ORIGINAL ARTICLE

Waning immunity to inactive SARS-CoV-2 vaccine in healthcare workers: booster required

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Abstract

Aims Despite high vaccination rates, increasing case numbers continue to be reported with the identification of new variants of concern, and the issue of durability of the vaccine-induced immune response remains hot topic. Real-life data regarding time-dependent immunogenicity of inactivated COVID-19 vaccines are scarce. We aimed to investigate the changes in the antibody at the different times after the second dose of the CoronaVac vaccine.

Methods The study included 175 HCWs vaccinated with inactive CoronaVac (Sinovac Life Sciences, China) SARS-CoV-2 vaccine in two doses. Anti-spike/RBD IgG levels were measured first, third, and sixth months after the second dose. Chemi-luminescent microparticle immunoassay (IgG II Quant test, Abbott, USA), which is 100% compatible with plaque reduction neutralization test, was used.

Results Mean age of the participants was 38 ± 11.23 years (range between 22 and 66) of whom 119 (63.9%) were female, and 56 (32%) were male. Dramatic reductions were demonstrated in median antibody levels particularly in the infection-naïve group, comprising 138 HCWs compared to those with prior history of COVID-19 infection ($n = 37$) ($p < 0.001$). There was no difference between the two groups in terms of age, gender, blood groups, BMI, and comorbid diseases.

Conclusions While antibody positivity remained above 90% in the 6th month after two doses of inactivated vaccine in HCWs, the median titers of neutralizing antibodies decreased rapidly. The decrease was more rapid and significant in those with no history of prior COVID-19 infection. In this critical phase of the pandemic, where we are facing the dominance of the Omicron variant after Delta, booster doses have become vital.

Keywords COVID-19 · Inactive vaccine · Neutralizing antibody · Sinovac

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Introduction

The COVID-19 pandemic has emerged as a severe public health emergency and as of March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic in accordance with the International Health Regulations (IHR) [1]. The first year of the fight against the pandemic passed with heavy costs for healthcare workers (HCWs). In Turkey, the first cases and first deaths were reported among healthcare workers in March 2020. At the 10th month following the first reported case, after obtaining the interim results of phase III study, vaccination campaign was launched on 14th January 2021 with inactive COVID-19 vaccine (CoronaVac, Sinovac Life Sciences, Beijing, China) starting from healthcare workers, following the emergency use approval given by the Ministry of Health

[2]. The vaccine was administered as two doses, 28 days apart, and the coverage was subsequently expanded to the elderly, the disabled, those living, and working in nursing and foster homes. Afterwards, the vaccination coverage was extended gradually to other occupational and age groups [3]. On April 12, 2021, the BNT162b2 (Comirnaty®; BioNTech and Pfizer, Germany) vaccine has also started to be applied after CoronaVac. The Ministry of Health announced on February 03, 2022, that 84.52% of the population aged 18 and over had received two doses of the COVID-19 vaccine.

Despite the high vaccination rates, increasing case numbers continue to be reported with the identification of new variants of concern, and the issue of protectional duration of the immune response induced by vaccines remains hot topic [4]. Several studies on the immune response in people with a prior history of COVID-19 infection showed that antibody levels decrease at 4 months after contracting the virus [5, 6]. Variants of concern, particularly B.1.617.2 (Delta) and B.1.1.529 (Omicron), do reportedly evade the immune response and thus decrease the effect of neutralizing antibodies [7–9]. Although the effectiveness of vaccines decreases due to diminishing antibody titers over time and escape mechanisms of variants from the immune system, the role of vaccines in preventing transmission in the community and reducing the severity of COVID-19 disease cannot be denied [9]. Moreover, it is crucial to see the change of immune response over time for planning booster doses.

In this study, we aimed to evaluate and monitor the time-dependent variations in the antibody levels in a cohort of HCWs at the first, third, and sixth months after the second dose of the CoronaVac vaccine.

Materials and methods

Participants

The study cohort comprised 330 HCWs whose peripheral blood samples were obtained at 28–32 days after the second dose of CoronaVac (Sinovac Life Sciences, Beijing, China), upon their informed consent. It was planned to investigate SARS-CoV-2 IgG levels at the first (March 2021), third (May 2021), and sixth month (August 2021) time points following the second dose. After excluding those not available for blood sampling at the second and third time points, 175 HCWs were included in the final evaluation.

Prior infection status

Of those 175 HCWs, 138 had no history of clinical or laboratory-based COVID-19 (infection-naïve group) and 37 had a prior history of PCR-confirmed SARS-CoV-2 infection (with or without clinical symptoms).

Immuno-serological tests

Chemiluminescent microparticle immunoassay (CMIA) method was used to detect SARS-CoV-2 IgG titers (ARCHITECT IgG II Quant test, Abbott, USA), demonstrating the quantity of neutralizing antibodies against the receptor-binding region (RBD) of the spike protein S1 subunit of SARS-CoV-2. 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 [10]. Accordingly, 50 AU/mL or 7.1 BAU/mL and above concentrations were considered positive. This test has been reported to be 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 [11].

Demographic and clinical data

The demographic data of all participants (age, gender, blood group type, the symptoms, the presence of comorbidities, etc.) were recorded in the follow-up electronic sheets. In addition, the features of prior infection (diagnosis, clinical signs, and symptoms) in those who had history of COVID-19 were evaluated together with the antibody results.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 21 (IBM Corp.; Armonk, NY, USA) was used to evaluate the data. Qualitative data are presented as numbers and percentages, and quantitative data are presented as median and IQR25-75. Chi-square and Fisher's exact test were used in the evaluation of qualitative data, and 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 analyses.

Results

HCWs ($n = 175$) included in the study had a mean age of 38 ± 11.23 years (range between 22 and 66) of whom 119 (63.9%) were female, and 56 (32%) were male. Of the 37 participants with prior history of COVID-19, 17 (45.9%) were male, and 20 (54.1%) were female, with a mean age of 43.4 ± 11.09 years. Of the infection-naïve group, 40 (28.99%) were men, 98 (37.01) were women, and the mean age was

40.84 ± 11.25 years. Of the participants with a prior history of COVID-19, 3 had asymptomatic COVID-19, 14 had moderate, and 2 had severe clinical forms of the disease. Fever (43.2%), fatigue (74.6%), arthralgia (59.4%), loss of taste and smell (72.9%), and headache (43.2%) were the most common symptoms in these individuals. 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 ($p > 0.05$). The percentage of antibody positivity was found to be 92.4% and 93.0% in males and females after 3rd month of the second dose vaccination, respectively ($p = 0.0885$). In the 6th month, we found that 94.1% of females and 91.2% of males remained antibody seropositive ($p = 0.486$). In the 3rd month, the percentage of antibody positivity was 90.3% and 94.2% in under 40 and over 40 years old ($p = 0.333$). In the 6th

month, the percentage of antibody levels of 50 AU/mL and above was 95.8% under 40 years old, while it was 91.3% at over 40 years old ($p = 0.239$). No significant difference was detected between antibody positivity according to body mass index (BMI), both 3rd and 6th months ($p = 0.604$, $p = 0.298$, respectively). No significant difference was detected between antibody responses in individuals who remained the seropositivity after 3rd and 6th months according to comorbidities and blood groups (Table 1). Median antibody titer was 729.1, 316.1, and 231.8 AU/mL after the second dose of vaccine, at 1st, 3rd, and 6th months, respectively (Table 2) (Fig. 1). IgG antibody titers of over 1050 AU/mL (which is equivalent to 1:80 dilution in the plaque reduction neutralization test) were detected in HCWs 32%, 13.7%, and 15.4% after the second dose of vaccine, at 1st, 3rd, and 6th months, respectively. Median antibody titer was 674.25, 237.75, and

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

	Third month			Sixth month		
	< 50 AU/mL	≥ 50 AU/mL	p	< 50 AU/mL	≥ 50 AU/mL	p
	n = 13 (%)	n = 162 (%)		n = 13 (%)	n = 162 (%)	
Gender						
Male	4 (7.0)	53 (93.0)	.885	5 (8.8)	52 (91.2)	.486
Female	9 (7.6)	109 (92.4)		7 (5.9)	111 (94.1)	
Age						
< 40	7 (9.7)	65 (90.3)	.333	3 (4.2)	69 (95.8)	.239
≥ 40	6 (5.8)	97 (94.2)		9 (8.7)	94 (91.3)	
Body mass index						
Normal	5 (6.0)	78 (94.0)	.604	3 (3.6)	80 (96.4)	.298
Overweight	5 (8.3)	55 (91.7)		6 (10.0)	54 (90.0)	
Obese	3 (12.0)	22 (88.0)		2 (8.0)	23 (92.0)	
Department						
Basic Medical Sciences	0 (0.0)	9 (100.0)	.844	0 (0.0)	9 (100.0)	.641
Internal Medical Sciences	7 (8.3)	77 (91.7)		7 (8.3)	77 (91.7)	
Surgical Medical Sciences	3 (7.5)	37 (92.5)		2 (5.0)	38 (95.0)	
Other staff	2 (7.1)	26 (92.9)		1 (3.6)	27 (96.4)	
Allergy						
Absent	12 (7.5)	148 (92.5)	.692	12 (7.5)	148 (92.5)	.603
Present	1 (6.7)	14 (93.3)		0 (0.0)	15 (100.0)	
Autoimmune disorder						
Absent	13 (7.6)	159 (92.4)	.792	11 (6.4)	161 (93.6)	.193
Present	0 (0.0)	3 (100.0)		1 (33.3)	2 (66.7)	
Neurologically disorder						
Absent	13 (7.5)	161 (92.5)	.926	12 (6.9)	162 (93.1)	.931
Present	0 (0.0)	1 (100.0)		0 (0.0)	1 (100.0)	
Malignity						
Absent	13 (7.5)	161 (92.5)	.926	11 (6.3)	163 (93.7)	.069
Present	0 (0.0)	1 (100.0)		1 (100.0)	0 (0.0)	
Diabetes mellitus						
Absent	13 (7.8)	154 (92.2)	.532	11 (6.6)	156 (93.4)	.440
Present	0 (0.0)	8 (100.0)		1 (12.5)	7 (87.5)	

Table 1 (continued)

	Third month			Sixth month		
	< 50 AU/mL	≥ 50 AU/mL	p	< 50 AU/mL	≥ 50 AU/mL	p
	n = 13 (%)	n = 162 (%)		n = 13 (%)	n = 162 (%)	
Hypertension						
Absent	12 (7.3)	153 (92.7)	.548	11 (6.7)	154 (93.3)	.518
Present	1 (10.0)	9 (90.0)		1 (10.0)	9 (90.0)	
Hypothyroid						
Absent	13 (7.9)	151 (92.1)	.332	12 (7.3)	152 (92.7)	.447
Present	0 (0.0)	11 (100.0)		0 (0.0)	11 (100.0)	
Chronic cardiovascular disease						
Absent	13 (7.5)	160 (92.5)	.687	12 (6.9)	161 (93.1)	.867
Present	0 (0.0)	2 (100.0)		0 (0.0)	2 (100.0)	
Chronic lung disease						
Absent	13 (7.6)	158 (92.4)	.732	12 (7.0)	159 (93.0)	.751
Present	0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	
Prior history of COVID-19						
Absent	12 (8.7)	126 (91.3)	.305	11 (8.0)	127 (92.0)	.234
Present	1 (2.7)	36 (97.3)		1 (2.7)	36 (97.3)	
Blood type						
O (− or +)	3 (7.3)	38 (92.7)	.432	4 (9.8)	37 (90.2)	.528
A (− or +)	6 (9.1)	60 (90.9)		6 (9.1)	60 (90.9)	
B (− or +)	3 (14.3)	18 (85.7)		1 (4.8)	20 (95.2)	
AB (− or +)	0 (0.0)	18 (100.0)		0 (0.0)	18 (100.0)	

191.75 AU/mL after the second dose of vaccine, at 1st, 3rd, and 6th months in the infection-naïve group, respectively. Of the individuals with a prior history of COVID-19, median antibody titer was found to be 1047.1, 649.6, and 494.5 AU/mL, respectively. When the median antibody titer after two doses of vaccination was compared to the with and without a prior history of COVID-19, the difference was statistically significant ($p < 0.001$) (Table 2). The evaluated median antibody titers in terms of gender, age, blood type, BMI, and comorbidities did not differ significantly in terms of time-dependent variation ($p > 0.05$) (Table 3).

Discussion

Overcoming the pandemic invariably depends on the success of widespread vaccination, and however, efficacy and durability of immune responses largely vary depending on

Table 2 SARS-CoV-2 IgG median levels in blood samples taken at different times from HCWs who participated in the study

Antibody measurement time	Median (IQR %25–%75)
First month; AU/mL	729.10 (443.80–1285.70)
Third month; AU/mL	316.10 (137.50–564.00)
Sixth month; AU/mL	231.80 (128.00–631.80)

the vaccine type and the characteristics of the vaccinated population. In this study, time-dependent variations of antibody titers were determined in 175 HCWs vaccinated with two doses of CoronaVac (Sinovac) 37 of whom with history of SARS-CoV-2 infection 4–10 months prior to 1st dose of
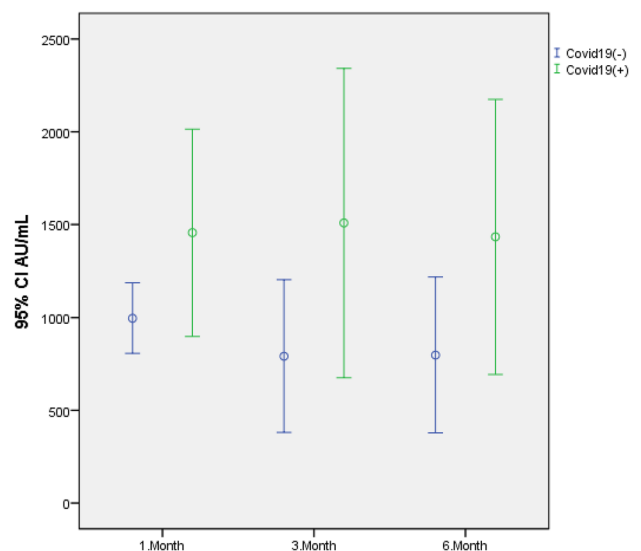
Fig. 1 SARS-CoV-2 IgG averages in blood samples taken at different times from healthcare workers who have prior history of COVID-19 and who are infection naïve

Table 3 Evaluation of antibody titers in HCWs according to demographic and clinical data

	First month (AU/mL) Median (IQR %25–%75)	Third month (AU/mL) Median (IQR %25–%75)	Sixth month (AU/mL) Median (IQR %25–%75)
Gender			
Male	636.10 (408.50–1414.60)	329.30 (139.45–595.55)	270.10 (106.35–796.65)
Female	768.20 (460.20–1181.83)	315.80 (132.80–562.05)	214.10 (129.95–572.25)
Age			
< 40	791.70 (428.78–1222.02)	311.70 (114.58–515.88)	217.75 (127.20–617.03)
≥ 40	707.10 (450.00–1388.60)	339.50 (144.50–662.40)	234.70 (130.80–654.10)
Body mass index (BMI)			
Normal (BMI < 24.9)	810.40 (482.90–1161.80)	337.40 (147.90–561.40)	258.10 (138.40–654.10)
Overweight (25 < BMI < 29.9)	657.15 (418.15–1340.55)	311.10 (124.33–735.18)	214.10 (108.98–732.18)
Obese (BMI > 30)	636.10 (438.90–1280.05)	300.90 (138.55–403.60)	224.30 (121.65–460.40)
Department			
Basic Medical Sciences	729.10 (358.70–1632.50)	329.30 (149.60–428.25)	257.00 (121.35–460.40)
Internal Medical Sciences	724.70 (468.58–1256.43)	336.05 (128.98–588.63)	209.10 (113.63–734.38)
Surgical Medical Sciences	903.20 (483.95–1339.40)	326.65 (176.88–652.53)	228.70 (132.40–478.23)
Other staff	545.60 (348.55–1312.38)	327.50 (122.60–602.48)	359.55 (184.88–1365.03)
Allergy			
Absent	723.85 (451.55–1258.38)	315.80 (134.88–563.35)	233.25 (127.85–624.97)
Present	990.60 (386.80–1752.80)	361.80 (150.70–601.50)	189.30 (139.10–1278.50)
Diabetes mellitus			
Absent	730.80 (427.30–1297.50)	327.10 (137.50–564.00)	242.30 (130.80–631.80)
Present	505.00 (468.58–1054.07)	240.95 (135.03–863.50)	122.80 (79.30–714.40)
Hypertension			
Absent	730.80 (446.90–1291.60)	327.10 (135.75–561.40)	231.80 (133.30–593.80)
Present	647.45 (352.90–1458.18)	172.65 (135.25–1504.38)	351.35 (77.82–1402.28)
Hypothyroid			
Absent	723.85 (435.85–1256.43)	314.35 (132.13–561.40)	231.15 (127.20–599.15)
Present	989.90 (450.00–1981.10)	381.80 (212.60–2061.90)	309.20 (159.60–1198.10)
Prior history of COVID-19			
Absent	674.25 (431.73–1181.83)	237.75 (115.18–439.80)	191.75 (111.00–436.45)
Present	1047.10 (597.25–2020.10)	**649.60 (374.95–1601.00)***	**494.50 (309.10–1379.55)***

$^{*}p = 0.000$***

vaccine. We demonstrated dramatic reductions in median antibody levels following two doses of CoronaVac vaccine, particularly in the infection-naïve group, comprising 138 HCWs ($p < 0.001$). There was no difference between the two groups in terms of age, gender, blood groups, and other comorbid diseases.

Real-life data regarding time-dependent variations of the SARS-CoV-2 IgG antibodies following inactivated COVID-19 vaccine are limited [12]. A study conducted in Brazil evaluated anti-S1 protein antibody levels in HCWs at 0, 40, and 110 days after the first dose of the CoronaVac vaccine. Although there was a significant decrease in the antibody titers when compared on day 40 to day 110, it was found to be significantly higher than on day 0 [13]. In a study conducted in Hong Kong involving 850 vaccinated participants, it was reported that while the

median antibody titers in the BNT162b2 mRNA vaccine group remained above the threshold value for 6 months, the median antibody titers decreased significantly after 2 months in the CoronaVac vaccine group [14].

Jantarabenjakul et al. [15] from Thailand showed that the median percentage of inhibition was found to be 77% and 38.7%, respectively, by surrogate viral neutralization test 4 and 12 weeks after the second dose in healthcare workers who received CoronaVac vaccine, and a statistically significant decrease. When the anti-SARS-CoV-2 total antibody titers were evaluated, total antibody titers among the older age group tended to be decreased but were not statistically significant (275.8 U/ml in the 20–30 years group vs. 185.6 U/ml in the 5–60 years group) [15]. Similarly, our study also showed a decrease in antibody titers after the 3rd month.

In a study from our hospital in which quantitative SARS-CoV-2 antibody titers were evaluated after two doses of CoronaVac vaccine with 330 HCWs, it was shown that significantly higher antibody titers were found with prior history of COVID-19 compared to without prior history of COVID-19 [16].

Similarly, we found that antibody titers remained high in the group with a prior history of COVID-19 in the 3rd and 6th months after the second dose of the vaccine. However, the rate of decrease in antibody titer over time is lower compared to the infection-naïve group. A study from Chile reported that vaccination with two doses of CoronaVac or one dose of BNT162b2 vaccine showed similar neutralizing antibody levels within 4–13 months in those with and without prior history of COVID-19 [15]. The researchers have also reported that the neutralizing antibody levels in individuals with a prior history of COVID-19 were more significantly increased after two doses of vaccine, resulting in an apparent induction of B-cell memory responses [17].

There are some limitations to our study. RT-PCR test, the gold standard in the acute diagnosis of COVID-19, could not be routinely performed for screening at the blood sampling time points or in the follow-up periods. Hence, we could not determine the number of asymptomatic infected individuals with any of the variants of concern defined by WHO. The second limitation is the methodology that we preferred over standard PRNT method (*IgG antibody titers > 1050 AU/mL 100% correlated to 1:80 dilution in PRNT*), due to technical and financial reasons [18].

This study presents real-life data regarding inactive CoronaVac vaccine efficacy and demonstrates relevant long-term (6 months) results in HCWs.

In conclusion, while antibody positivity remained above 90% in the 6th month after two doses of inactivated vaccine in HCWs, the median titers of neutralizing antibodies decreased rapidly. The decrease was more rapid and significant in those who had no history of prior COVID-19 infection, regardless of age, gender, comorbidity, and BMI. In this critical phase of the pandemic, where we are facing the dominance of the Omicron variant after Delta, booster doses have become vital.

Data availability All relevant data are available in the manuscript and the supplementary files.

Declarations

Ethics approval This study was approved by the Republic of Turkey Ministry of Health General Directorate of Health Services Scientific Research Studies Commission (Date: April 11, 2021), Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Scientific Research and Evaluation Commission (Date: May 7, 2021, and Number: 91630), and Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Clinical Research Ethics Committee approval (Date: June 2, 2021, and Decision No: 103545).

Informed consent and data privacy Written informed consent was obtained from the HCWs participated in this study. Personal data privacy has been protected.

Conflict of interest The authors declare no competing interests.

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