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Investigation of IgG antibody levels among healthcare workers vaccinated with inactivated COVID-19 vaccine using indirect ELISA

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ABSTRACT

This study was conducted to investigate variations in SarsCoV-2-specific IgG levels over a 5-month period in healthcare workers who received two doses of CoronaVac vaccine. Blood samples were collected from 122 participants on days 14, 56 and 150 following the second dose of the vaccination. SarsCoV-2 specific IgG antibody titres of the participants were measured using the QuantiCOR ELISA kit. Demographic data of the participants were recorded. Seropositivity on 14th, 56th and 150th days in the previously uninfected group was 44.8%, 50.7% and 32.8%, respectively. In the previously infected group, seropositivity was detected in 87.2%, 92.7% and 43.6% of the participants, respectively. While a statistically significant difference was determined between the two groups in terms of seropositivity on the 14th and 56th days, no statistical difference was found on the 150th day. The data of this study indicated that the CoronaVac vaccine provided sufficient immunity in previously infected individuals, though the duration of immunity was short. It is suggested that CoronaVac vaccine would be more appropriate to use as a booster in order to increase the effectiveness of a vaccine rather than the first vaccination, or to vaccinate people who have been infected before.

1. Introduction

COVID-19, regarded as the most important global health crisis since the flu outbreak period in 1918, is a pandemic disease that still threatens the whole world causing 243 million confirmed cases and more than 4.9 million deaths worldwide as of October 2021 (WHO, 2021a). Since there is currently no effective treatment procedure against COVID-19 disease, vaccination trials have been accelerated all over the world in order to generate herd immunity. For this purpose, various vaccine types such as live virus vaccines, purified inactivated vaccines, recombinant protein vaccines, vector vaccines and RNA and DNA-based vaccines have been studied and some of them have been put into use with emergency approval (Zhao et al., 2020). Among the traditional vaccines, purified inactivated virus vaccines are the first

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granted for emergency use against COVID-19 following the completion of phase-3 trials (Bueno et al., 2021; Tanriover et al., 2021). Inactivated vaccines are intended to synthesize neutralizing antibodies against SARS-Cov-2 virus in order to obtain an optimal and effective humoral immunity by targeting various structures of the virus such as spike (S) proteins, nucleocapsid (N) proteins and receptor binding domain (RBD) (Yang et al., 2020; Dai and Gao, 2021). Humoral immunity is a key component of adaptive immunity against virus infections. Specific antiviral antibodies secreted by mature plasma B cells form an immune protective barrier against the infection (Janeway et al., 2004).

CoronaVac, an inactivated whole virion SARS-Cov-2 vaccine developed by Sinovac Life Sciences (Beijing, China), has been reported to produce neutralizing antibodies against SARS-Cov-2 virus and induce a good immune response in mice, rats and non-human primates. It has also been showed that the CoronaVac vaccine provided partial or complete protection in macaques experimentally infected with SARS-Cov-2 virus (Gao et al., 2020). Phase-3 trials of the CoronaVac have also been conducted in Turkey, Brazil, Chile and Indonesia since mid-2020, and the proportions for the efficacy level of the vaccine have been reported to be 84%, 50%, 67% and 65%, respectively (WHO, 2021b).

Vaccination-induced immunity against SARS-Cov-2 has been shown to provide some degree of protection against re-infection and/or reduce the risk of clinically relevant outcomes (Khoury et al., 2021b). It has been stated that in phase-3 trials, hospitalization and death rates decreased significantly in people vaccinated with the inactive vaccine (MacMullan et al., 2020). However, because phase-3 trials were carried out in a narrow time period in the field, there is a paucity of information about the long-term protection of the vaccine. It is important to determine immunity duration in terms of planning vaccination schedules and keeping the herd immunity at a certain level. In particular, in order to provide effective protection against new variants that are highly contagious and can escape form the immune system, it is necessary to ensure protective antibodies at a certain level and make a vaccination program accordingly. This study was carried out to determine the immunity duration of CoronaVac vaccine by investigating the variations in IgG levels specific to SARS-CoV-2 over a 5 month period in healthcare workers who received two doses of the vaccine.

2. Materials and Methods

2.1. Ethical Statement

This study was carried out with the official permission taken from the Ministry of Health. The study was also ethically approved by the Non-Interventional Research Ethics Committee of Firat University with the protocol number 30.02.2021/2345. The participants were informed about the study and their consent documents were signed and recorded.

2.2. Participants

This study was originally conducted on 131 healthcare workers who received two doses of CoronaVac vaccine in two provinces located in eastern Turkey. During the five-month time period, nine participants that were determined to be positive for COVID-19 were excluded from the study. Therefore, serum samples collected from a total of 122 participants were subjected for analysis in the study. In our country, all healthcare workers were included in the vaccination program at first place, regardless of whether they previously contracted COVID-19. Therefore, the participants in the study were divided in to two groups: people who suffered from COVID-19 previously with a PCR positive test and various clinical signs of the disease (n=55), and those with no history of the disease (n=67). In order to avoid confusion caused by possible antibodies produced following natural infection and measure solely the vaccine-induced immune response, the participants who were positive for COVID-19 up to five months before the first dose of vaccination were included in the study. Because of the fact that adequate immunity with the inactivated vaccines is accomplished after the second dose application, blood samples were collected from the participants on days 14, 56 and 150 following the second dose of the vaccination. Serum samples obtained from the participants by taking 3 ml blood intravenously using vacuum tubes were frozen at -20 °C until testing by ELISA.

A face to face questionnaire was also conducted before each sample collection in order to obtain data from the participants on demographic information, side effects following vaccination and occurrence of COVID-19 infection after two doses of CoronaVac vaccine.

2.3. ELISA

Serum samples were analysed by a commercial anti SARS-Cov-2 IgG test kit (QuantiCOR, Y Immunotek A.S., Malatya, Turkey). The test kit had sensitivity and specificity values between 95-100% and was approved for diagnostic use by Ministry of Health of Turkey, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products, which applies the rules and criteria of World Health Organization (WHO) for test approval for COVID-19. The cut-off for samples to be considered positive was ≥ 1.1 and borderline positive from 0.9 and 1.09. Borderline results were counted as positive for easier interpretation of the results.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS package program (Version 22.0. Armonk, NY, USA). Normality of data and homogeneity of variances were determined by Kolmogorov–Smirnov and Levene tests, respectively. One way ANOVA test was used for comparisons between the days, while Tukey post hoc test was applied for pairwise comparisons. Student's t test was used for comparisons within the days. A chi squared test, where applicable, was employed for the comparisons of seropositivity within the days and between the days and for the comparison of side effects among the participants. Otherwise, Fisher's Exact Test was applied. Data were presented as mean and 95% confidence intervals (95% CI) and significance at $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Demographic and some characteristic features of the participants associated with post-vaccination

The data for demographic characteristics of the participants were presented in Table 1. Side effects were noted in 31.3% (21/67) and 43.6% (24/55) of participants in the previously uninfected and previously infected groups, respectively, within seven days following the second dose of vaccination. The most common symptoms were recorded as pain at injection site and headache which were mild (grade 1) in both groups. There was no statistically significant difference between the both groups in terms of side effects with the exception for the headache ($p=0.016$) (Fig. 1).

During the five-month study period, a total of nine participants, six in previously uninfected group and three in previously infected group, were determined to be positive for COVID-19 following the second dose of vaccination. While alpha or delta variants were detected in eight patients, SARS-Cov-2 variant strain was not found in one patient (Tab. 2). The data were obtained from the Ministry of Health. Serum antibody data of these infected individuals were excluded from the study for accurate determination of vaccine efficacy.

3.2. ELISA Results

The seropositivity on the 14th day after the second dose of vaccination was 44.8% (mean: 2.13, 95% CI: 1.54-2.6) in the previously uninfected group, but it decreased to 32.8% (mean: 2.04, 95% CI: 1.37-2.76) on the 150th day. While the seropositive on the 14th day after the second dose of vaccination was 87.2% (mean: 4.22, 95% CI: 3.42-5.02) in the previously infected group, it decreased to 43.6% (mean: 2.37, 95% CI: 1.59-3.17) on the 150th day. The highest antibody titres were detected on the 56th day after the second dose of vaccination in both previously uninfected group (mean: 2.22, 95% CI: 1.65-2.9) and previously infected group (mean: 5.31, 95% CI: 4.23-6.16) (Tab. 3). Although the difference between the groups in terms of antibody titres on the 150th day after second dose of vaccination was not significant, the differences obtained on the 14th and 56th days were determined to be statistically significant (Fig. 2).

The seropositivity of the women participants in the previously uninfected group on the 14th and 56th days was higher than the men, and the difference was found to be statistically significant. In the previously infected group, though seropositivity was higher in women on

the 14th and 150th days, no statistically significant difference could be detected (Fig. 3). There was also no association between age and seropositivity within each group. However, a statistically significant difference was found between the two groups in terms of seropositivity in the age group of 41 and over on the 14th day, and in the 31-40 age group on the 56th and 150th days (Fig. 4).

Table 1. Demographic features of the participants.

Group	Age (years)	Female (%)	Male (%)	Total (%)
Previously uninfected	20-30	11 (57.9)	8 (42.1)	19 (28.4)
	31-40	8 (44.4)	10 (55.6)	18 (26.9)
	41 and above	13 (43.3)	17 (56.4)	30 (44.7)
	Total	**32 (47.8)**	**35 (52.2)**	**67 (54.9)**
Previously infected	20-30	4 (44.4)	5 (55.6)	9 (16.4)
	31-40	17 (81)	4 (19)	21 (38.2)
	41 and more	13 (52)	12 (48)	25 (45.4)
	Total	**34 (61.8)**	**21 (38.2)**	**55 (45.1)**
Overall		**66 (54.1)**	**56 (45.9)**	**122**

Table 2. Information on the participants who were determined to be positive for COVID-19 in the five-month study period after the second dose of vaccination

Group	**Gender/ Age**	**Day of illness after second dose vaccination**	**Symptoms**	**Duration of illness (days)**	**Medical treatment**	**Variant**
Previously uninfected	M/37	14th	Headache, backache, cough	3-4	Not treated	Alpha
	M/49	30th	General body pain, Fever, joint pain, memory loss	14	Not treated	Not detected
	M/29	74th	Weakness, joint pain, cough, headache, low back pain, shortness of breath, fatigue, chest pain	10	Favipiravir	Delta
	M/30	80th	Fever, neck pain, loss of odor and taste	14	Not treated	Delta
	F/48	50th	Loss of taste and smell, joint pain, weakness	15	Favipiravir	Alpha
	F/47	72th	Cough, shortness of breath	20	Favipiravir	Alpha
Previously infected	F/38	90th	Headache, backache, cough	21	Favipiravir	Delta
	F/34	54th	Taste-smell loss, fatigue	10	Not treated	Delta
	F/25	15th	Headache, Muscle pain, weakness	7	Not treated	Alpha

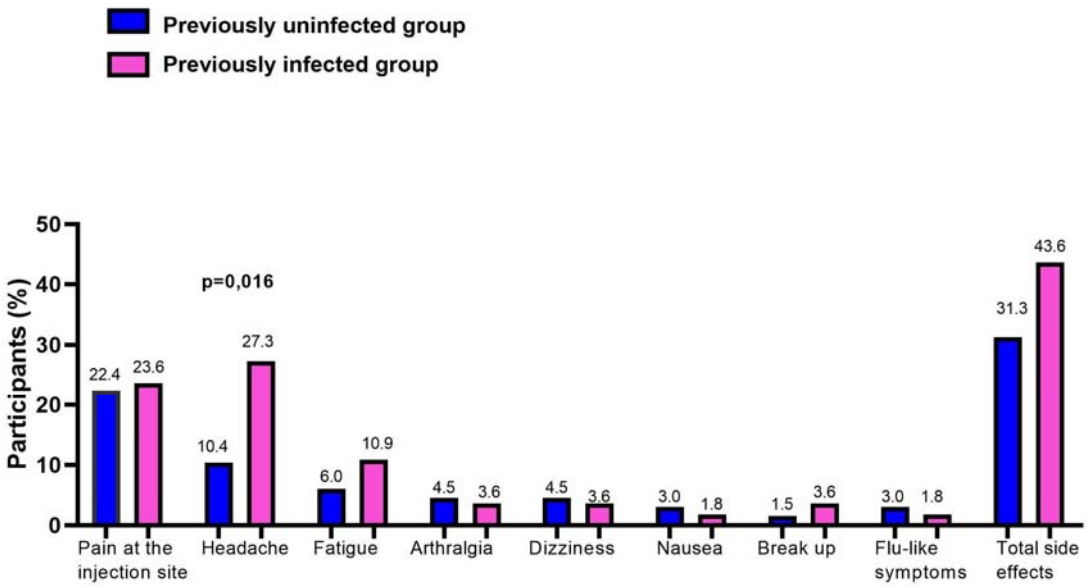

Figure 1. Side effects after the second dose of vaccination. p values are shown only for significant differences determined by the $\chi 2$ test.

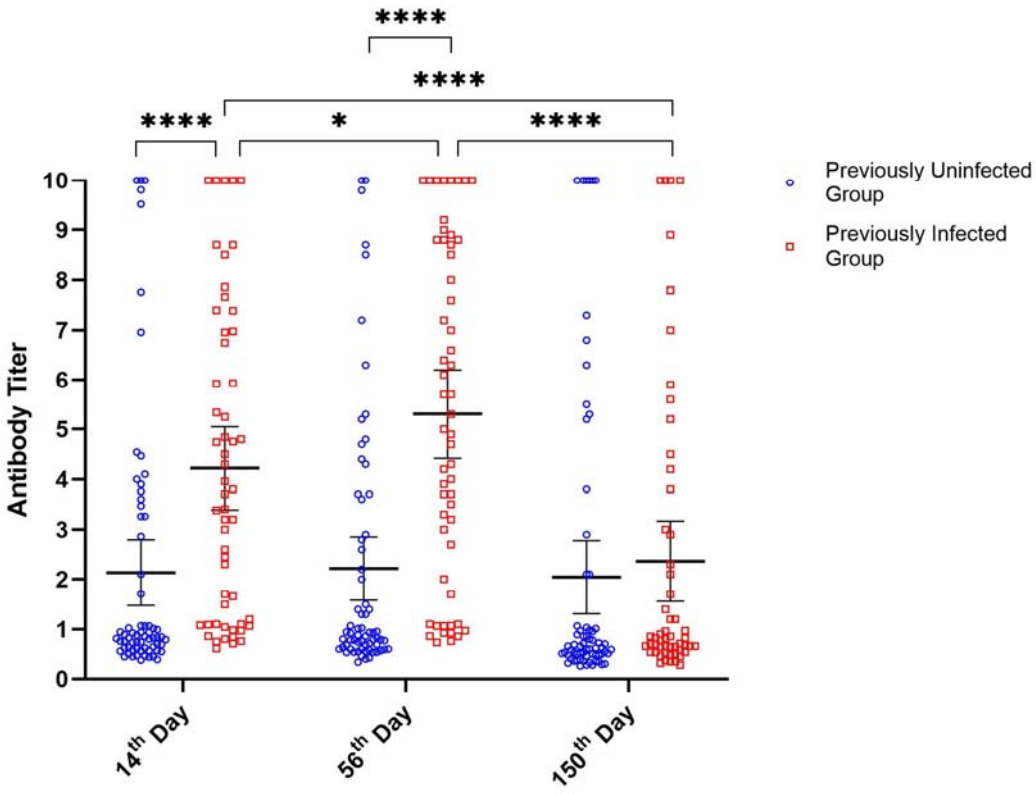

Figure 2. Antibody titres in healthy and previously infected groups after the second dose of vaccination. Data are presented as mean and 95% CI. Statistical difference is indicated with asterisks (* $p< 0.05$ and **** $p< 0.0001$).

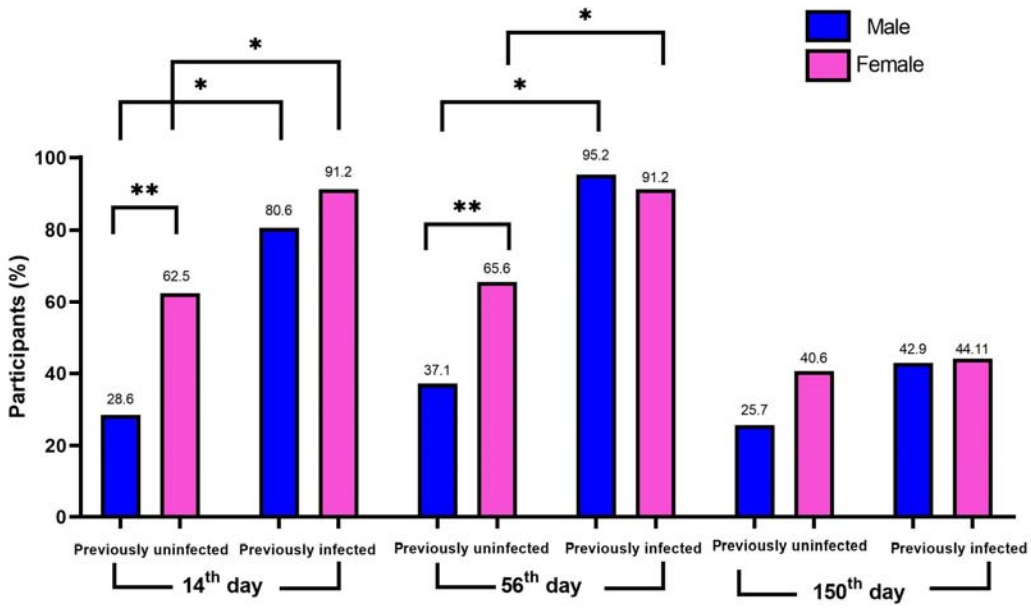

Figure 3. Seropositivity by gender in previously uninfected and previously infected groups. Statistical difference is indicated with asterisks (*p< 0.05 and **p< 0.001).

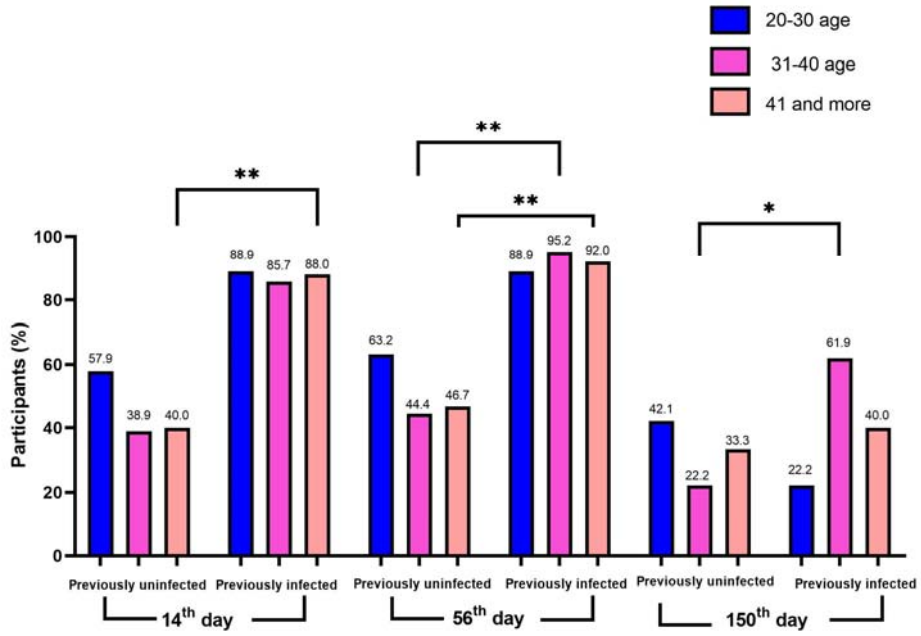

Figure 4. Seropositivity by age in previously uninfected and previously infected groups. Statistical difference is indicated with asterisks (*p< 0.05 and **p< 0.001).

4. Discussion

Neutralizing antibodies that prevent the SARS-CoV-2 virus from binding to the target cell have an important role in the protection against COVID-19 disease. For this reason, plaque reduction neutralization tests, that detect the level of neutralizing antibodies after vaccination and are regarded as the gold standard test, are very important in determining the efficacy of the vaccines. However, the long duration of the test and the need for biosafety

level 3 laboratories limit the use of these tests in routine laboratories. For this reason, simple, time-saving and low-cost ELISA methods based on various antigenic structures of the virus have been developed and used as an alternative to determine vaccine efficacy (MacMullan et al., 2020; Yassine et al., 2021). The specificity and sensitivity of these tests vary depending on the methodology used and the variation of the antigen. In a study conducted to evaluate performance of five ELISA test kits used to measure anti SARS-CoV-2 IgG antibody levels, the highest specificity (98.6%) was obtained with the Lionex kit, while the lowest specificity (75.7%) with the Anshlab kit (Yassine et al., 2021). Also, previous studies have suggested that the anti-nucleocapsid (anti-N) antibody response may arise earlier and attenuate more rapidly than the anti-spike (anti-S) response (Chia et al., 2021; Coste et al., 2021). Therefore, targeting different antigens of the virus might result in differences in specificity and sensitivity of ELISA (16). In the present study, the QuantiCOR SARS-CoV-2 IgG test kit, which was based on the receptor binding site of spike proteins was employed. The sensitivity and specificity of this test were calculated to range between 95% and 100% (unpublished data).

Studies with the CoronaVac vaccine in people showed that most of the vaccine-related side effects were mild. Tanriover et al. reported that in the phase-3 trial of the CoronaVac vaccine, the frequency of any side effects was 18.9% in the vaccine group, and no death or grade 4 side effects were observed (Tanriover et al., 2021). Phase-1 and phase-2 studies conducted in healthy adults aged between 18 and 59 years in Chile revealed that the vaccine was well tolerated with the seroconversion rate ranging from 97% to 100%, 28 days after the second dose of vaccination depending on the amount of antigen (Bueno et al., 2021). The most common side effects seen in all these studies were reported to be fatigue and pain at the injection site. In the current study, mild side effects were detected in 36% (44/122) of all the participants after the second dose of vaccination. It was determined that there was no statistically significant difference between the healthy and previously infected groups in terms of side effects which were similar in both groups. Likewise, Soysal et al. (2021) reported that there was no statistically significant difference between the healthy and previously infected groups in terms of side effects, and that there was pain in the injection site at a rate of 41% after the first dose and 30% after the second dose. No serious side events, such as allergic reactions, occurred in any of the healthcare workers vaccinated in this study. The Turkish Ministry of Health decided to administer a third dose of vaccine at the end of the fifth month to healthcare workers who have already received two doses of CoronaVac vaccine. Two healthcare workers participated in this study received the BioNTech vaccine as the third dose and experienced two allergic reactions, one of which was severe and required hospital support. Although there was no confirmed information on side effects related to the use of a different vaccine as a booster after two doses of CoronaVac vaccination, our finding showed that allergic reactions might occur, albeit at a low rate.

In the five-month period during which the study was conducted, 6.9% (9/131) of the participants showed the symptoms of COVID-19 confirmed by PCR. Alpha or delta variants were detected in these participants with one exception. In a phase-3 study conducted in Turkey, the proportion of COVID-19 cases was reported to be lower (3.7%) in the vaccine group (Tanriover et al., 2021). It was not possible to measure the effect of the CoronaVac vaccine on variants, as they were not yet reported in the world during the abovementioned study. CoronaVac, Novartis, Johnson & Johnson, and AstraZeneca vaccines have been reported to have decreased efficacy against the B.1.351 variant (Bian et al., 2021). Studies showed that the effectiveness of vaccines against other variants decreases as well (Lopez Bernal et al., 2021; Nasreen et al., 2021). The spread of variants poses an enormous challenge to the prevention and control of the SARS-CoV-2 pandemic through vaccination. Therefore, there is a need to develop various strategies, including accelerating the mass release of existing vaccines, increasing vaccine immunogenicity by increasing vaccine doses, and increasing vaccine efficacy by incorporating variants into next-generation vaccines.

In this study, the antibody titres on the 14^{th} and 56^{th} days after the second dose of vaccination were significantly high in healthcare workers who had previously contracted COVID-

19 when compared to those with no infection history. In the literature review, no study was found that measured the antibody titre of the CoronaVac vaccine in a 5-month period. However, in a study conducted by Soysal et al. with similar groups, anti-SARS-CoV-2 spike protein antibody titres were reported to be higher in previously uninfected healthcare workers on the 28th day after the second dose of vaccination than in previously infected individuals (Soysal et al., 2021). It has been reported that memory T and B lymphocytes were formed in those who have been infected with Coronavirus, and therefore, the majority of these people did not get COVID-19 for a certain period of time. Studies showed that memory cells were active for 7-8 months, and then the immune response decreased over time (Turner et al., 2021). The higher antibody titres in previously infected individuals in this study and other studies are thought to be due to the effective immunological response of memory B lymphocytes to the antigen. Interestingly, at the end of the 150th day in this study, it was found that the antibody titres in both groups decreased, but there was no statistically significant difference between the groups. Previous studies have also shown that the antibody titre decreased over time following vaccination (Israel et al., 2021, Khoury et al., 2021a). It is believed that the findings of the current study provided important information regarding the timing of the third dose of vaccination for persons receiving two doses of CoronaVac vaccine. Actually, this study was originally planned to measure the antibody titres of the CoronaVac vaccine over a 6-month period, but owing to sudden decision of the Ministry of Health for the application of the third dose of vaccination to people who received two doses of CoronaVac vaccine, we had to terminate the study in the five month period. However, our data supported the decision of the Ministry of Health to bring forward the third dose of vaccination.

Many studies have been conducted to demonstrate the effect of gender on serum antibody levels following COVID-19 vaccinations. Saure et al. (24) reported that IgG positivity following CoronaVac and BNT162b2 COVID-19 vaccination was higher in women than in men. Yalcin et al. (2021) reported in a study conducted in Turkey that the antibody titres after the first and second doses of vaccination were significantly higher in women than in men. In general, it has been scientifically proven that females typically develop higher antibody responses than males in all vaccinations (Fischinger et al., 2019). It has been reported that hormonal, genetic and microbiota differences are at the forefront of the underlying causes of gender differences in vaccine-induced immunity (Ruggieri et al., 2016). However, in some studies conducted in recent years, results contrary to this general view have been reported. For instance, in a study aiming to demonstrate the association between four different vaccines (BNT162b2-BioNTech, mRNA-1273-Moderna, Ad26.COV2.S Johnson &Johnson, am-COVID-Vac-Gamaleja) and gender, higher efficacy has been recorded in men (Bignucolo et al., 2021). In the present study, the antibody titres on the 14th and 56th days were determined to be significantly higher in women in the previously uninfected group. However, interestingly, no significant difference between the sexes was detected in the previously infected group at all time periods. In addition, there was no statistically significant differences between the genders in both groups on the 150th day after the second dose of vaccination. These data suggested that there can be a difference between the sexes at the beginning of vaccination, but as time progresses, antibody levels decrease in both sexes. However, more work with a longer duration is required to better understand the association between antibody titres and gender.

Different results have been obtained in studies revealing the relationship between vaccine efficacy and age. Most of the studies indicated that as age progresses, the effectiveness of the vaccine decreases as well as the level of protective antibodies (Bartleson et al., 2021; Collier et al., 2021). However, some studies have failed to find a significant association between antibody titres and age (Bayram et al., 2021; Yalçın et al., 2021). Since the target population of this study was actively working health workers, antibody titres of people in certain age groups could be measured, but no significant differences were observed by age in either groups. Similar to our study, Yalcin et al. reported that there was no statistically significant difference between the antibody titres

and age following the second dose of vaccination (Yalçın et al., 2021).

The limitations of this study were that the cellular immune response was not measured after vaccination, neutralization antibodies were not investigated, antibody levels were not measured before the second dose of vaccination, and older groups were not included in the study. Despite these limitations, the present study provided important information about the efficacy of the CoronaVac vaccine by investigating serum antibody levels over a five-month time period following two doses of vaccination.

Conclusion

It was concluded that seropositivity decreased dramatically (below 50%) in both groups at the end of five-month period following the second dose of CoronaVac vaccine. The findings also showed that vaccine efficacy in previously infected people was higher than in uninfected people. It is therefore plausible to suggest that a different vaccination program can be applied to those who survived the disease and those who have not been sick before. Lastly, it is believed that this study provided useful data to policy makers for planning and scheduling vaccination programs.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

Refereces

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