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Original Research

Assessing humoral immune response after two doses of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthcare workers

H. Demirbakan, I. Koçer, M. Erdoğan, A. Bayram*

Department of Medical Microbiology, Sanko University School of Medicine, Gaziantep, Turkey

Objectives: During COVID-19 pandemic, the absence of immunity in the population left them susceptible to infection with SARS-CoV-2; healthcare workers (HCWs) being in the highest risk group. This study intends to assess and follow up the humoral immunity in HCWs vaccinated with an inactivated virus vaccine (CoronaVac).

Study design: This is a prospective observational study.

Methods: A total of 1072 HCWs were investigated for the presence of immunoglobulin G antibodies to the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 after vaccination. Blood samples were obtained after 28 days of the first dose, 21 days of the second dose, and 3 months after the second dose. Detection of antispike antibodies was performed by the chemiluminescent microparticle immunoassay method (SARS-CoV-2 IgG II Quant, Abbott, Ireland). The results greater than or equal to the cutoff value of 50.0 AU/mL were reported as positive.

Results: Four weeks after the first dose of vaccine, antispike antibodies were detected in 834/1072 (77.8%) of HCWs. Seropositivity was higher among females (84.6%) than males (70.6% p < 0.001) and was found to be highest in both women and men between the ages of 18–34 years. Antispike antibodies were detected in 1008 of 1012 (99.6%) after 21 days of the second dose and in 803 of 836 (96.1%) after 3 months of the second dose.

Conclusions: CoronaVac was found to be highly immunogenic after two consecutive doses performed 28 days apart to HCWs; however, the immunogenicity declined significantly (p < 0.001) after 3 months following the second dose of vaccine.

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Introduction

Since the COVID-19 outbreak began, researchers around the world have been trying to develop vaccines against ‘Severe Acute Respiratory Syndrome Coronavirus 2’ (SARS-CoV-2), with more than 200 vaccines being currently in preclinical or clinical development. Efforts toward the development of a vaccine have led to several candidate vaccines, including inactivated vaccines, live virus vaccines, recombinant protein vaccines, vectored vaccines, and DNA or RNA vaccines.

CoronaVac is a chemically inactivated whole virus vaccine for COVID-19 developed by Chinese biopharmaceutical company Sinovac Biotech (Beijing, China) and is created from African green monkey kidney cells (Vero cells) that have been inoculated with SARS-CoV-2 CN02 strain. It has shown good immunogenicity in mice, rats, and non-human primates with vaccine-induced neutralizing antibodies, which could neutralize 10 representative strains of SARS-CoV-2.

CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2, which supported the approval of emergency use of CoronaVac in China in July 2020. It is being used in vaccination campaigns by certain countries in Asia, South and North America, and Europe also. As of March 2021, 70 million doses of CoronaVac had been administered worldwide. CoronaVac elicited anti–receptor-binding domain (RBD) antibodies and neutralizing antibodies in 97.4% of individuals receiving the vaccine at 0 and 28 days.

Within the scope of combating COVID-19 pandemic, Turkish Ministry of Health had given emergency use approval for the use of CoronaVac and vaccination in Turkey started with priority groups, primary healthcare workers (HCWs) on January 14, 2021. On June 1, 2021, WHO validated CoronaVac for emergency use, giving...
countries, funders, procuring agencies, and communities the assurance that it meets international standards for safety, efficacy, and manufacturing.

Vaccination has been shown to provide potent protection from COVID-19; however, there are concerns that waning immunity and viral variation may lead to a loss of protection over time. Elucidation of the kinetics and duration of the humoral response induced by active immunization is important for interpreting results from serological surveys and for the management of COVID-19. To determine the humoral immune response induced by CoronaVac against SARS-CoV-2 after two consecutive doses and to guess the need for the administration of a third or booster dose, we planned to detect antispike antibodies in HCWs after the first and second doses, as well as after 3 months following the second dose of vaccine.

Methods

Study setting

HCWs of both genders, aged ≥18 years, who agreed to participate in this prospective study and those who underwent two-dose (28-day interval) SARS-CoV-2 vaccination with CoronaVac between January 14, 2021, and February 21, 2021, were included. The study, approved by the Ministry of Health Scientific Research Platform, was run at the microbiology laboratory of Sanko Hospital, which is a tertiary-care teaching university hospital located in Gaziantep, Turkey. Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Approval number: 2021/02/01). All participants signed the voluntary informed consent form ensuring they undergo screening evaluation and completed a questionnaire consisting of 17 questions designed to obtain information about demographic and clinical data including former exposure to COVID-19. HCWs who refused vaccination or were not able to finish sample collection were excluded.

Vaccination protocol

The vaccine used in this study was manufactured by Sinovac Biotech (Beijing, China) from inactivated CN02 strain of SARS-CoV-2 created from Vero cells and contained 3 μg/0.5 mL (equivalent to 600 SU per dose) and aluminum hydroxide as adjuvant. Vaccination of HCWs was performed in hospital with the schedule of two consecutive doses of 600 SU (0.5 mL) administered 28 days apart to deltoid.

Sample collection

Sequential blood samples were collected from HCWs to determine the levels of antispike IgG antibodies: first, 28 days after the initial dose (between February 11 and 17, 2021); second, after 21 days following the second dose (between March 4 and 10, 2021); and finally, 3 months after the second dose of vaccination (between May 17 and 23, 2021). Participants underwent blood sampling with standard venipuncture at the hospital. Transfer of the samples and serum separation was done at the laboratory within 2 h of collection.

Analysis of samples and interpretation of results

Immunoglobulin G (IgG) antibodies to the RBD of the S1 subunit of the spike protein of SARS-CoV-2 were quantitatively determined from the serum samples. The analysis was performed by the chemiluminescent microparticle immunoassay method using SARS-CoV-2 IgG II Quant kit (Abbott, Ireland) according to the manufacturer’s instructions. Detection was carried on with Architect i2000SR instrument (Abbott, IL). Test results greater than or equal to the cutoff value stated in assay’s package insert (50.0 AU/mL) were reported as reactive and interpreted as positive for SARS-CoV-2 antispike IgG antibodies. The results below the cutoff value are reported as non-reactive and interpreted as negative.

Statistical analysis

As descriptive statistics, median and minimum to maximum values for continuous variables and frequency and percentage values for qualitative variables were given. In group comparisons, chi-square test was used. When expected values were less than five Fisher’s exact test was used. In all evaluations, p < 0.05 was considered statistically significant.

Results

Of 1290 HCWs occupied at the research hospital, 1079 were vaccinated with CoronaVac, and 211 refused any vaccination throughout the study period. All vaccinated HCWs were approached for the present study; seven of them did not want to participate in the study, 1072 volunteers gave written informed consent and completed the two-dose vaccination program. HCWs who refused or were unable to give blood sample after the second dose and/or after 3 months of the second dose were excluded from the study.

The median age of the participants was 33.2 years (95% confidence interval [CI], 0.67: 32.6–33.9 years). The cohort had a slightly greater representation from female individuals, with 51.5% female and 48.5% male. The age distribution of this cohort was as follows: 18–34 years old, 642 (59.9%); 35–59 years old, 406 (37.8%); and 60 years and older, 24 (2.2%, Table 1).

HCWs consisted of academicians who were not actively dealing with patients (4.7%); doctors actively examining patients (7%); 4th, 5th, and 6th grade medical faculty students doing internship in several wards at the hospital (14.1%); other health care assistants, such as nurses, dieticians, physiotherapists, pharmacists, emergency medical technicians, radiology technicians, anesthesia technicians, and laboratory technicians (29.8%); and assistant staff, such as caregivers, patient counselors, security, transportation, cleaning staff (33.1%), and administrative staff (11.3%) working at Sanko University hospital. Occupational roles and COVID-19 history of HCWs including those working in units serving COVID-19 patients in the last 12 months are provided in Table 2.

After 28 days of the first dose of CoronaVac, antispike IgG antibodies were detectable in 834 of 1072 (77.8%; 95% CI, 0.025: 75.44%–80.4%) HCWs. Seropositivity was higher among females (467/552; 84.6%) than males (367/520; 70.6% p < 0.001) and was found to be highest in both women and men between the ages of 18–34 years (88.9% and 79.5%, respectively). Among HCWs aged between 35 and 59 years, antispike IgG antibodies in females and males were 75.3% and 64.2%, respectively, and among those ≥60 years, 37.5% in both genders. There was statistically significant

### Table 1

| Age (yrs) | No. (%) of HCWs | Margin of error (95% CI) |
|----------|-----------------|-------------------------|
|          | Female | Male | Total |                       |
| 18–34    | 398 (72) | 244 (47) | 642 (59.9) | 0.276 (25.3–25.8) |
| 35–59    | 146 (26) | 260 (50) | 406 (37.8) | 0.581 (42.5–43.7) |
| ≥60      | 8 (2)  | 16 (3)  | 24 (2.2)  | 1.783 (63.1–66.7) |
| Total    | 552 (51.5) | 520 (48.5) | 1072 (100) |                     |
difference between all age groups in terms of antibody positivity (p < 0.05 for all). Assessment of SARS-CoV-2 antispike IgG in HCWs on day 28 after the first dose of CoronaVac is given in Supplementary Table 3.

Of 1072 HCWs, 225 (21%) informed that they had at least one chronic disease; hypertension was the most common reported clinical complaint (59.6%). Only a minority of the participants (2.2%) reported receiving immunosuppressive therapy in the last 12 months. Clinical information of HCWs is given in Table 3.

Table 3

| Occupational role                  | No. (%) of HCWs | PCR-confirmed COVID-19 cases, n (%) |
|-----------------------------------|-----------------|-----------------------------------|
| Academic member                   | 50 (4.7)        | 6 (12)                            |
| Doctor of medicine                | 74 (7)          | 23 (31)                           |
| Medicine student                  | 152 (14.1)      | 15 (9.8)                          |
| Health care assistant             | 319 (29.8)      | 95 (29.7)                         |
| Assistant staff                   | 355 (33.1)      | 100 (28.1)                        |
| Administrative staff              | 122 (11.3)      | 38 (31.1)                         |
| **Total**                         | **1072 (100)**  | **277 (25.8)**                    |

Occupation of HCWs in units serving COVID-19 patients:

- Emergency: 139 (65.2) 63 (24.4)
- COVID-19 service: 37 (17.4) 15 (40.5)
- Intensive care unit: 24 (11.3) 10 (41.6)
- Radiology-CT unit: 10 (4.7) 4 (40)
- COVID-19 laboratory: 3 (1.4) 0 (0)
- **Total**: 213 (100) 63 (29.6)

Although all HCWs completed their allocated two-dose vaccination schedule, serum samples were obtained from 1012 of 1072 participants after 21 days following the second dose, 521 (51.5%) were female, and 491 (48.5%) were male. Sixty HCWs refused or were unable to give blood sample after the second dose of vaccine. After the second dose, antispike IgG antibodies were detected in 1008 of 1012 (99.6%) HCWs. There were only four of 1012 (0.39%) who were seronegative after the second dose of vaccine; none had a PCR-confirmed diagnosis of COVID-19 before. Assessment of SARS-CoV-2 antispike IgG in HCWs on day 21 after the second dose of CoronaVac is shown in Supplementary Table 6.

Three months after the second dose of vaccine, 836 HCWs gave blood samples for antibody detection. Antispike IgG antibodies were detectable in 803 of 836 (96.1%). It was observed that the percentage of antibody positivity declined with time, and the percentage of negative HCWs (n = 33) increased with age. The difference between positive antibody rates obtained 3 weeks and 3 months after the second dose (99.6% and 96.1%, respectively) was statistically significant (p < 0.001). Assessment of SARS-CoV-2 antispike IgG in HCWs 3 months after the second dose of CoronaVac is shown in Supplementary Table 7. Comparison of the quantitative values (AU/mL) of SARS-CoV-2 antispike IgG values depending on age and time is demonstrated in Fig. 1.

Discussion

Reports indicate that there are more than 200 SARS-CoV-2 vaccine candidates either in development, in initial preclinical stages, or have entered human clinical trials. Here, we demonstrate the results of a prospective longitudinal study of HCWs to assess the antispike IgG positivity after two consecutive doses of an inactivated virus vaccine, CoronaVac.

Generally, measurement of the seroprevalence of antibodies, especially neutralizing antibodies, against SARS-CoV-2 from population-based epidemiological surveys is informative for the assessment of the proportion of the population who have at some point been infected with the virus and provides insight into the design of vaccination programs.

The reference standard method for detection of neutralizing antibodies, which may be used as a correlate of protective immunity, remains plaque reduction neutralization tests. However, these tests are not routinely performed in clinical laboratories, as they require biosafety level 3 containment facilities, are laborious, and are not amenable to automation. The presence of neutralizing antibodies has been correlated to antibody reactivity to viral structural proteins, such as RBD, S, and N using in vitro immunoassays. Although data are still limited, there is mounting evidence that antibodies detected by commercial serologic assays correlate with in vitro neutralizing capacity. The sensitivity and specificity of immunoassays were reported to be excellent for detection of the antispike humoral response to SARS-CoV-2 infection with a sensitivity between 84% and 87.1%, specificity between

Table 2

| Occupational role                  | No. (%) of HCWs | PCR-confirmed COVID-19 cases, n (%) |
|-----------------------------------|-----------------|-----------------------------------|
| Academic member                   | 50 (4.7)        | 6 (12)                            |
| Doctor of medicine                | 74 (7)          | 23 (31)                           |
| Medicine student                  | 152 (14.1)      | 15 (9.8)                          |
| Health care assistant             | 319 (29.8)      | 95 (29.7)                         |
| Assistant staff                   | 355 (33.1)      | 100 (28.1)                        |
| Administrative staff              | 122 (11.3)      | 38 (31.1)                         |
| **Total**                         | **1072 (100)**  | **277 (25.8)**                    |

Table 4

| Adverse events seen in HCWs within 28 days following 1st dose of CoronaVac. |
|---------------------------------|-----------------|-----------------|-----------------|
| Adverse event                  | HCWs, n (%)     | Adverse events  |
| No                              | 687 (64.1)      | Yes             |
| Headache                       | 280 (26.1)      | Injection site pain |
| Fever/chills                   | 34 (3.2)        | Fatigue/weakness |
| Muscle/joint pain              | 61 (5.7)        | Fever/chills    |
| Vomiting/diarrhea              | 15 (1.4)        | Muscle/joint pain |
| Other                           | 24 (2.2)        | Vomiting/diarrhea |

Table 3

| Clinical characteristic          | HCWs, n (%) | Antispike IgG |
|---------------------------------|-------------|---------------|
| Chronic disease in HCWs         |             |               |
| No                              | 847 (79)    | 675 (79.7)    |
| Yes                             | 225 (11)    | 140 (62.2)    |
| Hypertension                    | 134 (59.6)  | 92 (35.8)     |
| Asthma                          | 20 (8.9)    | 18 (2)        |
| Diabetes mellitus               | 17 (7.6)    | 10 (7)        |
| Rheumatologic disease           | 9 (4)       | 6 (3)         |
| Heart failure                   | 4 (1.8)     | 1 (1)         |
| Hyperlipidemia                  | 2 (0.9)     | 0 (0)         |
| Malignancy                      | 1 (0.4)     | 1 (0)         |
| Hepatitis B                     | 1 (0.4)     | 1 (0)         |
| Other                           | 37 (16.4)   | 9 (28)        |

Immunosuppressive treatment:

| No                              | 1049 (97.8)  | 817 (77.9)    |
| Yes                             | 23 (2.2)     | 17 (73.9)     |

Adverse events HCWs, n (%)

Positive, n (%) Negative, n (%)

| Yes                              | 385 (35.9)   | 6 (29.6)      |
| Headache                        | 280 (26.1)   | 15 (73.1)     |
| Injection site pain             | 61 (5.7)     | 78 (7.3)      |
| Fever/chills                    | 34 (3.2)     | 34 (3.2)      |
| Muscle/joint pain               | 61 (5.7)     | 61 (5.7)      |
| Vomiting/diarrhea               | 15 (1.4)     | 15 (1.4)      |
| Other                           | 24 (2.2)     | 24 (2.2)      |
Antibodies to spike RBD can inhibit binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptor, generating a strong viral neutralizing response. A wide range of COVID-19 vaccines in development use strategies that generate antibody response to the spike protein and the RBD domain of the S1 subunit.\textsuperscript{16,17} Chemiluminescent anti-SARS-CoV-2 serologic assays, as used in this study, have been reported to exhibit high sensitivity (97.8%), as summarized in a systematic review and meta-analysis.\textsuperscript{22}

In this study, we used the Abbott SARS-CoV-2 IgG II Quant kit, which is designed to detect IgG antibodies, including neutralizing antibodies, to the RBD of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma. Serum samples obtained from HCWs after the first and second doses of vaccination with CoronaVac showed 77.8% and 99.6% seroconversion, respectively. If we extract HCWs who have had a PCR-con

\( \text{seroconversion} = \frac{\text{positive samples}}{\text{total samples}} \times 100\% \)

In messenger RNA (mRNA) vaccine trial studies, antispike seroconversion was observed 100% by day 15 following vaccination with mRNA-1273 and by day 21 following vaccination with BNT162b2.\textsuperscript{23,24} According to our results, CoronaVac reached the seroconversion rate of mRNA vaccines after the second dose (i.e. 99.6%), and we found that two doses of this vaccine were highly immunogenic in healthy adults aged 18–59 years.

People aged >60 years have an increasing risk of severe illness and death from COVID-19, especially those with underlying chronic conditions. The response to vaccines is usually reduced in older adults due to immune senescence. Zhiwei et al.\textsuperscript{25} reported in their phase 1/2 clinical trial that CoronaVac was well tolerated and immunogenic in healthy adults aged >60 years, and neutralizing antibody responses to live SARS-CoV-2 was not reduced in that population. Our findings showed that antispike antibody response in HCWs aged >60 years (n = 24) after the first dose was relatively low (37.5%); however, immunogenicity reached a level close to that in the 18–59 years age group after the second dose (95.6%).

Our study has some limitations; we did not check the seroprevalence of SARS-CoV-2 antispike antibodies in HCWs before vaccination; therefore, we could not give data for seroconversion. We mostly reported immune response for healthy adults aged between 18 and 59 years of age and included only a small number of individuals from more susceptible groups in our study population (e.g. individuals aged ≥60 years or with impaired immunity).

Another limitation of this study is although understanding the duration of the humoral response is essential toward determining immunogenicity obtained with vaccination, antibody testing is not currently recommended to assess immunity after vaccination against SARS-CoV-2.

The incidence of adverse reactions was not rare (35.9%), being the most common symptom headache (26.1%). This result was not in accordance with previous finding from another study performed with CoronaVac where the most common symptom was injection site pain.\textsuperscript{26} Compared with other COVID-19 vaccine candidates, such as viral-vectored vaccines or DNA/RNA vaccines, the occurrence of fever (3.2%) with CoronaVac was relatively low.\textsuperscript{27-29} Previous studies suggested that antibodies against SARS-CoV-2 were maintained for at least 4 months.\textsuperscript{26,27} Khoury et al.\textsuperscript{27} found that the decay of neutralizing titer in vaccinated subjects over the first 3–4 months after vaccination was at least as rapid as the decay observed in convalescent subjects. However, the SIREN study supported the hypothesis that the new licensed vaccines will provide high degree of immunity of prevention from symptomatic infection with SARS-CoV-2 for working-age adults for an average of 7 months.\textsuperscript{28}

In this study, we observed that the humoral immunity is sustained 96.1% after 3 months; however, the levels of antibody titers obtained in this study should not be used as a correlate of protection because the protective level of antibody titer was not established to date.

As a conclusion, in this study of immunogenicity of an inactivated SARS-CoV-2 vaccine, we found that two consecutive doses of CoronaVac were well tolerated with minor adverse reactions and were highly immunogenic in HCWs. As expected, the amount of antispike antibodies decreased after 3 months following the second dose of vaccine, and the difference was statistically significant (p < 0.001). The antibody level itself might not be the key for an intact immune response; however, it is highly predictive of immune protection and will assist in developing new vaccination strategies to control the pandemic. The durability of humoral responses against SARS-CoV-2 on vaccination needs to be further clarified with a longer follow-up time.
Author statements

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Ethical approval

Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Approval number: 2021/02/01).

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Competing interests

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.01.011.

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