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ORIGINAL RESEARCH

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Monitoring of adaptive immune responses in healthcare workers who received a Coronavirus disease 2019 vaccine booster dose

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Abstract

Background and Aims: Coronavirus disease 2019 (COVID-19) has become a global pandemic and led to increased mortality and morbidity. Vaccines against the etiologic agent; severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were approved for emergency use on different platforms. In the early phase of the pandemic, Thai healthcare workers (HCWs) received CoronaVac, an inactivated vaccine, as the first vaccine against SARS-CoV-2, followed by ChAdOx1 nCoV-19, a viral vector-based vaccine, or BNT162b2, an mRNA vaccine, as a booster dose. This preliminary study evaluated the immunogenicity of ChAdOx1 nCoV-19 and BNT162b2 as a booster dose in HCWs who previously received two doses of CoronaVac.

Methods: Ten HCW participants received ChAdOx1 nCoV-19 and another 10 HCWs received BNT162b2 as a booster dose after two doses of CoronaVac. Anti-RBD IgG, neutralizing antibodies (NAb), and cellular immunity, including interferon-gamma (IFN-γ)-releasing CD4, CD8, double negative T cells, and NK cells, were measured at 3 and 5 months after the booster dose.

Results: There was no significant difference in anti-RBD IgG levels at 3 and 5 months between the two different types of booster vaccine. The levels of anti-RBD IgG and NAb were significantly decreased at 5 months. HCWs receiving BNT162b2 had significantly higher NAb levels than those receiving ChAdOx1 nCoV-19 at 5 months after the booster dose. IFN-γ release from CD4 T cells was detected at 3 months with no significant difference between the two types of booster vaccines. However, IFN-γ-releasing CD4 T cells were present at 5 months in the ChAdOx1 nCoV-19 group only.

Conclusion: ChAdOx1 nCoV-19 or BNT162b2 can be used as a booster dose after completion of the primary series primed by inactivated vaccine. Although the levels of immunity decline at 5 months, they may be adequate during the first 3 months after the booster dose.

KEYWORDS
BNT162b2, booster, ChAdOx1 nCoV-19, CoronaVac, healthcare workers, SARS-CoV-2 vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first recognized in Wuhan, Hubei Province, China[1] and has caused a global pandemic since early 2020. Currently, Thailand has reported over 4 million confirmed cases, resulting in over 30,000 fatalities.[2] The rapid global COVID-19 pandemic has led to the appearance of several variants of concern (VOCs) becoming predominant over the original Wuhan strain. The delta variant, a VOC originating from India[3,4] was predominant in Thailand throughout 2021, and subsequently, the omicron variant emerged in 2022.[5] The emergency use of COVID-19 vaccines, including inactivated vaccines, viral vector-based vaccines, and mRNA-based vaccines has been authorized worldwide.[6] Healthcare workers (HCWs) including frontline workers dealing with COVID-19 patients during the pandemic era needed effective protection from vaccination. Due to limitations in access to COVID-19 vaccines in Thailand at the beginning of the pandemic, an inactivated vaccine (CoronaVac) was primarily given to HCWs in April 2021, followed by the subsequent administration of a booster dose with ChAdOx1 nCoV-19, a viral vector-based vaccine, or BNT162b2, an mRNA-based vaccine. Since neutralizing antibodies (NAb) elicited by immunization with CoronaVac only may not be sufficient,[7] a booster dose with different vaccine platform is required to increase the neutralizing antibody level. Though this strategy may not be able to totally prevent the infection, this would mitigate the severity of infection. This strategy would be an important element to facilitate patient transition from hospital-based care to home-based care.[8]

A booster dose with viral vector-based vaccine or mRNA-based vaccine after primary series of inactivated vaccine was safe and provided good immunogenicity in Thai healthy adult.[9] The incremental cost-effectiveness ratio (ICER) demonstrated that a booster dose either with viral vector-based vaccine or mRNA-based vaccine in Thai population during the omicron period was cost-effective as a booster dose could reduce both numbers of infected cases and death.[10]

Humoral and cellular immune responses play roles in host defense against viral infection, including COVID-19.[11–13] The levels of NAb after vaccination against SARS-CoV-2 infection were reported in a previous study.[14–16] Several methods to measure cellular immune responses after vaccination or infection with SARS-CoV-2 have been reported including IFN-γ enzyme-linked immunosorbent spot,[17] IFN-γ release assay,[18] and intracellular cytokine staining (ICS).[19–21] This study aimed to evaluate the levels of SARS-CoV-2 receptor binding antibody (anti-RBD IgG), NAb, and cellular immune responses by intracellular cytokine staining at 3 and 5 months after receiving a booster dose of a viral vector-based vaccine (ChAdOx1 nCoV-19) or mRNA-based vaccine (BNT162b2) in HCWs who were previously vaccinated with the inactivated vaccine against SARS-CoV-2 as a primary series.

2 | METHODS

2.1 | Study design and participants

All participants were enrolled between September 2021 and September 2022. All were healthy without any underlying diseases. Twenty HCWs from Ramathibodi Hospital, aged 25–60 years old and who previously received two doses of CoronaVac 3 weeks apart, were recruited to the study. Participants who had been diagnosed with SARS-CoV-2 infection, had received immunosuppressive drugs, or were immunocompromised were excluded. Ten HCWs receiving ChAdOx1 nCoV-19 and 10 HCWs receiving BNT162b2 as a booster dose of vaccination were enrolled. In our institution, during the study period, weekly self-testing with antigen test kit (ATK) was required for every personnel and those who had positive test would be asked to refrain from work. Written informed consent was obtained from all the participants before their involvement in the study. The study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (approval number MURA2021/788).

2.2 | Sample collection

Blood samples were collected from all participants for the analysis of SARS-CoV-2 RBD IgG, NAb, and cellular immune responses against SARS-CoV-2 at 3 and 5 months after the booster dose of vaccine.

2.3 | Humoral immune responses

Sera from all participants were obtained by centrifugation of clotted blood at 3500 rpm for 10 min at room temperature, and the sera were stored at −80°C until use. Anti-RBD IgG levels were measured by chemiluminescent microparticle immunoassay, reported as AU/mL, and converted to World Health Organization (WHO) reference standard units in terms of binding antibody units or BAU/mL by multiplying them by 0.142. Seropositive was defined as anti-RBD IgG levels ≥50 AU/mL or ≥7.1 BAU/mL. NAb was reported as a percentage of inhibition (%IH). The positive cut-off was >35% IH.

2.4 | Cell-mediated immune responses (CMIR)

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood by Lymphoprep™ (STEMCELLS) density gradient centrifugation at 900*g* for 30 min. PBMCs were washed with phosphate buffered saline (PBS) (Sigma Aldrich) and stored in cells freezing medium containing 10% DMSO (Sigma Aldrich) and 90% fetal bovine serum (FBS) (GIBCO). PBMCs were kept in liquid nitrogen vapor until use.

2.5 | Detection of SARS-CoV-2-specific T cells

PBMCs were thawed and dissolved in RPMI-1640 medium (GIBCO) containing 10% FBS. PBMCs were stimulated with S1-SARS-CoV-2 PepTivator peptide pools (Miltenyi Biotec) at a concentration of 2 µg/mL for 18 h at 37°C with 5% CO_2. Brefeldin A was added to a final concentration of 1 mg/mL during the last 4 h of incubation. Cells treated with 12.5 ng/mL of phorbol 12-myristate 13-acetate (PMA) (Sigma Aldrich) and 2 µg/mL of ionomycin (Sigma Aldrich) were used as a positive control. Untreated cells were used as a negative control.

2.6 | Intracellular cytokine staining by flow cytometry (ICS)

After cultivation, the harvested cells were fixed in 1% formaldehyde solution (Sigma Aldrich) for 15 min at room temperature (RT) and washed once with PBS (Sigma Aldrich). The cells were then permeabilized with 0.1% Saponin in PBS (Sigma Aldrich) for 15 min at RT. After being washed, cells were stained with fluorescent-labeled antibodies from ThermoFisher Scientific as follows: anti-CD3 FITC (clone HIT3a), anti-CD4 APC (clone OKT4), anti-CD8a APC/EF780 (clone RPA-T8), anti-CD56 PE (clone CMSSB), and anti-IFN gamma PE-Cyanine7 (clone 4S.B3). Cell staining was performed at 4°C in the dark for 30 min. Stained cells were then washed once with PBS and resuspended with 100 µL of PBS. All samples were acquired on a FACSVerse Flow cytometer (BD Biosciences). Data were analyzed by FlowJo version 10.8.0 (FlowJo LLC). SARS-CoV2-specific CD4, CD8, and double negative T cells were those stained positive for IFN-γ after being stimulated with peptides. SARS-CoV2 reactive NK cells were NK cells that stained positive for IFN-γ after being stimulated with peptides.

2.7 | Data analysis

Demographic data were described using descriptive statistics. Continuous data were presented as the median with interquartile range (IQR). The Mann–Whitney *U* test was used to compare the results between groups. Comparisons between two time points within the same group were performed by paired *t*-test and Wilcoxon signed-rank test based on normality test. All graph plots and statistical analyses were performed using Prism 9.4.0 software (GraphPad Software).

3 | RESULTS

3.1 | Study participants

Twenty HCWs who received two doses of CoronaVac were recruited, with a median age of 39 years. Ten HCWs (50%) had received ChAdOx1 nCoV-19 and 10 HCWs (50%) had received BNT162b2 as a booster SARS-CoV-2 vaccination. The characteristics of the participants are shown in Table 1. The mean duration between the second dose of CoronaVac and the subsequent booster dose was 68 days and 76 days in ChAdOx-1 group and BNT162b2 group, respectively. All participants had no evidence of COVID-19 infection based on the patients' self-reporting during the follow-up period.

TABLE 1 Demographic data of the participants.

Characteristics of participants	Number of HCWs (*n* = 20)
Sex	
Male *n*; (%)	2 (10)
ChAdOx1 nCoV-19	1 (5)
BNT162b2	1 (5)
Female *n*; (%)	18 (90)
ChAdOx1 nCoV-19	9 (45)
BNT162b2	9 (45)
Age (years); median (IQR)	39 (10.5)
ChAdOx1 nCoV-19	39.5 (35.25,41.5)
BNT162b2	35 (30,41)
BMI; median (IQR)	22.7 (4.6)
ChAdOx1 nCoV-19	21.7 (2.5)
BNT162b2	24.7 (7.7)

Abbreviations: BMI, body mass index; HCWs, health care workers; IQR, interquartile range.

3.2 | Humoral immune responses

Sera from all participants were measured for SARS-CoV-2 anti-RBD IgG and NAb at 3 and 5 months after receiving the booster dose of SARS-CoV-2 vaccine. The average time from the booster dose to the 3-month time point of blood draw was 94 days in both groups while the average time from the booster dose to the 5-month time point of blood draw was 173 days and 147 days in ChAdOx1 nCoV-19 group and BNT162b2 group, respectively.

All 20 participants had seropositive levels of anti-SARS-CoV-2 RBD IgG at 3 and 5 months after the booster vaccination. There was no significant difference in anti-SARS-CoV-2 RBD IgG levels between those who received the viral vector-based vaccine (ChAdOx1 nCoV-19) and those who received the mRNA-based vaccine (BNT162b2) at 3 and 5 months. The median levels of anti-SARS-CoV-2 RBD IgG at 3 months were 435.65 (IQR 202.31–1749.28) and 985.44 (IQR 877.63–1547.25) BAU/mL in the ChAdOx1 nCoV-19 and BNT162b2 groups, respectively. The level significantly declined 5 months after receiving ChAdOx1 nCoV-19 ($p = 0.002$) or BNT162b2 ($p = 0.0005$). The median level declined to 227.61 (IQR 90.60–656.39) and 483.22 (IQR 399.18–723.37) BAU/mL in the ChAdOx1 nCoV-19 and BNT162b2 groups, respectively (Figure 1).

Protective NAb levels with >35% IH against SARS-CoV-2 were detected in all HCWs 3 months after receiving a booster dose and there were no significant differences between the ChAdOx1 nCoV-19 and BNT162b2 groups. The median percentages of NAb levels at

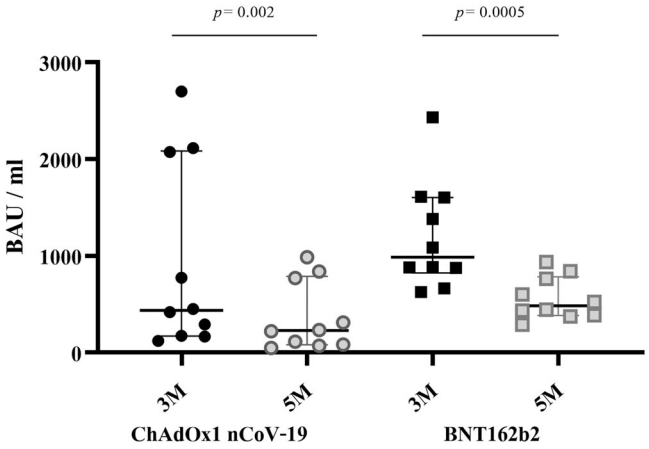

FIGURE 1 Anti SARS-CoV-2 RBD IgG levels at 3 and 5 months after a booster vaccination. 3M and 5M refer to 3 and 5 months after the booster dose, respectively.

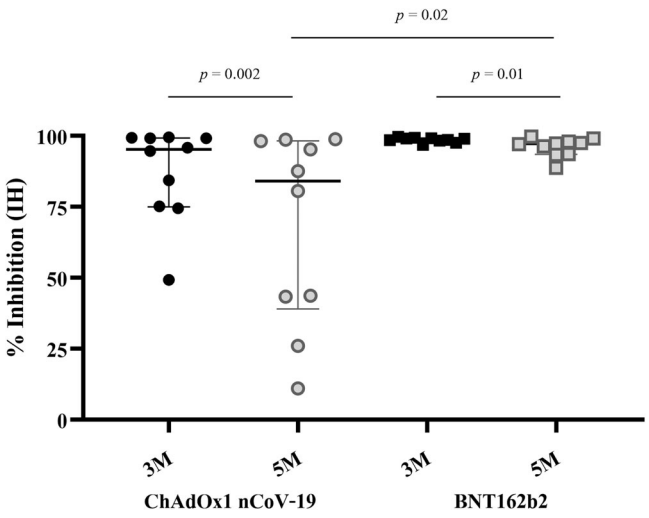

FIGURE 2 Neutralizing antibody (NAb) levels at 3 and 5 months after a booster vaccination. 3M and 5M refer to 3 and 5 months after the booster dose, respectively.

3 months were 95.3% IH (IQR 77.5–99.2) and 98.8% IH (IQR 98.43–99.18) in the ChAdOx1 nCoV-19 and BNT162b2 groups, respectively. At 5 months, the ChAdOx1 nCoV-19 and BNT162b2 groups had significantly lower NAb levels compared with those at 3 months ($p = 0.002$ and $p = 0.01$, respectively). NAb median levels at 5 months were 84.1% IH (IQR 43.48–97.48) in the ChAdOx1 nCoV-19 group and 97.25% IH (IQR 94.3 - 97.88) in the BNT162b2 group ($p = 0.02$) (Figure 2). Moreover, two HCWs who received the ChAdOx1 nCoV-19 vaccine as the booster dose had no protective levels of NAb, with levels less than 35% IH at 5 months.

3.3 | CMIR

An S1 overlapping peptide pool from the spike domain of SARS-CoV-2, responsible for the recognition of, and binding to, the ACE2 receptor of host cells, was used to stimulate PBMCs. Intracellular cytokine staining (ICS) of IFN-γ in CD4, CD8, and double negative T cells, and NK cells was used as a surrogate measure of cellular immune responses after booster vaccination. The flow cytometry gating strategy of ICS is shown in Figure S1. There was significant difference in the mean of IFN-γ secreting cells in CD4 T cells at 3 months ($p = 0.01$) and 5 months ($p = 0.02$) after receiving the booster dose of ChAdOx1 nCoV-19, whereas IFN-γ secreting CD4 T cells were detected only at 3 months in those who received BNT162b2 as the booster dose. There were no significant differences in IFN-γ secretion from CD4 T cells between the two groups of HCWs at 3 months after the booster dose. The mean of IFN-γ secreting cells was expressed per 1×10^6 cells (Table 2).

4 | DISCUSSION

In this study, humoral and cell-mediated immune responses to SARS-CoV-2 in HCWs who received a booster dose of COVID-19 vaccine were evaluated. We found that HCWs who had completed the primary series of the inactivated COVID-19 vaccine had high anti-RBD IgG and NAb levels after receiving ChAdOx1 nCoV-19 or BNT162b2 as a booster dose, especially at 3 months after the booster vaccination. At 5 months after the booster vaccination, NAb levels in the ChAdOx1 nCoV-19 group were lower than in the BNT162b2 group. However, cellular immune responses were similar between the two groups. We provided evidence that the viral vector platform could be used as a booster vaccine in those who received the inactivated vaccine and who had complications or adverse events after receiving the mRNA platform vaccine.

A previous study in HCWs who received two doses of BNT162b2 vaccine as a primary series also revealed a rapid decline of antibodies at 5 months after a second dose, suggesting that a booster dose was needed.[22] A booster dose has shown to enhance the humoral and cell-mediated immune response to SARS-CoV-2.[23–25] In this study, after a booster dose in participants who had completed a primary series of the inactivated vaccine, anti-RBD IgG levels at 3 and 5 months were high but not significantly different between the ChAdOx1 nCoV-19 and BNT162b2 groups though the level tended to be higher in the latter group. The levels of anti-RBD IgG were significantly decreased at 5 months compared with at 3 months after the booster dose in both groups and there was no significant difference between the two groups. Although the levels of anti-RBD IgG were lower at 5 months, seropositivity was still present in all participants. A similar study in Thai HCWs, aged 18–60 years who previously received CoronaVac followed by ChAdOx1 nCoV-19 found that anti-spike IgG Ab and NAb levels were significantly increased 1 month after receiving a booster dose and significantly decreased at 3 months.[26] In this study, NAb levels that were sufficiently inhibitory against SAR-CoV-2 virus at 3 months were not significantly different between the two groups. This result was supported by a previous study showing that NAb levels were not significantly different in Thai elderly HCWs who received ChAdOx1 nCoV-19 or BNT162b2 as a booster dose after being fully vaccinated with CoronaVac.[27] The NAb levels against the wild-type

TABLE 2 The cellular immune response at 3 and 5 months after the booster dose.

Vaccines	Cells	IFN-γ secreting cells per 10^6 cells (mean ± SD)		
		Nonstimulated cells	S1-stimulated cells	Positive control
ChAdOx1 nCoV-19 at 3 months	CD4	280 ± 196	606 ± 322***	12,562 ± 8096
	CD8	395 ± 431	694 ± 496	18,049 ± 11,042
	Double negative	353 ± 390	916 ± 1048	26,431 ± 19,621
	NK cells	3578 ± 5505	7646 ± 10,836	9075 ± 6743
ChAdOx1 nCoV-19 at 5 months	CD4	625 ± 1221	1183 ± 1976**	31,678 ± 22,557
	CD8	21,281 ± 66,691	18,917 ± 57,964	173,661 ± 122,428
	Double negative	608 ± 770	1297 ± 2147	103,890 ± 129,218
	NK cells	11,757 ± 16,172	8809 ± 12,566	162,323 ± 161,741
BNT162b2 at 3 months	CD4	160 ± 132	499 ± 418*	13,569 ± 6968
	CD8	499 ± 364	908 ± 1698	52,895 ± 35,350
	Double negative	1693 ± 1731	4242 ± 6196	64,927 ± 63,986
	NK cells	23,853 ± 23,308	22,558 ± 23,733	20,474 ± 14,146
BNT162b2 at 5 months	CD4	267 ± 408	383 ± 472	22,095 ± 24,943
	CD8	567 ± 612	496 ± 680	108,412 ± 70,348
	Double negative	712 ± 1542	1282 ± 3165	40,668 ± 40,625
	NK cells	40,148 ± 124,988	42,060 ± 125,846	172,656 ± 145,233

Abbreviations: HCWs, health care workers; SD, standard deviation.

*$p = 0.03$ (nonstimulated cells vs. S1-stimulated cells); **$p = 0.02$; ***$p = 0.01$.

strain declined significantly at 5 months with a more pronounced decrease in those who received ChAdOx1 nCoV-19. Moreover, negative NAb levels at 5 months were noted in 20% of HCWs who received ChAdOx1 nCoV-19 indicating the reduced effectiveness of SARS-CoV-2 neutralization compared with those receiving BNT162b2. A phase 4 randomized control trials in Brazilian adults revealed that at 28 days after a booster dose of SARS-CoV-2 vaccine, heterologous booster vaccination with either BNT162b2 (mRNA vaccine), ChAdOx1 nCoV-19 (adenoviral vectored vaccine) or Ad26.COV2-S (adenoviral vectored vaccine) resulted in higher IgG antibody levels compared to a third homologous boost in participants who previously received CoronaVac. BNT162b2 induced higher Ab levels than heterologous boosting with adenoviral vectored vaccines. Moreover, NAb levels in BNT162b2 participants were also boosted against Delta and Omicron variants more than those in participants who received ChAdOx1 nCoV-19, Ad26.COV2-S and CoronaVac.[28]

There have been several methods to demonstrate T-cell mediated immunity after SARS-CoV-2 vaccination. SARS-CoV-2 PepTivator S1 overlapping peptide pool was used in ELISA IFN-γ assay,[29] AIM assay in COVID-19 patients,[30] and ELISPOT in naive and breakthrough-infected HCWs after vaccination.[31] This study also demonstrated a cell-mediated immune response against SARS-CoV-2 after the booster dose using an ICS IFN-γ release assay for CD4, CD8, and double negative T cells, and NK cells at 3 and 5 months after the booster dose of vaccine.

From previous studies, mRNA and viral vector vaccination could induce robust CD4 and CD8 T-cell responses, while inactivated vaccine and protein-adjuvanted were less effective in stimulating CD8 T-cell response and early T-cell response was associated with a better clinical outcome after infection.[32] CD4 T-cells or helper T-cells, which are adaptive immune cells that provide help to other immune cells such as B cells and CD8 T cells, secreted IFN-γ upon stimulation with SARS-CoV-2 peptide pools, indicating these cells may also have protective roles against this virus.[33,34] In addition, vaccination with the Wuhan ancestral linage mRNA-based, viral vector-based and protein recombinant-based vaccines could induce cross-variant recognition of T cell memory from Alpha to Omicron variants in adults.[35,36] According to the roles of cellular immune response against severe SARS-CoV-2 infection, monitoring the levels and long-term specific T- cell response is mandatory for assessing vaccine immunogenicity in vaccinees. This T-cell assay is particularly useful in immunocompromised individuals and other vulnerable population during the COVID-19 pandemic.[37]

The cellular immune response in HCWs was not significantly different regardless of boosting with ChAdOx1 nCoV-19 or BNT162b2. This was congruent with a previous study in older HCWs who were fully vaccinated with CoronaVac.[27] However, our study showed that cell-mediated immune responses persisted for at least 5 months after the booster dose in those who received ChAdOx1 nCoV-19 but could not be detected in those who received BNT162b2. This finding needs further confirmation with a larger sample size.

This study is the first pilot study to investigate immunogenicity as long as 5 months after a booster dose with viral vector or mRNA platforms in HCWs who had been fully immunized with an inactivated vaccine. Furthermore, we assessed cell-mediated immune responses and found they were not different between the two groups at 3 months after the booster dose. This study had some limitations. First, this was a pilot study. A bigger sample size is needed to confirm the study findings. Second, the study did not include information on vaccine effectiveness or efficacy for protection against infection or a reduction in disease severity. The levels of anti-RBD, NAb, or cell-mediated immune responses may not correlate well with the vaccine effectiveness or efficacy. Third, detailed lymphocyte subset enumeration, which might affect the immune response to vaccination, was not performed in this study. Fourth, baseline levels of antibodies and cellular immunity function before the booster dose were not determined; thus, we could not investigate a correlation between immune responses before and after the booster dose. Last, the humoral and cell-mediated immune responses presented in this study might not extrapolate to responses elicited by other vaccines against variants of SARS-CoV-2, as the detection of humoral and cell-mediated immune responses in this study was based on the original Wuhan strain of SARS-CoV-2. However, this study highlights that a booster dose delivered by viral vector or mRNA vaccine platforms against SARS-CoV2 is promising if an inactivated vaccine was used previously for priming. This study supports the use of an inactivated vaccine followed by a viral vector-based vaccine if subjects have a history of adverse events or are at risk of developing adverse events after receiving mRNA-based vaccines. This study did not determine when the next booster dose should be implemented. However, this study suggests that those who received a booster dose of an mRNA-based vaccine may not have to receive another booster dose within 5 months after the most recent booster dose. The next booster dose in those who received ChAdOx1 nCoV-19 may need to be earlier. This may guide when booster doses of vaccines for VOCs of the omicron strain may be needed. This study suggests that viral vector- or mRNA-based vaccines can be used as a booster vaccine.

5 | CONCLUSIONS

Humoral immunity to SARS-CoV2 3 months after a booster dose of the viral vector-based vaccine (ChAdOx1 nCoV-19) or mRNA-based vaccine (BNT162b2) in HCWs fully vaccinated with CoronaVac was not significantly different. However, NAb levels at 5 months in those receiving ChAdOx1 nCoV-19 were lower than those in the BNT162b2 group, and some participants in the ChAdOx1 nCoV-19 group did not have levels sufficient to inhibit the wild-type SARS-Cov-2 strain. These two different types of heterologous booster vaccines induced cellular immune responses to a similar level 3 months after a booster dose. Viral vector-based (ChAdOx1 nCoV-19) or mRNA-based (BNT162b2) vaccines can be used as a booster vaccine; however, the duration of the next booster dose may be shorter in those who received ChAdOx1 nCoV-19.

AUTHOR CONTRIBUTIONS

Chompunuch Klinmalai: Conceptualization; writing—original draft; funding acquisition; investigation. **Supanart Srisala**: Investigation; validation. **Thiantip Sahakijpicharn**: Resources. **Nopporn Apiwattanakul**: Writing—review & editing; conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Nopporn Apiwattanakul affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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