SARS-CoV-2 Infections in Vaccinated vs Unvaccinated Healthcare Workers: Assessment of the Effectiveness of CoronaVac

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Abstract

Although several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been efficient against clinically significant coronavirus disease 2019 (COVID-19), breakthrough infections are being reported for several months. Here we conducted a prospective cohort study to assess the effectiveness of an inactive vaccine (CoronaVac; Sinovac, China) against SARS-CoV-2 by following cases of COVID-19 among vaccinated healthcare workers. Between March and September 2021, 1012 vaccinated and 211 unvaccinated healthcare workers from a tertiary care university hospital were followed for PCR-confirmed SARS-CoV-2 infections. COVID-19 active surveillance of the healthcare workers was carried out by the Infection Prevention and Control Unit of the institution. Anti-spike antibody values before and after COVID-19 were recorded. During a six-month follow-up program, in 35 out of 1012 (3.5%) fully vaccinated and in 16 out of 211 (7.6%) unvaccinated healthcare workers SARS-CoV-2 infections were documented. There was a statistically significant difference between vaccinated vs. unvaccinated workers regarding SARS-CoV-2 infections (P=0.003). Although all unvaccinated healthcare workers experienced symptomatic COVID-19, the vaccinated group suffered less from symptoms (100% vs. 77.1%, respectively; P=0.045). CoronaVac was 64.5% and 88.4% effective in preventing symptomatic and severe disease, respectively, and had an efficacy of 100% in preventing death among healthcare workers. In accordance with our findings, it was seen that CoronaVac could not prevent breakthrough infections, but was highly effective in preventing severe disease and death in healthcare workers for a period of six months after two consecutive doses.

Key words: SARS-CoV-2; COVID-19; CoronaVac; healthcare workers

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Introduction
As of December 2019, COVID-19 disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) spread rapidly all over the world and was declared a pandemic by the World Health Organization (WHO) in March 2020 (1). In November 2021, it was reported that there were more than 240 million cases of COVID-19 worldwide with more than five million deaths (2). Efforts towards the prevention of the pandemic have led to the development of several vaccines including inactivated vaccines, live virus vaccines, recombinant protein vaccines, vectored vaccines, and DNA or RNA vaccines (3, 4). Healthcare workers are in the high-risk group due to frequent exposure to SARS-CoV-2 compared to other individuals during the pandemic. Emergency use approval was given for an inactivated COVID-19 vaccine (CoronaVac; Sinovac, China) as of January 2021 in Turkey and the vaccine was administered as two doses 28 days apart, primarily to healthcare workers (5). CoronaVac induced %99.6 humoral immunity in healthcare workers 21 days after the second dose, however data on the effectiveness of this vaccine for the prevention from COVID-19 are limited (6).

In this study, the efficacy of CoronaVac was monitored over a six-month period in healthcare workers who received full-dose vaccination at a tertiary-care university hospital. During the same period of time, COVID-19 cases in healthcare workers who refused the vaccine were followed up. Symptomatic and asymptomatic SARS-CoV-2 infections confirmed via polymerase chain reaction (PCR) were evaluated in both vaccinated and unvaccinated healthcare workers.

Materials And Methods
Study Design
This was a prospective observational cohort study designed to estimate the association between vaccination with the CoronaVac vaccine and SARS-CoV-2 infections among healthcare workers. The study was carried out for a period of six months (24 weeks) between 15 March 2021, and 15 September 2021, at Sanko University Hospital, which is a tertiary-care teaching hospital, located in Gaziantep, southeastern part of Turkey staffed by about 1300 healthcare workers. Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Date: 04.02.2021 Decision no: 01).

Participants
Healthcare workers who received two vaccine doses between January 14, 2021, and February 21, 2021, were assigned to the vaccinated group. The unvaccinated group was composed of healthcare workers who did not receive any doses of vaccine during this period. Study was started three weeks after all staff members had received a second dose of the vaccine. Participants in both groups were healthcare staff such as doctors, nurses, caregivers, medical technicians, laboratory staff, cleaning staff, students of medicine, academic and administrative staff. All participants were included in the study after completing the informed consent form. Demographic information and presence of chronic disease of the participants were recorded. COVID-19 active surveillance of the healthcare workers was carried out by the Infection Prevention and Control Unit of the institution. Routine controls of healthcare workers were managed by filling out the COVID-19 contact/case follow-up form and monitoring symptoms
such as fever, cough, cold, body aches, and fatigue weekly. Testing for the presence of SARS-CoV-2 by means of PCR assay remained readily available for fully vaccinated and unvaccinated staff who were symptomatic or had been exposed to an infected person, regardless of symptoms.

**Vaccination Protocol**

CoronaVac is an inactivated virus vaccine developed against SARS-CoV-2 infection (3). It is manufactured by Sinovac Life Sciences (Beijing, China) and is produced from a novel coronavirus (strain CZ02) grown in the kidney cell cultures (Vero Cell) of the African green monkey. The vaccine contains inactivated SARS-CoV-2 virus, aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, and sodium chloride. Vaccinations of participants were performed intramuscularly to deltoid with the recommended dose of 0.5 mL containing 600 SU of SARS-CoV-2 virus antigen with interval of 28 days between the first and second doses. Status of vaccination of the healthcare workers was ascertained from the employee health database. Full vaccination was defined as more than 21 days after receipt of the second dose.

**Antibody Detection**

To record the vaccine-induced antibody response to SARS-CoV-2, serum samples were obtained three weeks after the second dose of CoronaVac in vaccinated group. Anti-spike antibody values were determined using the SARS-CoV-2 IGG Quant (Abbott, Ireland) kit in an immunoassay device (Abbott Architect i2000SR, USA) operating with the chemiluminescence method at the microbiology laboratory. In accordance with the recommendations of the manufacturer, the results were considered positive if they were greater than or equal to 50.0 AU/mL, and negative if they were below this value. Samples with values above 40,000AU/ml were analyzed after being diluted 1:2.

**Diagnosis of COVID-19**

The follow-up period for SARS-CoV-2 infection in both study groups was six months (24 weeks). In case of a symptomatic or asymptomatic suspected infection, the filiation process was initiated by the nurse of the Hospital’s Infection Prevention and Control Unit. The diagnosis of COVID-19 was performed from nasopharyngeal and oropharyngeal swab samples via Coronagen RT-qPCR SARS-CoV-2 Variants Detection Kit (Gensutek, Turkey). Samples with a cycle threshold (Ct) value of <38 and sigmoidal curves were considered positive in line with the manufacturer's recommendation. PCR tests of the cases with negative results and continuing clinical suspicion were repeated with a new sample 24 hours later. Participants infected with SARS-CoV-2 were defined as symptomatic if they had any of the following complaints: temperature > 37.2°C, flu-like symptoms such as headache, sore throat, cough, dyspnea, rhinorrhea, myalgia, joint pain, malaise, and loss of sense of taste or smell.

**Statistical Analysis**

Mean and standard deviation or median and minimum-maximum values were given for the continuous variables as descriptive statistics, and frequency and percentage values were given for categorical variables. Chi-square test was used for group comparisons of categorical variables. P < 0.05 was considered statistically significant in all evaluations.
Results
The study group consisted of 1223 healthcare workers, out of which 1012 (82.7%) (age range, 18-69; mean [SD] age, 33.1 [10.8] years; 521 [51.5%] women) received two doses of vaccination with CoronaVac. The unvaccinated group consisted of 211 (17.3%) (mean [SD] age, 30.3 [6.9] years; 146 [69.2%] women) healthcare workers who refused vaccination throughout the study period.

Among 1012 fully vaccinated healthcare workers enrolled in the COVID-19 follow-up program, 35 (3.5%) SARS-CoV-2 infections were documented within six months. In this cohort (age range, 21-56; mean [SD] age, 34.8 [10.4] years; 22 [62.9%] women) COVID-19 cases occurred more frequently in females (62.9% vs 37.1%). Staff members, such as nursing staff and administration or maintenance workers were more frequently infected compared with academic staff (82.9% vs 17.1%). Demographic properties of the participants in both study groups were given in Table 1.

Twenty-seven (77.1%) of COVID-19 positive participants were diagnosed in the first 3-month period, and 8 (22.9%) in the second 3-month period. Though 34 (97.1%) of 35 healthcare workers diagnosed with COVID-19 had no previous history of COVID-19, one (2.9%) nurse working at the emergency unit had reinfection. She was asymptomatic when she was diagnosed for the second time.

During the 6-month follow-up of 211 unvaccinated participants, 16 (7.6%) (age range, 22-51; mean [SD] age, 30.3 [6.9] years; 9 [56.3%] men) became infected with SARS-CoV-2 confirmed by PCR. As expected, COVID-19 cases were more frequently seen in unvaccinated group compared to vaccinated group (7.6% vs 3.3%, respectively; P=0.003).

Eight (22.9%) of the vaccinated healthcare workers with COVID-19 were asymptomatic. They had to perform PCR test because they were in close contact with people who had COVID-19, as per the contact/case follow-up guide rules. Out of 35 vaccinated healthcare workers who were SARS-CoV-2 PCR positive 27 (77.1%) had at least one symptom at the time of diagnosis.

Most common symptoms were flu-like symptoms such as runny nose, joint pain, fatigue, and headache. Out of 35 healthcare workers with COVID-19, 6 (17.1%) had coexisting illnesses; diabetes mellitus (n=4 [11.4%]), hypertension (n=3 [8.6%]), hyperlipidemia and sleep apnea (n=1 [2.9%] each). Four (11.4%) of them were followed up in hospital due to their existing diseases, one of who (2.9%) developed COVID-19 pneumonia and was discharged with recovery within two weeks.

All unvaccinated participants who became SARS-CoV-2 PCR positive during the study period admitted with several symptoms to the hospital prior to their diagnosis. The most common symptoms were fever, malaise, cough, and joint pain. Four (25%) of 16 were hospitalized with the diagnosis of pneumonia due to COVID-19. One (6.3%) of those with pneumonia, a 46-year-old male radiology technician, died due to respiratory failure. Although all unvaccinated healthcare workers experienced symptomatic COVID-19, the vaccinated group suffered less from symptoms (100% vs 77.1%, respectively; P=0.045).

The incidence rate of symptomatic SARS-CoV-2 infection was 1.8 vs 4.4 per 10000 person-days in the vaccinated and unvaccinated cohorts, respectively, corresponding with an unadjusted IRR of 0.41 (95% CI, 0.23-0.74). Unvaccinated healthcare workers were 2.4 times more at risk of contracting COVID-19 than those of vaccinated. CoronaVac was 64.5% and
88.4% effective in preventing symptomatic and severe disease, respectively, and had an efficacy of 100% in preventing death among healthcare workers.

Anti-spike antibody evaluation of vaccinated healthcare workers (n=1012) showed that 99.6% had antibody results greater than 50.0 AU/mL (mean level, 1022.4 AU/mL) three weeks after the second dose of CoronaVac. All vaccinated participants with COVID-19 (n=35) had positive antibody levels before infection, and their mean antibody titer was higher than the mean antibody titer of all healthcare workers (1022.4 vs 1406.8 AU/mL) (Figure 1). The humoral immune response before and after SARS-CoV-2 infection was analyzed in 23 of 35 vaccine breakthrough cases. The antibody results revealed that the median value of anti-spike antibodies (919.2; 351.1-1939.2 AU/mL) detected after two doses of vaccination in this group was extremely lower than the median value of antibodies (13743; 983.9-32148.2 AU/mL) detected after the diagnosis of COVID-19 (Figure 2).

Table 1. Demographic properties of healthcare workers with COVID-19

<table>
<thead>
<tr>
<th>Properties</th>
<th>n (%):</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Female</td>
<td>22 (62.9%)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>18 (51.4%)</td>
</tr>
<tr>
<td>35-59</td>
<td>17 (48.6%)</td>
</tr>
<tr>
<td><strong>Units</strong></td>
<td></td>
</tr>
<tr>
<td>Academic Staff</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>Hospital Staff</td>
<td>29 (82.9%)</td>
</tr>
<tr>
<td>Consultant</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Doctor</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Nurse</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>Administrative Staff</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Medical Student</td>
<td>1 (2.95%)</td>
</tr>
<tr>
<td>Auxiliary Staff</td>
<td>8 (22.95%)</td>
</tr>
</tbody>
</table>
Figure 1. Anti-spike antibody levels of vaccinated healthcare workers before COVID-19.

Figure 2. Immune response in healthcare workers (a) before and (b) after COVID-19.
Discussion

The effects of COVID-19 pandemic are seen more commonly in healthcare workers than in other occupational groups as they are at significant risk from prolonged direct exposure to the virus via patients with COVID-19. For this reason, priority was given to healthcare workers and older adults when vaccination programs were initiated (6).

Although they have completed the full-dose vaccination program, the rate of COVID-19 in the first six months after CoronaVac was determined as 3.5% in healthcare workers of our hospital. About four-fifths (77%) of COVID-19 cases occurred within the first three months following vaccination, which made us think that the decrease in the number of cases in the second 3-month period may be due to the initiation of the vaccination program in the general population.

It was seen that a widespread and effective vaccination program was one of the most effective methods of preventing the spread of the virus (7). Especially for RNA viruses, the higher the spread of the virus among humans, the higher the likelihood of mutations. While some mutations may make the virus more advantageous in terms of infectivity, in some mutations, the virus may cause more severe disease (8).

The Center for Disease Control and Prevention (CDC) has determined various classifications for variants (9). Concern variants (Variant of Concern, VOC) of SARS-CoV-2 are variants that have increased infectivity by reducing the efficacy of vaccines or drugs. The Alpha (B.1.1.7) variant, which was the first identified variant in the VOC group, was seen first in the United Kingdom in September 2020 and has spread rapidly globally (10). While the Alpha (B.1.1.7) variant was dominant at a rate of 85% in April in our country, the Delta (B.1.617.2) variant became more dominant as of July through August 2021 as in many other countries worldwide.

The increase of COVID-19 cases in healthcare workers, especially in April 2021, made us think that the Alpha (B.1.1.7) variant may have effect in the spread of the virus within the first 3-month period of the follow-up.

With the emergence of highly infectious variants, there was a need to evaluate cases of reinfection to demonstrate the protective effect of vaccines against new mutations. The fact that
A fully vaccinated nurse working in emergency unit had COVID-19 confirmed by PCR after eight months for a second time, suggested that she was infected with a different variant of the virus. Among vaccinated healthcare workers, COVID-19 was mostly seen in nurses with a rate of 22.9%. In various studies, it has been reported that nurses have a higher incidence of disease compared to other healthcare professionals, and it is thought that this situation may be caused by a longer time of direct contact of nurses with the patients (11, 12).

In our study all (100%) unvaccinated healthcare workers with COVID-19 (n=16) admitted with several symptoms. Four (25%) of them developed COVID-19 pneumonia and one (6.3%) died due to respiratory failure caused by SARS-CoV-2. In vaccinated group however, symptomatic disease was seen in 77.1% of cases and only one (2.9%) out of 35 healthcare workers with COVID-19 developed pneumonia. This observation confirmed that CoronaVac prevented moderate and severe disease in vaccinated individuals (13).

Breakthrough infections after BNT162b2 messenger RNA vaccine have been reported in various studies. The incidence of COVID-19 was reported 2.6% (n=35) among 1497 vaccinated healthcare workers during 4-month period in Israel (14). Regev-Yochay et al. reported 1.8% COVID-19 in full-dose vaccinated healthcare workers, while this rate was 5.2% in unvaccinated staff. They reported that the incidence of symptomatic cases was significantly lower among fully vaccinated vs unvaccinated workers (15).

In Chile in a period of six months 45 (2%) breakthrough cases among 2263 volunteers were reported with SARS-CoV-2 infection over 14 days after the second dose of CoronaVac (16). In the present study, 3.5% SARS-CoV-2 infections were documented within the first six months following vaccination with CoronaVac. Both of the above studies were conducted at the same time period and in people vaccinated with the same vaccine which makes it easier to compare their results. We suggest that the volunteers being composed of healthcare workers may have increased the rate of contracting COVID-19 in our study.

Palacios et al. (17) found the efficacy of CoronaVac as 50.7% in volunteers between 18-59 ages. They reported that vaccination protected individuals 100% from very severe and moderately severe disease. Tanrıover et al. (18) reported 83.5% efficacy of CoronaVac in preventing symptomatic SARS-CoV-2 infection in a phase 3, placebo-controlled randomized clinical trial with 10214 participants between ages of 18-59. In a study conducted in Brazil the efficacy of CoronaVac was found as 77.6% in symptomatic cases and as 83.9% against hospitalization and death (19).

In our study, the incidence of COVID-19 among vaccinated vs. unvaccinated healthcare workers during a six-month follow up was 3.5 vs 7.6%, respectively, and the difference was statistically significant (P=0.003). The efficacy of CoronaVac was 64.5% in preventing symptomatic COVID-19, 88.4% in preventing severe disease, and 100% in preventing death among healthcare workers. It was thought that the differences in vaccine efficacy between studies were due to the different number of volunteers and the diversity of COVID-19 case definitions.

All healthcare workers with COVID-19 had antibody titers above the threshold value (≥ 50.0 AU/mL) after the second dose of CoronaVac. This finding suggested that, at least in some cases of our study, the effect of vaccine-induced humoral immunity was limited and protected against symptomatic disease but not against infection. Immunity induced with BNT162b2 vaccine has been shown to be greatly protective against clinical disease but somewhat less protective against
both infection and infectivity also (15). The degree of protection may depend more on the initial immune response than on the decay of antibody levels since memory cells are expected to respond to future exposures (14).

This study has some limitations; first, the cohort represented mostly young and healthy individuals, thus we could not guess protection from infection in vulnerable or older populations with coexisting diseases. Second, since we did not analyze the cycle threshold (Ct) values in COVID-19 cases, we could not make any comment regarding the viral load and infectivity of cases.

As a result of long-term exposure to SARS-CoV-2, mask and distance measures become ineffective from the protection of infection and more reliable results are obtained with vaccination. It is seen that the increase in the number of cases due to the increase of the variants in the circulation affects the protection of the inactivated vaccine. In accordance with our findings, it was concluded that CoronaVac was highly effective in preventing severe disease and death in healthcare workers for a period of six months after two consecutive doses.

Competing interests statement
The authors declare that they have no conflicts of interest.

References


