Original Article

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# Immunogenicity and adverse effects of the third booster dose with ChAdOx1 among dental care workers after receiving a full dose of CoronaVac.

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Dental care workers have very high risks of SARS-CoV-2 infection since most of the dental operations require aerosol-generating procedures which could potentially spread the virus in treatment areas. As a result, vaccination can be an important tool in protecting dental care workers from infection.

**Objective:** To investigate the adverse effects and immunogenicity after receiving third dose of viral vector (ChAdOx1) vaccine among dental care workers who fully vaccinated with inactivated (CoronaVac) vaccine.

**Materials and Methods:** Blood samples from 57 subjects were collected three times. Sixty days after fully vaccinated with CoronaVac (baseline), 14-21 days and 90-104 days after receiving ChAdOx1 booster dose. Blood samples were tested for immunity against SARS-CoV-2, including Anti-SARS-CoV-2 spike receptor-binding domain (RBD) IgG, Neutralizing antibody (sVNT) and Anti-nucleocapsid (N) protein IgG. Adverse effects were reported using questionnaire.

**Results:** At baseline, all subjects had an anti-RBD IgG titer greater than the cut-off value, while 43.8% had sVNT lower than the cut-off value. The anti-RBD IgG titer and sVNT appeared to increase in the second serum test yet reduced in the last test. At baseline, 40% of participants had anti-N IgG levels that were higher than the cut-off value. Anti-N IgG levels, along with the number of participants with values above the cut-off, have been declining in the other two serum tests. The majority of the participants experienced mild to moderate symptoms. Most of the symptoms subsided after a few days.

**Conclusion:** Receiving booster dose of ChAdOx1 after CoronaVac full vaccination can stimulate strong immune response against SARS-CoV-2 with no serious adverse effects. Although level of immunity declines within 3 months, neutralizing activity is still high. However, the protective efficacy tended to reduce overtime. To minimize the risk of infection, healthcare workers should follow prevention guidelines both inside and outside working hours.

**Keywords:** antibody, booster vaccine, Covid-19, dental care workers, SARS-CoV-2, viral vector

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## Introduction

The vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an important factor in reducing the COVID-19 pandemic. In February 2021, Thailand confronted with a widespread COVID-19 outbreak. The Thai government had approved an inactivated

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COVID-19 vaccine (CoronaVac) as a primary vaccine for Thai citizens. Healthcare workers aged 18-59-year-old were considered at a high risk of infection; hence, they are the first group who received two doses of CoronaVac [1].

The data indicated that receiving fully vaccinated CoronaVac can strengthen the immune system against SARS-CoV-2 and prevent symptomatic infection [2, 3] but after a while waning immunity and mutation of SARS-CoV-2 occurred leading to the diminishing of vaccine efficiency [4, 5]. Subsequently, many countries supplement the third vaccine injection to increase immunity [6-8]. In addition, the previous data illustrated that mRNA or viral vector vaccines are capable of neutralizing mutated SARS-CoV-2 variants [9, 10].

Dentists, including dental care workers, have a very high risk of infection from their routine practice because they are directly exposed to patients' secretion, such as saliva and blood. Furthermore, many dental operations are aerosol-generating procedures that potentially spread the virus inside treatment areas and possibly lead to infection [11, 12]. Thus, receiving a booster dose of vaccine can be crucial tool to increase immunity and prevent infection among dental care workers. Nonetheless, there is insufficient information on efficiency and side effects after the third booster dose injection. This study aims to investigate the immunogenicity in 3 months and the adverse effects after receiving AZD1222 (ChAdOx1 nCoV-19) following two doses of CoronaVac vaccination.

## Materials and Methods

Participants were healthy dental care workers (age: ≥18 years), including dentists, dental assistants, nurses, and laboratory technicians from the dental clinic Ramathibodi hospital (Bangkok, Thailand). All participants were fully vaccinated with two doses of CoronaVac and intended to receive ChAdOx1 as a vaccine booster. The study proceeded following the protocol shown in Figure 1. The participants who developed SARS-CoV-2 infection during the study interval, preferred other vaccines, denied blood collection or intended to withdraw from the study were excluded.

Participants were monitored for SARS-CoV-2 infection using a questionnaire and antibody level during the study. If the participant has any conditions presented in Table 1, they will be tested with the Real-Time polymerase chain reaction (RT-PCR) method. In case of positive, they will be treated following the Thai Department of Disease Control's COVID-19 treatment guideline [13]. The study protocol was approved by the human research ethics committee, faculty of medicine, Ramathibodi hospital, Mahidol university (COA.MUR 2021/729).

**Table 1** Criteria for testing RT-PCR.

| Criteria for RT-PCR test |
|---|
| - develop symptoms of respiratory tract infection [14] |
| - history of close contact with COVID-19 people [14] |
| - anti-N IgG higher than the cut-off value in the first serum test |
| - anti-N IgG increase and higher than cut-off in the second and the third serum test |
| -anti-RBD IgG antibody or sVNT increased in the second and the third serum test |

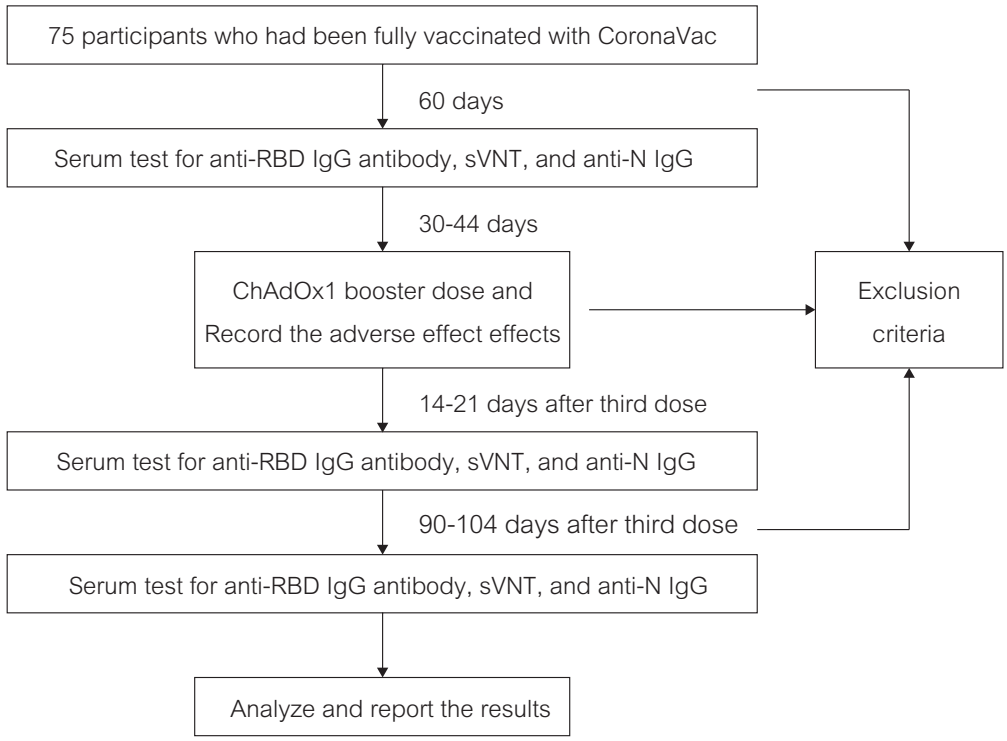


Figure 1 Schematic diagram of this study.

## Antibody assays

Blood samples were collected three times in total. First, at 60 days after being fully vaccinated with CoronaVac (baseline). Second, between 14-21 days after receiving the ChAdOx1 booster dose. Last, between 90-104 days after receiving the ChAdOx1 booster dose. Each time, blood samples were tested for immunity against SARS-CoV-2, including

1) Anti-SARS-CoV-2 spike receptor-binding domain (RBD) IgG

Anti-RBD IgG was tested using the chemiluminescent microparticle immunoassay method (Alinity, Abbott, IL, USA). Values ≥ 7.1 BAU/mL was considered positive.

2) Neutralizing antibody

Neutralizing activity against wild-type SAR-CoV-2 was tested using ELISA-bases surrogate virus neutralization test (sVNT) (NeutraLISA, Euroimmun, Lübeck, Germany). Values ≥ 35% inhibition was defined as positive.

3) Anti-nucleocapsid (N) protein IgG

Anti-N IgG was tested using the chemiluminescent microparticle immunoassay method (Alinity, Abbott, IL, USA). Values ≥ 7.1 BAU/mL was interpreted as positive.

Blood sample collection and antibody testing were conducted in the immunology laboratory, faculty of medicine, Ramathibodi hospital. The immunologist evaluated antibody testing results.

## The booster vaccine

Participants freely chose their vaccine booster type based on the Covid-19 vaccine guideline from Department of Disease Control of Thailand [15]. For ChAdOx1, participants will be received at least 90 days after being fully vaccinated with CoronaVac.

### Adverse side effect

The adverse effects after third dose vaccination were reported using an online questionnaire. Participants had to record any symptoms that occurred until they completely disappeared.

### Statistical analysis

Demographic data and side effects were presented as frequency or percentage. Statistical analysis was performed using GraphPad Prism version 9.0 for Microsoft Windows. Data distributions were investigated using the Kolmogorov-Smirnov test. Antibody titers and percent inhibition were reported as geometric mean titers (GMT) with 95% confidence interval (95% CI) or median with interquartile range (IQR) when appropriate. The difference of antibody titers and percent inhibition among groups was calculated using the Friedman test. A P-value $< 0.05$ was considered statistical significance.

## Result

### Demographic data

In the beginning, there were 75 participants enrolled in this study; however, a total of 18 people had been excluded. Eight persons chose other vaccines; nine were denied blood collection, and one developed SARS-CoV-2 infection on the 63rd day after receiving ChAdOx1. The patient reported mild symptoms, including sore throat, fever, loss of taste and smell. People who had close contact with the patient were quarantined and tested for SARS-CoV-2 infection using RT-PCR technique. No positive result was found. The patients received appropriate treatments under the responsibility of Ramathibodi hospital. As a result, 57 participants remained in the study and were included in the data analysis. Among the samples, one had closed contact with an infected person, which occurred 35 days after receiving ChAdOx1. Without symptom and negative result of RT-PCR confirmed that this person had not been infected. Details are provided in Table 2.

Table 2 The demographic data.

| Characteristics | n = 57 |
|---|---|
| Mean age, years (SD) | |
| - Male | 46.6 (15.8) y |
| - Female | 38.9 (9.2) y |
| Participants grouped by sex and age range | |
| - Male (percentage) | 6 (10.5) |
| o 18-29 y | 1 |
| o 30-59 y | 3 |
| o ≥ 60 y | 2 |
| - Female (percentage) | 51 (89.5) |
| o 18-29 y | 11 |
| o 30-59 y | 40 |
| o ≥ 60 y | - |
| - Infected participant (excluded) | 1 |
| - Participants who were in close contact with infected participant but did not get infected | 6 |

### Anti-RBD IgG and neutralizing antibody (sVNT)

After receiving CoronaVac, all participants had anti-RBD IgG titer more than the cut-off value, there were 25 participants (43.8%) with sVNT lower than the cut-off value; moreover, the distribution was abnormal. During 14 to 21 days after receiving ChAdOx1, the anti-RBD IgG titer and sVNT were increased. However, anti-RBD IgG titer and sVNT during 90-104 days after receiving ChAdOx1 showed declination (Table 3).

The differences in anti-RBD IgG and sVNT among baseline, during 14-21 days, and 90-104 days after receiving booster dose of ChAdOx1 are shown in Figure 2.

**Table 3** Anti-RBD IgG titer and sVNT reported in values and percentage change.

| Interval | Anti-RBD IgG (BAU/mL) | | sVNT (%) | |
|---|---|---|---|---|
| | GMT, 95% CI | % Change from previous value | Median, IQR | % Change from previous value |
| Baseline | 86.4 (69.3-107.7) | - | 39.8 (27.6-59.8) | - |
| 14-21 days after booster dose | 1,683.2 (1,417.8-1,998.3) | +1848.2% | 99.4 (99.0-99.6) | +149.7% |
| 90-104 days after booster dose | 455.4 (380.6-544.9) | -72.9% | 96.1 (89.1-98.3) | -3.3% |

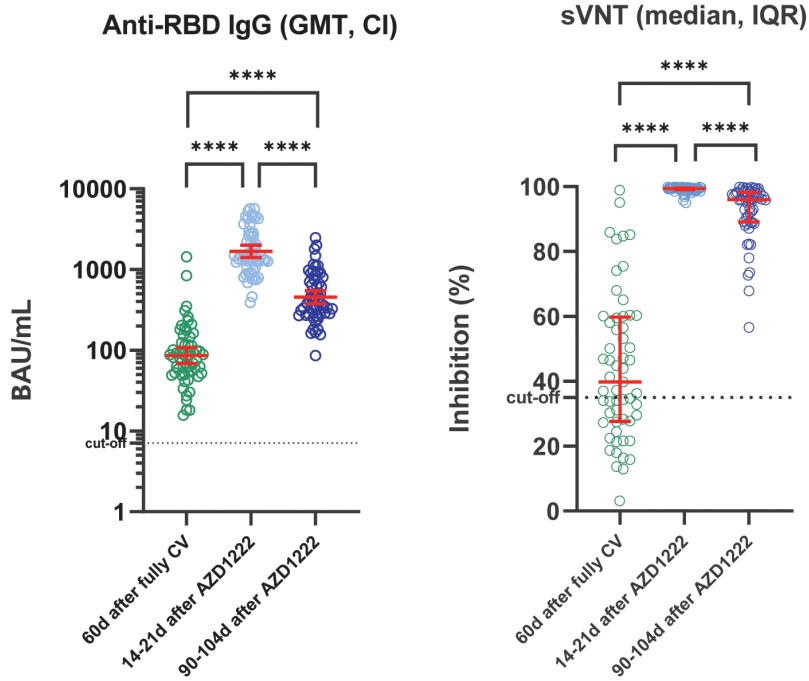


**Figure 2** (A) anti-RBD IgG titer and (B) sVNT at baseline, 14-21 days, and day 90-104 after receiving third dose vaccination. (*$P$<0.05, **P<0.01, ***$P$<0.001, ****$P$<0.0001)

### Anti-nucleocapsid protein IgG

At baseline, 23 participants (40.4%) with anti-N IgG were higher than the cut-off value. All of them were evaluated with RT-PCR. No positive result was found. However, anti-N IgG continuously declines in the other two serum testing and the number of participants with value over the cut-off. The differences in anti-N IgG among baseline, 14-21 days, and 90-104 days after being boosted with ChAdOx1 are shown in Figure 2.

### Adverse effects

In our finding, seven participants (12.3%) reported symptom-free after receiving ChAdOx1. However, the remaining participants developed adverse effects within the same day of vaccination and lasted within 1-7 days. Most participants reported that the adverse effects completely resolved within three days (63.1%), while the rest took 4-7 days for full recovery. The most frequently reported adverse effects was fever (21.3%), followed by pain at the injection site (20.1%), chilling (15.2%), myalgia (14.2%), and headache (13.4%). The less frequent adverse effects were dizziness (7.3%), swelling (4.9%), diarrhea (2.4%), joint pain (0.6%), and nausea (0.6%). There was no report of serious adverse effects (Figure 4).

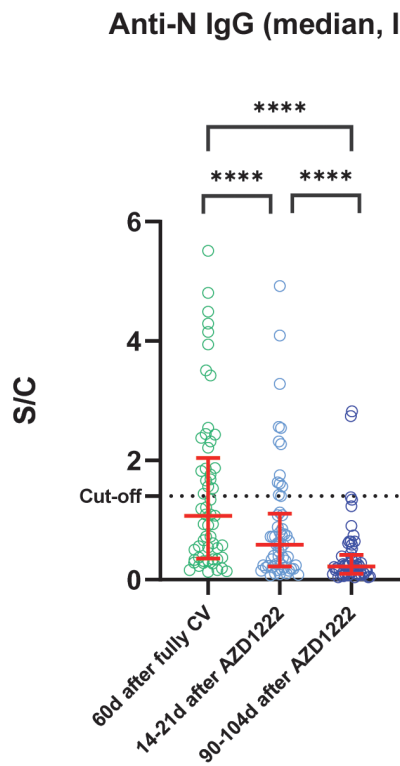


Figure 3 anti-nucleocapsid protein IgG at baseline, 14-21 days, and day 90-104 after receiving third dose vaccination. (*$P$<0.05, **$P$<0.01, ***$P$<0.001, ****$P$<0.0001)

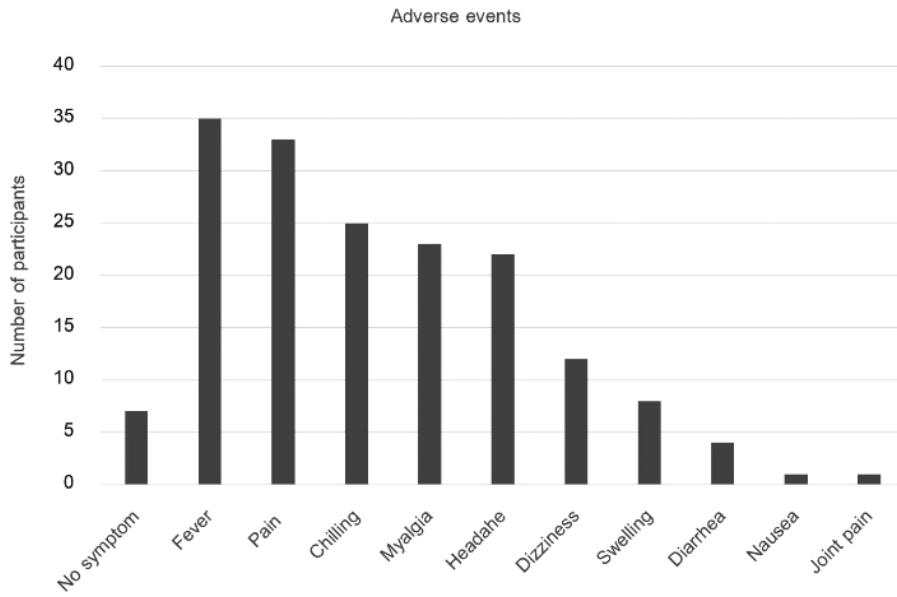


Figure 4 Type and amount of adverse effects

## Discussion

In March 2021, the surge of COVID-19 outbreaks had caused vaccines' supply shortage resulting in deprivation of vaccination particularly in middle-income and low-income country [16]. The idea of heterologous COVID-19 vaccine schedules had emerged to improve access to the vaccines. Several observational studies demonstrated the benefit of mixed-scheduled vaccination with acceptable or minor adverse effects. CombiVacS trial showed robust humoral and cellular immune response after a second dose of BNT162b2 in individuals primed with ChAdOx1-S for 8-12 weeks prior [17-20]. In the Com-COV study, the Oxford/AstraZeneca was followed by Pfizer or vice versa. In the Com-CoV2 study, mixed-schedules (Oxford/AstraZeneca followed by Novavax or Moderna and Pfizer followed by Novavax or Moderna) produced antibody and T cell responses higher than two doses of Oxford/AstraZeneca [18, 21]. In addition, the COV-BOOST trial showed differences in humoral and cellular responses to seven COVID-19 vaccines as a third dose (booster) following COV-BOOST [6].

In Thailand, when this study was carried out, the variant of SARs-CoV-2 that spread throughout Bangkok (Thailand) was the Delta variant [22]. Compared with the original variant (wild type), it is highly contagious, capable of creating severe symptoms and resisting the vaccine's immunity [23]. At that time, most of Thai healthcare workers were already vaccinated with CoronaVac. The previous study found that immunity from 2 doses of CoronaVac significantly decreases after 2 months, reducing efficiency in preventing infection and severe symptoms [24]. In July 2021, Department of Disease control of Thailand recommended that healthcare workers should receive the viral vector or mRNA vaccine as a vaccine booster dose. However, the shortage of vaccines had resulted that the only ChAdOx1 were available enough for healthcare workers [15]. Nonetheless, the efficiency and safety of heterologous vaccination regimens were unclear, especially for the third dose vaccination.

Our study indicated that after receiving ChAdOx1 for 14-21 days, anti-RBD IgG titer and

sVNT were significantly increased. Conform to the study from Yorsaeng *et al.*, reported that 14-35 days after receiving vaccine booster dose subsequent 2-3 months of fully vaccinated with CoronaVac significantly elicited anti-RBD IgG titer and sVNT. This heterologous vaccine booster dose potentially neutralized SARS-CoV-2 variants of concern, such as B.1.17 (Alpha), B.1.351 (Beta) and B.1617.2 (Delta) [25]. A previous study from Kanokudom *et al.* indicated that receiving ChAdOx1 as third booster does not only stimulate humoral immune response but also efficiently generated cell-mediated immune response [26, 27]. In addition, at 28 days after receiving booster dose, anti-RBD IgG titer and sVNT were insignificantly decreased [28]. However, our study showed that anti-RBD IgG titer and sVNT significantly dropped at 90-104 days after receiving ChAdOx1. Even though sVNT reduced, the median and IQR were slightly changed. According to US FDA recommendations, the percent inhibition utilizing the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript) for a high titer of COVID-19 convalescent plasma should be $\geq$ 68% [29], whilst the sVNT at 90-104 days after booster in our study was 96.1% (median). This analysis suggests that efficiency of ChAdOx1 in 3-months intervals is more likely high, in contrast with the reduction of anti-RBD IgG titer. Based on the results, this may be one of the factors that caused the low infection rate among participants. This data suggests that with the combination of proper vaccination and complying with prevention guidelines, the risk of infection among dental care workers is not higher than other healthcare workers. However, because the infection does not often occur during the working hours, healthcare workers should follow the prevention guideline even though they are off duty.

Nucleocapsid protein is a component of SARS-CoV-2's genetic materials. It has been documented to be involved in various aspects of virus replication [30]. Previous literature found that an infected person can develop immunoglobulin against N-protein. However, a recent study showed that it could also be found in inactivated virus vaccinees. Our study found that 60 days after receiving CoronaVac, several participants developed an anti-N IgG titer higher than the cut-off value. Still, when RT-PCR was performed, no positive result was found. Our data confirmed the results which Kanokudom *et al.* had reported that after receiving BBIBP, the anti-N IgG level is significantly increased yet possibly more than the cut-off value. Without an additional dose of inactivated vaccine or SARS-CoV-2 infection, the level of anti-N IgG should gradually reduce over time [28].

In this study, there is no difference in the adverse effects (variety and duration of symptoms) between receiving the first two doses of ChAdOx1 and receiving it as a third booster dose [31]. Most participants developed mild to moderate common side effects which disappear within 2-3 days and relieved by taking acetaminophen or NSAIDs. These findings conform to the previous study by Kanokudom *et al* [28].

In addition, SARS-CoV-2 B.1.1529 (Omicron) variant, the latest VOCs currently spread worldwide, did not emerge at the time this study was carried out. Due to multiple mutations in the receptor-binding domain of the Omicron variant, it may mediate vaccine-induced neutralizing antibodies [32]. It was noted to have a very low neutralizing antibody response against Omicron after two doses of CoronaVac, even after 14 days after completing the vaccine course [33]. The recent evidence from Jantarabenjakul *et al.* which conducted similar vaccine regimen with ours, revealed that neutralizing performance against

Omicron elicited by ChAdOx1 as booster dose after full CoronaVac at 4 weeks and 12 weeks were 61.2% and 26.6%, respectively. Such was much lower compared to other VOCs and seemed not enough to prevent the infection. While the participants who received BNT162b2 as third booster clearly presented higher anti-RBG IgG, sVNT and T-cell response against Omicron strain [34]. Their results were similar to the COM-BOOST study which conducted in larger samples size [6, 35]. These findings indicated that in Omicron era, the mRNA vaccine (BNT162b2 and m-1273) is the most potentially appropriate booster vaccine candidate especially among healthcare workers who received full CoronaVac, regardless with or without ChAdOx1 booster. However, despite receiving the most effective vaccine course, waning immunity is inevitable [36]. Therefore, healthcare workers should consider the prevention guidelines as the important tool to prevent them from infection.

The limitations of this study are a small samples size, number of female participants higher than males, lack of various vaccine platforms and T-cell response was not measured, which affect the data precision and the power of statistical analysis. Thus, to obtain more precise data, further study with multi-age groups, larger sample sizes, comparable number of male and female participants with various vaccine types and T-cell response measurement should be undertaken in the area where the Omicron variant is spreading.

## Competing interests

The authors declare that there were no financial, commercial, or personal relationships that could have affected the work reported in this study.

## Ethical approval

The ethics committee on human research, Ramathibodi hospital (MURA2021/729)

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## Conclusion

Receiving a booster dose of ChAdOx1 after CoronaVac full vaccination can stimulate a strong immune response against SARS-CoV-2 with tolerable adverse effects. Even though the level of immunity significantly decreases within 3 months after receiving third dose vaccination, the efficacy in neutralizing the viruses is still high. However, new variants of SARS-CoV-2 continuously emerge with higher transmissibility and immunity evasion capability. Healthcare workers should comply with prevention guidelines both inside and outside working hours to diminish the opportunity of SARs-CoV-2 infection.

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