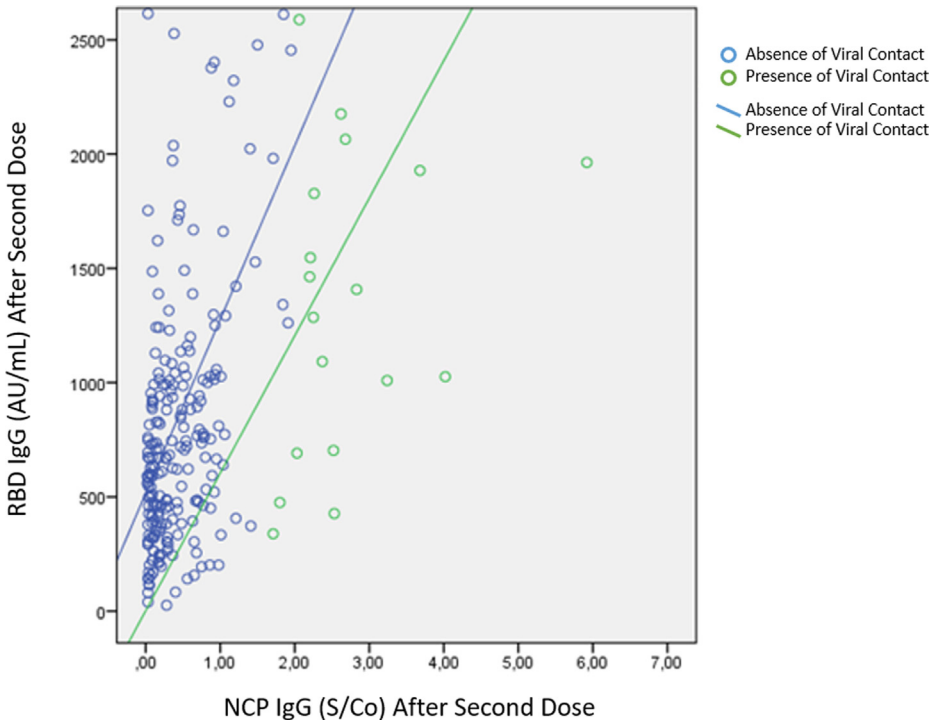


**Fig. 3.** SARS-CoV-II (RBD) IgG results by depending on viral contact in the Infection-Naive group.

In COVID-19 infection-naive group, NCP IgG positivity was detected in 35 participants. In this group, SARS-CoV-2 NCP IgG seropositivity due to contact with the virus was detected in a total of 24 participants (12 females, 12 males), 4 after the first dose and 20 after the second dose. These 24 participants were questioned retrospectively, and it was found that they did not have any clinical signs of COVID-19. It was observed that the SARS-CoV-2 IgG (RBD/S1) antibody titer values of these 24 individuals were 2-fold higher than the median antibody titer values of the people (n:231) who did not have contact with the virus and without a prior history of COVID-19 (Fig. 3) (Table 4). A low degree of significant positive correlation was observed between NCP IgG values and RBD/S1 IgG titers in those without viral exposure ($r = 0.41$, $p<0.001$). A moderately significant positive correlation was observed in those with viral contact ($r = 0.59$, $p<0.01$). Regarding the gender distribution among those in contact with the virus, males were found to be significantly dominant ($p<0.05$).

## 4. Discussion

Ensuring widespread access to a safe and effective vaccine against the pandemic has been the most vital challenge of the past year. Immediate vaccination of HCWs is a critical step both in mitigating the pandemic and in guiding widespread vaccination programs. In this study, the antibody response rates and vaccine efficacy in HCWs, both infection-naïve and with a prior history of COVID-19, with and without comorbidities were determined. Those with a prior history of COVID-19 developed significantly higher antibody responses after the first dose of vaccine (96.4% vs. 48%), yet the antibody development rates after the second dose were similar (%99 vs. %100). Hence, there was a significant decrease in the median antibody titers of HCWs with hypertension (488.9 vs. 731.5) without prior history of infection. There was no difference between the two groups when evaluated in terms of other comorbid diseases and blood groups. We also observed that the antibody response detected in two HCWs in the infection-naive group was below the protective level (<50 AU/mL). One of these HCWs was a diabetic patient over 60 years old and the other was receiving immunosuppressive therapy. No significant difference was detected in HCWs with prior COVID-19 in terms of comorbid diseases.

In addition to basic measures such as hand hygiene, social distancing, and universal use of mask; a safe and effective vaccine is pivotal in curbing the pandemic. In this context, various vaccines, based on various production methodologies are currently available worldwide with emergency use approval. The efficacy rates of AstraZeneca/Oxford, Johnson and Johnson, Moderna, Pfizer/BionTech, and Sinopharm, which are on the WHO's emergency use list,

have been reported as 63.09%, 66%, 92%, 95%, and 79%, respectively [10]. The efficacy rates of CoronaVac (Sinovac), which received WHO emergency use approval on 01.06.2021, were announced as 51% in Brazil, 65% in Indonesia and 84% in Turkey, according to Phase 3 studies [5].

Although the efficacy of COVID-19 vaccines has been investigated and different efficacy rates have been reported, the real-life efficacy data are not yet fully elucidated. In a study conducted in Israel, it was reported that the BNT162b2 (Pfizer/BionTech) vaccine had an efficacy of 66–85% in reducing SARS-CoV-2 positive cases and efficacy over 90% in reducing hospitalizations [11]. In a study with healthcare professionals in Brazil, the efficacy rate of CoronaVac, two weeks after the second dose of CoronaVac was reported as 50.7% (95% CI: 33.3–62.5%). It has also been reported that this efficacy rate was increased further in the next two weeks (68.4% at 4 weeks and 73.8% at 5 weeks) [12]. After vaccination, 142 samples that were detected PCR positive, were evaluated for SARS-CoV-2 variants and 47% (67) of these samples were found to harbour mutations related to "Variant of Concern (VOC)" announced by WHO, majority of which were P.1. variant [12]. It is crucial to monitor the efficacy of existing COVID-19 vaccines for new variants of SARS-CoV-2, including B.1.1.7, 501Y.V2 and P.1. In a study investigating the efficacy of inactivated SARS-CoV-2 vaccines in Jordanian and Egyptian populations, although it has been reported to reduce the risk of symptomatic COVID-19 risk, but its efficacy against variants has not been tested [13]. While new variants are alarming, it is promising to observe a significant reduction over time by vaccination in confirmed symptomatic COVID-19 cases [12]. We aim to continue monitoring vaccine efficacy in the participants against these emerging SARS-CoV-2 variants in the second phase of our study.

One of the most critical problems in COVID-19 vaccination is the duration and the extent of protection of the developed antibodies. Therefore, it was planned to follow up the vaccinated patients for up to 6 months. SARS-CoV-2 NCP IgG positivity was detected in 35 participants. Although it has been suggested that anti-nucleocapsid antibodies may also develop in response to inactivated SARS-CoV-2 vaccines, preclinical studies demonstrate their levels to be approximately 30 times lower than anti-RBD antibodies [14]. No data were presented regarding IgG response against the nucleocapsid of SARS-CoV-2 in the Phase1/2 study of the CoronaVac vaccine. However, B cells are known to generate antibody responses initially to the nucleocapsid antigens in individuals exposed to the SARS-CoV-2, and nucleocapsid IgG is known to serve as one of the clinical diagnostic markers [15–17]. Since we could not detect NCP IgG in 86.27% of those without a prior history of COVID-19 in this study, the possibility of contact with the virus during this process worths considering for the individuals who were NCP IgG positive. Based on the NCP IgG results, we suggest that 11 people may have developed a vaccine-induced NCP IgG response, while 24 people may have developed a virus-induced NCP IgG response. In addition, when we questioned these 24 people for 60 days from the beginning of the vaccination process, these people did not report any symptoms or clinical findings and only 12 of these people had a history of close contact with a COVID-19 positive individual. These findings suggest that people (n:24) with an elevated positive NCP IgG result may have had the COVID-19 asymptomatically and very recently, probably before the second vaccination or more earier but later than the contact time of the COVID-19 group with the COVID-19. Although the COVID-19 inactivated vaccines don't provide a 100% protection against infection, we suggest that they may effectively prevent severe disease since none of the HCWs that were followed during this period developed a symptomatic COVID-19 infection.

Determining the duration of protective efficacy and the requirement for a booster dose remain among unsolved problems. It was reported that IgG antibodies developed by the COVID-19 infection largely protects from re-infection for about 6 months in a study conducted in healthcare professionals who had COVID-19 [18]. In the SIREN study conducted on 20,787 HCWs in England, it was reported that the protection rate for the first 5 months after infection was 83%, but the contagiousness of healthcare personnel could continue during this period, and attention was drawn to the possibility of re-infection [19].

Data are scarce regarding the protective efficacy of natural antibodies developed post-infection. Therefore, vaccination is recommended regardless of prior COVID-19 infection status [20]. One of the critical questions is whether a single dose of vaccine will be sufficient for these people. Antibody positivity in the group that had the COVID-19 before vaccination was 96%. It was also observed that the antibody titers of 75 people who had COVID-19 at least four months ago increased three-fold after the first dose of vaccination. Although there is a slight decrease in the median antibody titers (16%) after the second dose, the median antibody titers are approximately 2.5 times higher than in the infection-naïve group. When all data are evaluated together, it can be suggested that a single dose of vaccine administered 3–6 months apart to the infection may be sufficient for those with confirmed prior COVID-19, thus the limited resources of vaccine can be mobilized to a larger extent of vulnerable populations. Memory B and T cell responses play a vital protective role in case of re-exposure to the virus. It is well documented that T cell response develops within the first 14 days after a single dose of the CoronaVac vaccine, while B cell response improves after the second dose [21]. Given the results of recent studies, including ours, it is still vital to administer vaccines in two doses to those with no known exposure to SARS-CoV-2.

There are very limited number of studies for the efficacy of COVID-19 vaccines in those with chronic diseases and those who have had COVID-19 before. Our study, comprising a population of HCWs with and without chronic diseases besides those with and without prior infection, provides a set of real life data. Since only the Sinovac vaccine was available in Turkey during this period, the results of this vaccine were evaluated in the healthcare personnel. The inability to evaluate the cellular immune responses of the participants is among major limitations of this study, conducted in a single center, on a limited population. Although, the possibility of exposure to the SARS-CoV-2 virus between the blood collection periods after the first and second dose vaccination was taken into account, the PCR test, which is considered the gold standard in acute diagnosis of COVID-19, could not be routinely performed on the participants before the study. Instead, nucleocapsid IgG-targeted antibody testing was used for the serum samples obtained between the indicated time periods.

Demonstrating the presence of the SARS-CoV-2-specific neutralizing antibodies developed after infection and vaccination is very important in terms of protective immunity. However, it is difficult to perform PRNT in routine practice, which is the reference standard method, due to the need for special laboratory conditions with biosafety level 3 (BSL3) and experienced specialists. Therefore, we used an antibody test with 100% correlation with PRNT and another limiting factor is that the evaluation was made according to the cut-off value of the manufacturer. Although the World Health Organization (WHO) is working to establish a standard for antibody tests with a reference serum sample (NIBSC code 20/136) and its dilutions, a safe cut-off value indicating the protective immunity has not been defined yet [22]. Only the FDA has defined a cut-off value for convalescent plasma, and this value is > 840 AU/ml for the test we used in this study [23].

As a result, while the vaccine response was 45% two weeks after the first dose in HCWs, the rate of it reached to 99% within one month after the second dose. Two doses of inactivated CoronaVac (Sinovac) vaccine produced effective humoral immunity in HCWs.

Response to the vaccine is similar following the first and second doses in those with a prior history of COVID-19. Moreover, antibody levels are significantly higher in comparison to the infection-naive group. Given no significant benefit of the second dose, in terms of antibody titers, a single shot of vaccination may be sufficient for those with prior history of COVID-19. Monitoring humoral and cellular immune responses, considering new variants, is required to validate this approach.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgment

We thank Songül Gedik Koç, Feray Ergen, Yasemin Öztürk, Elfide Şentürk Yurdatapan, Demet Durgun Karakaş, Nafiye Güder and Fatih Hekimoğlu for thier contributions the paper.

## Financial support

This work was supported by IU- Cerrahpaşa Scientific Research Projects Unit (Project ID: 35691).

## References

[1] Walker PGT, Whittaker C, Watson OJ, Baguelin M, Winskill P, Hamlet A, et al. The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. Science 2020;369(6502):413–22. https://doi.org/10.1126/science:abc0035.

[2] Coronavirus disease (COVID-2019) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports [Accessed 4 Oct 2021]

[3] Republic of Turkey, Ministry of Health COVID-19 Information Platform https://covid19.saglik.gov.tr/ [Accessed 4 Oct 2021]

[4] Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181–92. https://doi.org/10.1016/S1473-3099(20)30843-4.

[5] WHO. Evidence Assessment: Sinovac/CoronaVac COVID-19 vaccine. https://cdn.who.int/media/docs/default-source/immunization/sage/2021/april/5_sage29apr2021_critical-evidence_sinovac.pdf [Accessed 2 June 2021]

[6] World Health Organization (2020). Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody. WHO/BS/2020.2403. Available at: https://www.who.int/publications/m/item/WHO-BS-2020.2403 [Accessed 2 June 2021]

[7] Abbott SARS-CoV-2 Immunoassays https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2 [Accessed 2 June 2021]

[8] Dinç HÖ, Özdemir YE, Alkan S, Güngördü Dalar Z, Gareayaghi N, Sirekbasan S et.al. Evaluation of the Diagnostic Performance of Different Principles of SARS-CoV-2 Commercial Antibody Tests in COVID-19 Patients. 2021;55(2):207-222/doi: 10.5578/mb.20219907

[9] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.2.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ [Accessed 2 June 2021]

[10] WHO. Strategic Advisory Group of Experts on Immunization (SAGE): COVID-19 vaccines technical documents. https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials [Accessed 2 June 2021]

[11] Aran D. Estimating real-world COVID-19 vaccine effectiveness in Israel. medRxiv preprint doi: https://doi.org/10.1101/2021.02.05.21251139

[12] Hitchings MDT, Ranzani OT, Scaramuzzini Torres MS, Barbosa de Oliveira S, Almiron M, Said R et.al. Effectiveness of CoronaVac in the setting of high SARS-CoV- 2 P.1 variant transmission in Brazil: A test-negative case-control study. MedRxiv preprint doi: https://doi.org/10.1101/2021.04.07.21255081; this version posted April 7, 2021.

[13] Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA 2021;326(1):35. https://doi.org/10.1001/jama.2021.8565.

[14] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369(6499):77–81. https://doi.org/10.1126/science:abc1932.

[15] Tan Y-J, Goh P-Y, Fielding BC, Shen S, Chou C-F, Fu J-L, et al. Profiles of antibody responses against severe acute respiratory syndrome coronavirus recombinant proteins and their potential use as diagnostic markers. Clin Diagn Lab Immunol. 2004;11(2):362–71. https://doi.org/10.1128/CDLI.11.2.362-371.2004.

[16] Wu H-S, Hsieh Y-C, Su I-J, Lin T-H, Chiu S-C, Hsu Y-F, et al. Early detection of antibodies against various structural proteins of the SARS-associated coronavirus in SARS patients. J Biomed Sci. Jan-Feb 2004;11(1):117–26. https://doi.org/10.1007/BF02256554.

[17] Liu L, Liu W, Zheng Y, Jiang X, Kou G, Ding J, et al. A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. Microbes Infect. May-Jun 2020;22 (4-5):206–11. https://doi.org/10.1016/j.micinf.2020.05.008.

[18] Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med. 2021;384(6):533–40. https://doi.org/10.1056/NEJMoa2034545.

[19] Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet 2021;397(10283):1459–69. https://doi.org/10.1016/S0140-6736(21)00675-9.

[20] CDC. About COVID-19 Vaccine: requently Asked Questions about COVID-19 Vaccination. (Updated May 12, 2021) https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html [Accessed 2 June 2021]

[21] Zhang H, Hu Y, Jiang Z, Shi N, Lin H, Liu Y et al. Single-Cell Sequencing and Immune Function Assays of Peripheral Blood Samples Demonstrate Positive Responses of an Inactivated SARS-CoV-2 Vaccine. Available at SSRN: https://ssrn.com/abstract=3774153 or http://dx.doi.org/10.2139/ssrn.3774153.

[22] Kristiansen PA, Page M, Bernasconi V, Mattiuzzo G, Dull P, Makar K, et al. WHO International Standard for anti-SARS-CoV-2 immunoglobulin. Lancet 2021;397 (10282):1347–8. https://doi.org/10.1016/S0140-6736(21)00527-4.

[23] FDA. Convalescent Plasma. https://www.fda.gov/media/141477/download [Accessed 2 June 2021]