

# Detection and Evaluation of Antibodies to SARS CoV-2 Spike Protein in Healthcare Workers After Inactivated COVID-19 (CoronaVac) Vaccination

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## ABSTRACT

**Objective:** Antibodies against the S protein are used to investigate post-vaccine and post-infection immunity. In this study, it was aimed to determine the antibody levels and the efficacy of the vaccine after the CoronaVac vaccine in healthcare workers.

**Methods:** Data from 96 healthcare workers who had the CoronaVac vaccine were analyzed. From the first dose, monthly antibody measurements were made over a 5-months period with an interval of 28 days between two vaccine doses. Total antibodies (IgM and IgG) against SARS-CoV-2 were detected by the Electrochemiluminescence method using the Elecsys® Anti-SARS-CoV-2 S kit, which contains recombinant protein representing the receptor-binding site of the S1 antigen.

**Results:** 51% (n=49) of the volunteers aged 22-69 (39.75±11.19) were female. The mean antibody concentration was 8.93 U/mL one month after the first vaccine dose, 171.30 IU/mL one month after the second vaccine dose, 125.90 IU/mL two months after the second dose, 98.57 IU three months later, and 89.85 IU/mL after four months. Increase in antibody levels in the first and second months; The decreases in antibody levels in the in the following months were statistically significant. The proportion of subjects with antibody positivity  $\geq 0.8$  IU/mL and developing neutralizing antibodies ( $\geq 15$  IU/mL) was 68.75% and 5.21% after the first dose of vaccination. The rate of individuals developing neutralizing antibodies were 100%, 93.8%, 91.7%, and 89.6% with regard to the months after the second dose of vaccination. One person had SARS-CoV-2 D3L-containing variant (UK variant) PCR positivity 9 weeks after the second vaccine dose.

**Conclusion:** In the long-term follow-up, the neutralizing antibody level was found to be significantly higher even at the end of the 5th month, indicating that the vaccine is protective. The decrease in post-vaccination antibody concentrations and the emergence of new SARS-CoV-2 variants suggest that a booster dose may be beneficial.

## INTRODUCTION

Despite the control measures implemented all over the world, Coronavirus Disease 2019 (COVID-19) continues to spread.<sup>[1]</sup> According to the data of the World Health Organization (WHO) dated 14 August 2021, 205.338.159 cases and 4.333.094 deaths were reported,

and 4.428.168.759 doses of vaccine were administered.<sup>[2]</sup>

COVID-19 causes humoral immune response and antibody production against specific viral antigens such as N protein and S protein.<sup>[3]</sup> Since the beginning of the outbreak, more than 198 vaccines developed or in clinical development for COVID-19 have been reported.<sup>[4]</sup>

These include inactivated vaccines, recombinant protein vaccines, vectored vaccines, live virus vaccines, and DNA or RNA vaccines. Seroconversion occurs approximately two weeks later.<sup>[5]</sup> However, little is known about the successful induction of a protective immune response. This obscurity leads to distrust and non-acceptance towards vaccines in society. In a multicenter study conducted in African and Middle Eastern countries, it was reported that 33.19% of the population did not consider getting vaccinated.<sup>[6]</sup> In another study conducted in England and Turkey, the rate of those who were hesitant about the vaccine was found to be 31% and 14%, respectively, and 3% of the participants refused to be vaccinated.<sup>[7]</sup> Reasons such as fear of side effects and the thought of being infected with the vaccine are effective.<sup>[8]</sup> However, vaccination is known to reduce hospitalization, severe disease, and mortality rates.<sup>[9]</sup> To protect the global community from the threat of morbidity and mortality from SARS-CoV-2, the safety, and efficacy of the vaccine must be revealed for vaccinating individuals.

The first vaccine administered in our country is the adsorbed COVID-19 vaccine, approved for emergency use by the Ministry of Health, and CoronaVac (Sinovac Life Sciences, Beijing) containing 3 µg/0.5 mL (600 SU/dose) inactivated SARS-CoV-2 virus and aluminum hydroxide as an adjuvant, China vaccine. The vaccination protocol was administered in 2 doses with an interval of 4 weeks. This prospective, observational, clinical study aimed to investigate antibody levels and efficacy of antibodies that develop after the CoronaVac vaccine in healthcare workers.

## MATERIALS AND METHODS

### Study design

Following the approval of the Ethics Committee (24.02.2021, protocol number: 514/196/20), this study was designed as a prospective, observational, single-centered. Individuals working in University of Health Sciences, İstanbul Kartal Dr. Lütfi Kırdar City Hospital as healthcare professionals and scheduled to receive two doses of the CoronaVac vaccine were invited via e-mail to participate in the study. Age, gender, and body mass index (BMI) parameters of the volunteers participating in the study were recorded. The history of influenza vaccination before the COVID-19 vaccination was questioned and recorded.

Exclusion criteria included having COVID-19 infection prior to vaccination, suspected symptoms such as fever, cough, shortness of breath, sore throat, headache, muscle pain, loss of taste or smell, and diarrhea.

### Antibody measurements

Two doses of the vaccine were administered with an interval of 28 days. Antibody measurements were made with one-month intervals. The first measurement was performed one month after the first dose, the second measurement one month after the second dose, the third

measurement two months after the second dose, the fourth measurement three months, and the fifth measurement four months after the second dose. Venous blood samples were obtained from participants in 5 mL BD Vacutainer plastic SST gel tubes, the samples were centrifuged at 3000 rpm for 5 minutes, serum samples were separated, and antibodies were investigated. Total antibodies (IgM and IgG) against SARS-CoV-2 were quantitatively detected by the electrochemiluminescence immunological (ECLIA) method and the Elecsys® Anti-SARS-CoV-2 kit (Roche Diagnostics GmbH, Germany; Reference Number: 09289267190 containing recombinant protein representing the receptor-binding site (RBD) of S1 antigen. The measurement range of the kit is between 0.40–250 U/mL, and values above 0.80 U/mL are considered positive in the explanation of the results as recommended by the manufacturer.<sup>[10]</sup> The specificity of the kit used is 99.98% and the sensitivity is 98.8%.<sup>[10]</sup> Antibody values of 15 U/mL and above detected by the anti-SARS-CoV-2 S test correlate very well with neutralizing antibodies and are considered a qualified indicator for the presence of neutralizing antibodies: PPA: 88.87%, NPA: 90.00%, PPV: 99.10%.<sup>[11]</sup>

### Statistical analysis

The NCSS (Number Cruncher Statistical System) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the research data. The normal distribution conformity of the quantitative data was tested with the Shapiro-Wilk test and the graphical examinations. The Mann-Whitney U test was used for comparisons between two groups of more than two quantitative variables without showing normal distribution. Kruskal-Wallis test and Dunn-Bonferroni test were used for comparisons between groups with more than two quantitative variables not showing normal distribution. The Friedman test was used for intragroup comparisons of quantitative variables that did not show normal distribution, and the Wilcoxon signed-rank test with Bonferroni correction was used for the evaluation of pairwise comparisons. Wilcoxon signed-rank test was used for intragroup comparisons of non-normally distributed quantitative variables. Statistical significance was set to  $p < 0.05$ .

## RESULTS

105 people who received two doses of vaccine in our hospital were invited to the study, and 9 people were excluded from the study because they did not participate in the antibody level measurements on time. Data analysis of a total of 96 participants was performed. The ages of the 96 participants in the study ranged from 22 to 69 (mean  $39.75 \pm 11.19$ ), with 51% ( $n=49$ ) female and 49% ( $n=47$ ) male (Table 1). The BMI of 48 (50%) participants in the study was  $<24.9$  kg/m<sup>2</sup> and 48 (50%) were found to be  $>25$  kg/m<sup>2</sup>. No statistically significant difference was found in the vaccine antibody levels measured at the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> months of the cases compared to the body mass

index ( $p>0.05$ ) in our study. Influenza vaccination rate in volunteers within 1 month prior to COVID-19 vaccination was 21.9% ( $n=21$ ), and male gender (61.9%,  $n=13$ ) and 40–49 years-old age group (61.9%,  $n=13$ ) was found to be higher. There was no significant difference between the antibody values of the participants and being vaccinated ( $p>0.05$ ).

### Antibody levels

#### Measurement 1: Antibody concentration measured one month after the first dose of vaccine administration

Antibody positivity was detected in 66 people (68.75%) after the first dose of vaccination. An antibody concentration higher than 15 U/mL, which is compatible with neutralizing antibodies, was observed in five participants (5.21%). The mean antibody concentration was found to

be  $8.93\pm 35.59$  U/mL.

#### Measurement 2: Antibody concentration measured one month after the second vaccine dose administration

Taking both 0.80 and 15 U/mL values as cut-off, antibody positivity was found to be 100% in all individuals participating in the study after the second dose. The mean antibody concentration was  $171.30\pm 81.95$  IU/mL.

#### Measurement 3: Antibody concentration measured two months after the second vaccine dose administration

The antibody positivity of all participants was found to be 100%. The mean antibody concentration was  $125.90\pm 83.30$  IU/mL.

#### Measurement 4: Antibody concentration measured three months after the second vaccine dose administration

The mean antibody concentration was found to be  $98.57\pm 80.63$  IU/mL.

#### Measurement 5: Antibodies concentration measured four months after the second dose of vaccine administration

The mean antibody concentration was found to be  $89.85\pm 83.15$  IU/mL (Table 2). The  $162.35\pm 82.93$  U/mL increase in the vaccine antibody level detected in the first and second measurements was found to be statistically significant ( $p=0.001$ ). The decreases in vaccine antibody levels detected in the third, fourth and fifth measurements were found to be statistically significant ( $p=0.001$ , Table 2).

It was observed that 68.8% ( $n=66$ ) of the individuals who participated in the study had a vaccine antibody level of 0.8 and above in the 1<sup>st</sup> month, whereas 5.2% ( $n=5$ ) had an antibody level of 15 and above.

In the measurements performed a month after the second dose, it was observed that the antibody level of all participants was 15 and above. It was observed that the antibody levels of 90 (93.8%), 88 (91.7%), and 86 (89.6%) partici-

**Table 1.** Demographic data of participants

Demographic data of participants	
Gender	n (%)
Female	49 (51.0)
Male	47 (49.0)
Age (years)	
Median	39.75 (22–69)
20–29	24 (25.0)
30–39	24 (25.0)
40–49	27 (28.1)
≥50	21 (21.9)
Body mass index (kg/m <sup>2</sup> )	
<18.5	2 (2.1)
18.5–24.9	46 (47.9)
25–29.9	32 (33.3)
>30	16 (16.7)
Flu vaccination	
Yes	21 (21.9)
No	75 (78.1)

**Table 2.** Evaluation of post-vaccine antibody levels by months

	Vaccine antibody levels (IU/mL)		p
	Avg±SD	Percentile 25%–75%	
Measurement 1	8.93±35.59	0.61–5.93	<sup>a</sup> 0.001**
Measurement 2	171.30±82.0	106.3–250	
Measurement 3	125.90±83.30	57.10–206.4	
Measurement 4	98.57±80.63	33.43–152	
Measurement 5	89.85±83.15	25.70–121.70	
1 <sup>st</sup> and 2 <sup>nd</sup> measurement difference (Δ)	162.35±82.93	96.92–245.29	<sup>b</sup> 0.001**
2 <sup>nd</sup> and 3 <sup>rd</sup> measurement difference (Δ)	-45.36±42.15	-71.82–4.61	<sup>b</sup> 0.001**
3 <sup>rd</sup> and 4 <sup>th</sup> measurement difference (Δ)	-27.34±54.33	-52.5–1.02	<sup>b</sup> 0.001**
4 <sup>th</sup> and 5 <sup>th</sup> measurement difference (Δ)	-8.72±44.07	-20.65–0	<sup>b</sup> 0.001**

a: Friedman test b: Wilcoxon Signed-Rank test \*\* $p<0,01$  . SD: Standard deviation.

**Table 3.** Antibody positivity distribution by month

	Vaccine antibody positivity distribution	
	n	%
Measurement 1		
≥0.8 IU/mL	66	68.8
≥15 IU/mL	5	5.2
Measurement 2		
≥0.8 IU/mL	96	100.0
≥15 IU/mL	96	100.0
Measurement 3		
≥0.8 IU/mL	96	100.0
≥15 IU/mL	90	93.8
Measurement 4		
≥0.8 IU/mL	96	100.0
≥15 IU/mL	88	91.7
Measurement 5		
≥0.8 IU/mL	96	100.0
≥15 IU/mL	86	89.6

pants were 15 and above in the subsequent 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> measurements, respectively (Table 3). While there was no significant difference according to gender in the antibody levels measured in the first three months ( $p>0.05$ ), the antibody values detected in the 4<sup>th</sup> and 5<sup>th</sup> months in women were statistically significantly higher than in men ( $p=0.009$  and  $p=0.018$ , respectively). In general, the vaccine antibody levels of participants aged 50 years and older were significantly lower than those aged 20–29 and 30–39 years ( $p=0.003$ ;  $p=0.031$ , respectively). There was no statistically significant difference between the age groups in the 5<sup>th</sup>-month vaccine antibody levels of the cases ( $p>0.05$ ).

### Patients with post-vaccine COVID-19

One participant had Polymerase Chain Reaction (PCR) positivity for the SARS-CoV-2 D3L-containing variant (UK variant) 9 weeks after the second vaccine dose. The antibody value detected in the fourth month of this healthcare worker with COVID-19 was 188.2 IU/mL. In one person, 10 weeks after the second vaccine dose, PCR positivity, and clinical signs were not observed despite the close contact with a family member who was PCR positive for the SARS-CoV-2 D3L-containing variant. The antibody level measured in the fourth month of this healthcare worker was 59.35 AU/mL.

## DISCUSSION

In our study, antibody levels against proteins representing the receptor-binding domain of S1 antigen were investigated in healthcare workers who received inactivated vaccines. The long-term efficacy of the vaccine and the post-vaccine COVID-19 positivity rate was evaluated. Even after a single dose of inactivated vaccine, up to 70%

of protective antibody positivity was detected. Blood samples taken within one month of the second vaccine dose revealed that all participants were immune to SARS-CoV-2. This protection continued in the long term after the first dose of vaccine, and the mean antibody value was observed to persist at a high mean value of  $89.85\pm 83.15$  at the end of 5 months. At the end of the fifth month, it was revealed that the rate of individuals who developed neutralizing antibodies was close to 90%.

Phase 1/2 CoronaVac trials in volunteers aged 18–59 years and over 60 years revealed that the vaccine doses examined had similar safety and immunogenicity profiles.<sup>[4,12]</sup> Subsequently, Phase 3 study results from Turkey were reported.<sup>[13]</sup> In this study, in which 10218 volunteers were randomly divided into CoronaVac and placebo groups, the vaccine efficacy was determined as 83.5% 14 days after the second dose. There were no deaths or grade four adverse events. The most important difference of our study from this large series is that antibody values were also studied after a long 5-month study period. Another large series was studied on the Chilean population.<sup>[14]</sup> The authors evaluated antibody levels 14 days after the second dose of vaccine, which they considered to be fully immunized. One of the unique features of our study is that the level of protection, which was low in the early period, increased significantly from 2 months after the first dose. However, we report long-term immunization findings.

In a review in which the safety and efficacy of COVID-19 vaccines were discussed, the results of 19 studies of 11 different vaccines considered to be more than 90% effective were analyzed.<sup>[15]</sup> It was concluded that the vaccines in question were well tolerated by the recipients, were effective and safe regardless of age and gender. However, in our study, while there was no significant difference in antibody levels measured in the first 3 months by gender, it was determined that the antibody values detected in the 4<sup>th</sup> and 5<sup>th</sup> months in women were significantly higher than in men. In their studies, Takahashi et al.<sup>[16]</sup> observed that there are significant differences in immune responses during the SARS-CoV-2 infection in male and female patients. Levels of important pro-inflammatory chemokines and cytokines such as IL-8, IL-18, and CCL5 and monocytes count were higher in male patients. A stronger T-cell response and CD8 cell count were observed in female patients than in male patients. Poor T-cell responses and high innate immune cytokine levels in male patients have been associated with the course and deterioration of COVID-19 disease. The reason for the rapid reduction in antibody levels in men may be related to the differences in the immune systems of men and women. On the other hand, in our study, it was determined that the vaccine antibody levels of the participants aged 50 and over were significantly lower than those between the ages of 20–29 and 30–39. However, there was no significant difference between the age groups in terms of the 5<sup>th</sup>-month vaccine antibody levels of the participants. Pellini et al.<sup>[17]</sup> reported that the humoral immune response decreases with age and that COVID-19 antibody levels are

not associated with BMI. In our study, there was no statistically significant difference between vaccine antibody levels according to body mass index. Antibody response may decrease in advanced ages due to the weakening of the immune system. Further studies are needed on the impact of BMI on the COVID-19 vaccine response.

PCR positivity for the SARS-CoV-2 D3L containing the variant (UK variant) was detected in only one health-care worker 9 weeks after the second vaccine dose. Two months after the second dose of vaccine, it appeared that the antibody concentration gradually decreased. For this reason, we think that an effective reminder dose for variants at 3 months may be beneficial in those who have received two doses of the vaccine.

### Limitations

Our study had some limitations. First, the participants were generally young and mostly without comorbidities. The average age of the participants was under 40 years. The small sample size was another limitation. It is known that as the number of participants increases, the number of side effects or complications increases. Also, immunity to COVID 19 cannot be explained by antibody levels alone. Therefore, studies investigating immune mechanisms at the cellular level are needed.

### CONCLUSION

As a result, the antibody response is inadequate after the first dose of the inactivated vaccine CoronaVac, while the antibody response increases one month after the second dose. In the long-term follow-up, a significantly high level of neutralizing antibodies even at the end of the 5<sup>th</sup> month indicates that the vaccine is protective. The decrease in antibody concentrations after vaccination and the emergence of new SARS-COV-2 variants suggest that a booster dose may be beneficial.

### Ethics Committee Approval

This study approved by the University of Health Sciences, Istanbul Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 24.02.2021, Decision No: 514/196/20).

### Informed Consent

Prospective study.

### Peer-review

Internally peer-reviewed.

### Authorship Contributions

Concept: S.D.T., M.M.A., E.Y., K.S., R.D.; Design: S.D.T., M.M.A., E.Y.; Supervision: K.S., R.D.; Fundings: S.D.T.; Materials: S.D.T., M.M.A., E.Y.; Data: S.D.T., M.M.A., E.Y.; Analysis: S.D.T.; Literature search: S.D.T., K.S.; Writing: S.D.T., K.S.; Critical revision: K.S., R.D.

### Conflict of Interest

None declared.

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## İnaktif COVID-19 Aşısı (CoronaVac) Olan Sağlık Çalışanlarında SARS CoV-2 Spike Proteine Karşı Gelişen Antikorların Saptanması ve Değerlendirilmesi

**Amaç:** S proteini bir transmembran proteini olup bu proteine karşı gelişen antikorlar, aşı sonrası ve geçirilmiş enfeksiyon sonrası bağışıklığı araştırmak için kullanılmaktadır. Bu çalışmada sağlık çalışanlarında CoronaVac aşısı sonrası antikor düzeylerinin ve aşının etkinliğinin araştırılması amaçlanmıştır.

**Gereç ve Yöntem:** CoronaVac aşısı uygulanmış, 96 sağlık personeline ait verinin analizi yapılmıştır. İki aşı dozu arasında 28 gün bırakılarak birinci dozdan itibaren beş aylık periyotta aylık antikor ölçümleri yapıldı. SARS-CoV-2'ye karşı oluşan total antikorlar (IgM ve IgG), elektrokemilüminesans yöntemi ve S1 antijeninin reseptör bağlanma alanını temsil eden rekombinant protein içeren Elecsys® Anti-SARS-CoV-2 S kiti ile saptandı ve karşılaştırıldı.

**Bulgular:** Yaşları 22–69 ( $39.75 \pm 11.19$ ) arasında değişen gönüllülerin %51'i (n=49) kadındı. Ortalama antikor konsantrasyonu birinci doz aşısı uygulamasından bir ay sonra 8.93 IU/mL, ikinci doz aşısından bir ay sonra 171.30 IU/mL, ikinci doz aşısından iki ay sonra 125.90 IU/mL, üç ay sonra 98.57 IU/mL, dört ay sonraysa 89.85 IU/mL olarak tespit edilmiştir. Birinci ve ikinci aylarda antikor düzeylerindeki artış; üçüncü, dördüncü ve beşinci aylarda antikor düzeylerindeki azalmalar istatistiksel olarak anlamlı bulunmuştur. Antikor pozitifliği  $\geq 0.8$  IU/mL gözlenen ve nötralizan antikor ( $\geq 15$  IU/mL) gelişen gönüllülerin oranı ilk doz aşısı sonrası %68.75 ve %5.21 olarak bulunmuştur. Nötralizan antikor geliştiren birey oranı, ikinci doz aşısı sonrası ise aylara göre %100, %93.8, %91.7 ve %89.6 şeklindedir. Bir kişide, ikinci doz aşısından dokuz hafta sonra SARS-CoV-2 D3L içeren varyant (İngiltere varyantı) PCR pozitifliği saptanmıştır.

**Sonuç:** Uzun süreli takiplerde nötralizan antikor seviyesinin beşinci ayın sonunda dahi anlamlı olarak yüksek bulunması aşının koruyucu olduğunu göstermektedir. Aşı sonrası antikor konsantrasyonlarının düşmesi ve SARS-COV-2'nin yeni varyantlarının ortaya çıkması, destek aşı dozunun faydalı olabileceğini düşündürmektedir.

**Anahtar Sözcükler:** Antikor tespiti; CoronaVac; immünite; inaktif aşı; SARS-CoV-2.