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Dynamic of anti-spike receptor binding domain (RBD) levels and short-term adverse events following a heterologous booster dose of BNT162b2 after two doses of CoronaVac in Thai health care workers

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ABSTRACT

Background: CoronaVac was administered as the primary COVID-19 vaccine for Thai health care workers (HCWs) in early 2021 in response to the epidemic of new variants. This study aimed to evaluate the dynamic of humoral immune response as well as the short-term side effects resulting from the booster dose of BNT162b2 following completion of a CoronaVac double-dose in Thai HCWs.
Methods: This study was conducted at a teaching hospital in Northern Thailand during August and September 2021. The participants were 50 HCWs who were vaccinated with 2 doses of CoronaVac and were scheduled to receive a booster dose of BNT162b2. Anti-SARS-CoV-2 IgG antibodies levels and short-term side effects were assessed. The anti-RBD level was determined using Architect SARS-CoV-2 IgG II Quant (Abbott).
Result: Of the 50 participants, 37 were female. The median age was 33.0 years old. The average time between the second CoronaVac shot and the BNT162b2 booster shot was 81.7 days (SD = 25.0). The median anti-SARS-CoV-2 IgG antibody level on booster vaccination date, as well as day 14, and day 28 after the booster were 335.5 AU/ml, 31,613.5 AU/ml, and 20,311.9 AU/ml, respectively. Fourteen days after the booster, 94% of participants had anti-SARS-CoV-2 IgG antibody levels higher than 50.0 AU/ml. Being female, higher log anti-SARS-CoV-2 IgG antibodies prior to booster vaccination, and longer interval between the second shot and the booster shot were found to be significantly associated with higher levels of anti-SARS-CoV-2 IgG antibodies at both day 14 and day 28 after the booster. There were no reports of serious adverse events.
Conclusion: A booster dose of BNT162B2 promoted a high level of anti-SARS-CoV-2 IgG antibodies among HCWs who received 2 doses of CoronaVac. The time between the second CoronaVac shot and the booster shot should be at least three months. There were no severe adverse effects observed.

1. Introduction

The coronavirus disease (COVID-19) pandemic has caused more than 240 million infections and 4.9 million deaths worldwide since December 2019, and Thailand is not immune to this global calamity. While the local epidemic was under control for most of 2020, the situation worsened in April 2021. Emerging coronavirus variants of concern (VOC), including B.1.617 (Delta), B.1.1.7 (Alpha), and B.1.351 (Beta), replaced the wild-type virus resulting in widespread infection and a sharp increase in hospitalizations

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[1]. Recently, the total documented cases quickly topped one million, with between 10,000–20,000 new infections reported daily [2]. The epidemic has significantly impacted the country's social, economic, and health sectors despite implementation of disease control measures such as physical distancing, outdoor mask wearing, hand hygiene, travel restrictions, curfews, limitations on public gatherings, and working-from-home directives [3,4].

Vaccination has long been recognized as a fundamental preventative measure for infectious diseases which generated an immune response and provide protection against symptomatic illness, hospitalization, and fatality [5]. COVID-19 vaccines of various types were quickly developed and approved for emergency use. Thailand's first COVID-19 immunization campaign targeted older adults, people with multiple comorbidities, as well as healthcare workers (HCWs) [3]. In early 2021, the Thai government chose CoronaVac (Sinovac®), an inactivated vaccine, as the primary vaccine for the initial vaccination phase due to its immediate availability. The vaccine subsequently became the primary source of Thai HCWs vaccinations. The regimen was set as 2 doses of CoronaVac, 3–4 weeks apart [3]. Nonetheless, the emergence of SARS-CoV-2 variants raises concerns about the vaccine's efficacy. According to data from mass immunization efforts in Malaysia, the efficacy of CoronaVac vaccines has waned over a three- to five-month period. [6] As a result, only two CoronaVac shots may be insufficient to protect frontline HCWs and Thai people during this variant of concern outbreak in Thailand.

A study in Chile, demonstrated that the efficacy of CoronaVac against the wild-type strain was 65.9% for symptomatic infection, 87.5% for hospital admission, and 86.3% for ICU admission or death [5,7]. However, a study in the Thai population revealed low levels of neutralizing antibodies to the VOCs following a complete course of CoronaVac, with geometric mean values of 44.64, 35.03, and 24.48 AU/ml for VOCs B.1.1.7, B.1.351, and B.1.617, respectively [8]. According to the Ministry of Public Health, approximately 700 frontline HCWs who received two doses of CoronaVac became infected with COVID-19, with two deaths in the period of April to July 2021 [22]. As a result, there was concern that vaccinated Thai HCWs were still likely vulnerable to VOCs. Thus, Thailand vaccination campaign use AstraZeneca and Pfizer COVID-19 vaccine as a booster dose for those who previously received 2 dose regimens of CoronaVac [9].

In British and Qatari vaccine efficacy clinical studies of the BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines, protection against symptomatic infection of B.1.1.7, B.1.351, and B.1.617 was reported to be 85–95%, 89.5–100%, and 75–96.4%, respectively following full vaccination [10–13]. Another study documented that a single dose of BNT162b2 might offer partial protection with neutralizing antibodies 2.5 times greater than ChAdOx1 nCoV-19 vaccine (AstraZeneca) and quantitatively higher than CoronaVac [14,15,16]. Some European countries have experimented with mixing vaccines [17–19]. The participants who were vaccinated with the ChAdOx1 nCoV-19 vaccine followed by the BNT162b2 vaccine were found to have an anti-spike IgG geometric mean ratio (GMR) and neutralizing antibody titers 9.2 and 9.3 times higher than the control group who received two doses of the ChAdOx1 nCoV-19 vaccine [17]. In addition, seven weeks following the third AstraZeneca vaccination, the anti-RBD IgG titer in Thai healthcare workers who were fully vaccinated with CoronaVac was 1492 BAU/ml (95 percent CI = 1367–1629) with a GMR of 11.66 from baseline [9]. With the proliferation of VOCs, low antibody levels after two doses of CoronaVac, and evidence that mixing of vaccines was an effective strategy, the public and health administrators felt that a booster dose of high-efficacy vaccine for HCWs was urgently needed. Equally important, while 2 doses of CoronaVac might effectively prevent hospitalizations and deaths in HCWs, the impact of COVID-19-sick HCWs on the already strained health care system highlighted the urgency of booster doses. Booster vaccinations began in early August 2021 in Thai HCWs who received 2 doses of CoronaVac. Boosters used BNT162b2 donated by the US government.

This study aimed to offer preliminary findings on the dynamic of immune responses as well as the short-term side effects after a booster dose of BNT162b2 vaccine in Thai HCWs who have completed 2 doses of CoronaVac. The findings of this study would provide valuable information for health administrators in Thailand and other relevant countries on vaccine booster strategy.

2. Methods

2.1. Study design and settings

This prospective observational study was conducted in Chiang Mai, Northern Thailand from August to September 2021.

2.2. Study participants

The participants were HCWs at the Maharaj Nakorn Chiang Mai Hospital (Chiang Mai University teaching hospital), who were vaccinated with 2 doses of CoronaVac and were scheduled to receive a booster dose of BNT162b2. Other inclusion criteria were age 18 years old or older and ability to understand Thai. The exclusion criteria were having at least one contraindication for receiving the COVID-19 vaccine and a history of confirmed COVID-19 infection by RT-PCR technique. On the 1st of August 2021, all health care employees of Maharaj Nakorn Chiang Mai Hospital were given a digital flier encouraging them to register for a Pfizer booster shot. The research team advertised the study through social media. All 132 people who showed interest and registered as potential participants were eligible according to the eligibility criteria. The research team then randomly selected 50 individuals and invited them to join the study. All participants visited the immunization venue on the 10th and 11th of August when a blood draw and a Pfizer booster dose took place. Then, 14 and 28 days after the third dose, a secondary and third blood draw would be performed.

2.3. Measurements

To quantify the degree of immune response to COVID-19 after vaccination, various immunoassays were utilized to detect coronavirus recombinant proteins or synthetic peptides. These included spike antigen (S), receptor-binding domain (RBD), and spike unit1 (S1) [20]. A unified international standard for measuring SARS-CoV-2 antibodies was established given the different reprting methods for these assays. For binding antibody assays, WHO International Standard concentrations (Binding Antibody Unit per mL (BAU/mL)) was recommended for comparison of assays detecting the same class of immunoglobulins with the same specificity [21]. The antibody levels in samples should be measured in the units specific to each assay such as U/mL for Roche (Roche Diagnostics, Germany) and AU/ml for Abbott (Abbott, Ireland) [22]. Next, the data should be converted to BAU/ml based on the manufacturer's instructions regarding the WHO standard. The level of antibodies to the SARS-Cov-2 spike protein was measured using commercial immunoassays that have been validated against the level of neutralizing antibody [23,24]. The results suggested that the antibody levels to the SARS-Cov-2 spike protein analyzed by Architect SARS-CoV-2 IgG II Quant (Abbott) is highly correlated with neutralizing antibody as determined by Genscript cPass SARS-CoV-2 Kit [25].

The level of anti-SARS-CoV-2 IgG antibodies was defined as the main outcome of the study. Three blood samples were collected

from each participant: immediately before injection of 3rd vaccine dose (day 0), 2 weeks after vaccination (day 14), and 4 weeks after vaccination (day 28). To quantify the levels of anti-SARS-CoV-2 IgG antibodies, plasma samples were run on the ARCHITECT i System using the SARS-CoV-2 IgG II Quant assay (Abbott Laboratories, Sligo, Ireland). The principle of this assay relies on an automated chemiluminescent microparticle immunoassay (CMIA). The plasma IgG antibodies to the SARS-CoV-2 spike receptor-binding domain (RBD) were detected by incubating with SARS-CoV-2 antigen coated paramagnetic microparticles. After washing, acridinium-labeled anti-human IgG was added and incubated. Pre-trigger and trigger solutions were added following a wash cycle. The chemiluminescent reaction was measured as a relative light unit (RLU). The level of anti-SARS-CoV-2 spike RBD IgG antibodies was calculated and validated in arbitrary unit (AU)/mL. A level of 50 AU/ml of anti-RBD IgG antibodies was used as a positive cut-off of an assay and 40,000 AU/ml was the upper threshold of quantification The laboratory procedures were conducted at the Associated Medical Sciences Clinical Service Center, Faculty of Associated Medical Sciences, Chiang Mai University.

General and health information, such as gender, age, BMI (calculated from weight and height), and chronic co-morbidities (hypertension, dyslipidemia, diabetes, chronic respiratory diseases, heart diseases, chronic kidney disease, cerebrovascular diseases, and cancers) were collected. Participants were asked for the dates of their last two CoronaVac doses, any adverse effects after the previous CoronaVac vaccinations, as well as their history of contact with COVID-19 patients.

Systemic and local adverse effects within 7 days of receiving the third dose of BNT162b2 were collected. Fatigue, chills, high-grade fever, headache, myalgia, arthralgia, nausea, vomiting, dizziness, anorexia, abdominal pain, and allergic reactions such as rash, angioedema, dyspnea, and muscle weakness were defined as systemic adverse effects. Local swelling, itching, soreness, redness, tenderness, warmth, and bruising at or around the injection site were reported as local adverse effects.

2.4. Data collection process

Blood draws were performed by study phlebotomists or nurses on August 10–11 (day 0), August 24–25 (day 14), and September 7–8 (day 28), 2021. Ten ml of EDTA blood samples were collected for each test. To obtain plasma, blood samples were centrifuged, and the plasma was aliquoted and frozen at −20 °C.

Trained interviewers collected information on general characteristics, height, chronic co-morbidities, adverse effects after the previous CoronaVac vaccinations, and history of contact with COVID-19 patients prior to the vaccination. Weight was measured onsite. For accuracy, dates of previous COVID-19 vaccination were retrieved from the national COVID-19 vaccination online application upon participant approval.

Participants were instructed to record adverse effects for seven days by completing the daily side-effect logbook provided by the study. Participants who experienced no symptoms were encouraged to record in the logbook that they had zero side effects.

2.5. Statistical analysis

Demographic characteristics, BMI, side effects from previous vaccination, co-morbidities, and days from the last vaccination were described using descriptive statistics. These included frequency and percentages for category variables, mean with standard deviation (SD) for parametric data, and median with interquartile range (IQR) for non-parametric data.

Comparison of anti-SARS-CoV-2 IgG antibody levels at different periods was performed using the Friedman test with post-hoc pairwise comparison (Durbin-Conover test) for non-parametric dependent samples comparison more than 2 groups. To explore the linear correlation of anti-RBD IgG titer (at day 0, 14, 28), logarithmic transformation and Pearson's correlation test were performed.

The association between anti-SARS-CoV-2 IgG antibodies at various time points (day 0, 14, 28) and 3rd dose vaccination interval was explored using a multivariable linear regression adjusted for individual characteristics. Finally, the estimated marginal means of anti-SARS-CoV-2 IgG antibodies at day 14 and 28 by derived models was performed to present the effect of the vaccination interval and baseline anti-RBD IgG level.

2.6. Ethical considerations

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Ethics approval number: COM-2564-08458). All participants provided written informed consent prior to participating in the study and received 300 Baht (approx. 9 USD) to compensate for their time.

3. Results

Of the 50 participants, 74% (n = 37) were female. The median age was 33 years old (IQR = 29–33). For underlying chronic co-morbidities, 6.0% reported having hypertension and 8.0% reported having dyslipidemia. No other co-morbidities were reported. Thirty-four percent (n = 17) and 24% (n = 12) reported side effects from the first and second doses of CoronaVac, respectively. The average time between the last CoronaVac vaccination and the BNT162b2 booster shot was 81.7 days (SD = 25.0). (Table 1).

On day 0, day 14, and day 28, the median anti-SARS-CoV-2 IgG antibodies were 335.5 AU/ml (IQR = 213.7–499.7), 31613.5 AU/ml (IQR = 20,832.4–40,000), and 20311.9 AU/ml (IQR = 11,920.7–274 14.4), respectively (Table 2). On day 14 and day 28 after the booster shot, 94% (n = 47) and 86% (n = 43) of individuals had anti-SARS-CoV-2 IgG antibodies greater than 10,000 AU/ml, respectively. The median anti-SARS-CoV-2 IgG antibodies were significantly different between the three groups (day 0, day 14, and day 28) as determined by a post-hoc pairwise comparison with a p-value of 0.001 (Fig. 1).

There was a moderate correlation (R) of log anti-SARS-CoV-2 IgG antibodies between day 0 and day 14 after the booster shot (R = 0.46,95% CI = 0.21–0.65, p-value < 0.001). There was also a moderate correlation of log anti-SARS-CoV-2 IgG antibodies between day 0 and day 28 after the booster shot (R = 0.47, 95% CI = 0.22–0.66, p-value < 0.001). There was a strong correlation of log anti-SARS-CoV-2 IgG antibodies between day 14 and day

Table 1
Baseline demographic and health information.

Demographics	**Total (N = 50)**	
	n	**(%)**
Gender		
Female	37	74.0
Male	13	26.0
age median (IQR) 33.0 [29–33]		
BMI (kg/m^2), mean ± SD	23.1	± 5.0
Side effect from previous vaccine (any)		
1st dose	17	34.0
2nd dose	12	24.0
Co-morbidities		
Hypertension	3	6.0
Dyslipidemia	4	8.0
Day from latest vaccine, mean ± SD	81.7	±25.0

Table 2
Anti-SARS-CoV-2 IgG antibody levels after BNT162b2 booster vaccination.

Anti-RBD IgG titer (AU/mL)	Day 0	Day 14	Day 28	*p* value
Median (IQR)	335.5 (213.7–499.7)	31,613.5 (20,832.4–40,000)	20,311.9 (11,920.7–27,414.4)	<0.001*
Post-hoc pairwise comparison				
D0	–	<0.001***	<0.001***	
D14	–	–	<0.001***	

p value was obtained by * Friedman test, **Chi-square test of proportions, and ***Durbin-Conover test.

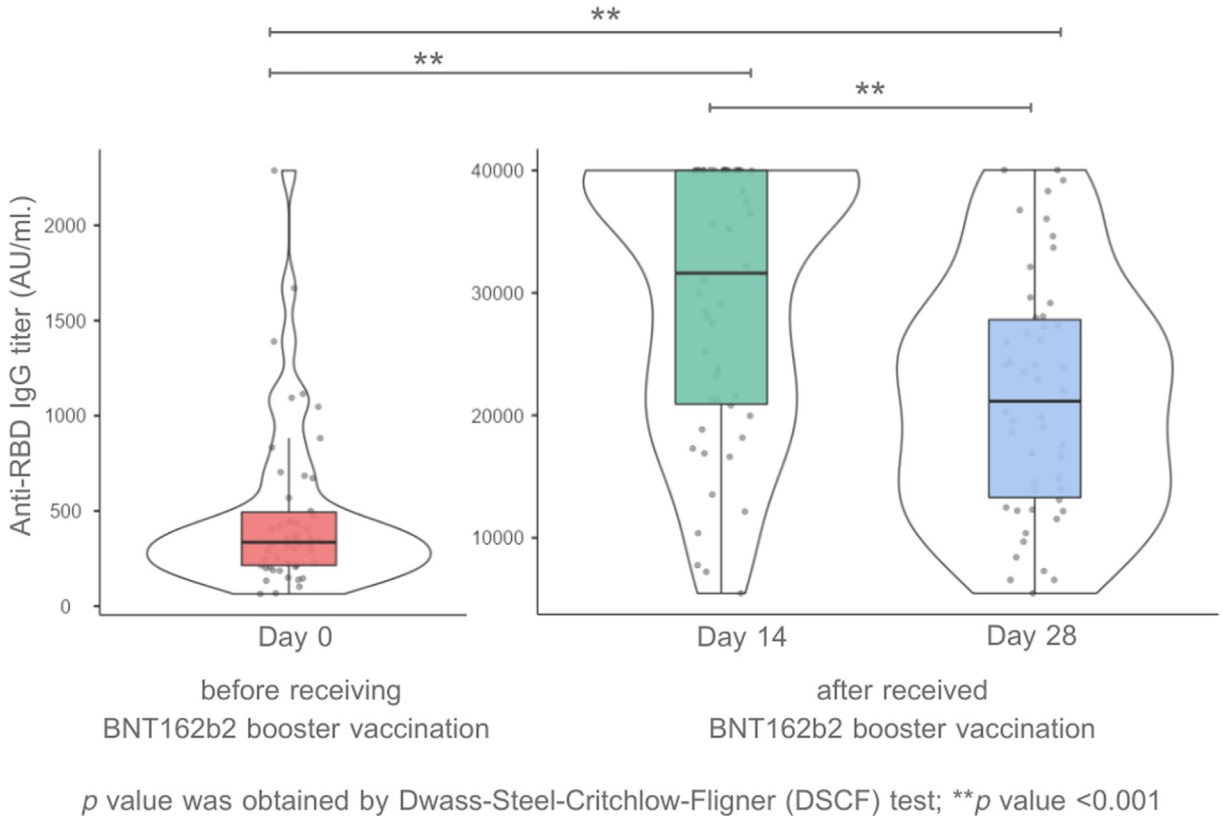


Fig. 1. Violin plots of anti-SARS-CoV-2 IgG antibody levels on day 0, day 14, day 28.

28 after the booster shot (R = 0.96, 95 %CI = 0.93–0.98, p-value < 0.001) (Fig. 2).

Characteristics associated with higher anti-SARS-CoV-2 IgG antibody levels on day 14 after the BNT162b2 booster were being male (β co-eff −8960.9, 95% CI −14,600.5 to −3321.3, p-value 0.003), BMI (β co-eff 437.3, 95% CI −55.2 to 929.9, p-value 0.080), number of days from last vaccination (β co-eff 178.2, 95% CI 71.95–284.4, p-value 0.002), and baseline anti-SARS-CoV-2 IgG antibodies at day 0 (β co-eff 18994.8, 95% CI 9590.5 to 26599.0, p-value < 0.001). (Table 3) The adjusted R^2 was 0.47.

Characteristics associated with higher anti-SARS-CoV-2 IgG antibody levels on day 28 after the BNT162b2 booster were being male (β co-eff −8652.2, 95% CI −13358.2 to −3946.3, p-value < 0.001), BMI (β co-eff 750.6, 95% CI 339.6 to 1160.6, p-value < 0.001), number of days from last vaccination (β co-eff 169.3, 95% CI 80.9–258.2, p-value < 0.001), and baseline anti-SARS-CoV-2 IgG antibodies at day 0 (β co-eff 7326.8, 95% CI 4244.8 to 10408.8, p-value < 0.001) (Table 3). The adjusted R^2 was 0.61 (Table 4).

The interval between the 2nd and 3rd doses of CoronaVac and BNT162b2 vaccination was related to the estimated marginal mean anti-SARS-CoV-2 IgG antibodies at day 14. The marginal mean was around 27,268.8 AU/ml (95% CI = 24,606.6–29,930.9) after an 82-day interval, while the higher marginal mean was 31,726.33 AU/ml (95% CI = 28,019.1–35433.6) after a 107-day (+1SD) delay. The lowest marginal mean was 22,811.2 AU/ml at 56 days (-1SD) (18996.2–26626.2). (Fig. 3a) Higher marginal mean (+1SD = 33,282.0; % CI = 29096.5–37367.5) was linked with higher log anti-SARS-CoV-2 IgG antibodies at day 0. (Fig. 3b).

The interval between the 2nd dose of the CoronaVac and the 3rd dose of the BNT162b2 vaccines was related to the estimated marginal mean anti-SARS-CoV-2 IgG antibodies at day 28. The marginal mean was 27,268.8 AU/ml (95% CI = 24,606.6–29,930.9) after an 82-day interval, while a higher marginal mean of 31,726.33 AU/ml (95% CI = 28,019.1–35433.6) was found after a 107-day (+1SD) interval. The lowest marginal mean was 22,811.2 AU/ml following a 56 day interval (-1SD) (18996.2–26626.2). (Fig. 4a) Higher marginal mean (+1SD = 33,282.0; % CI = 29096.5–37467.5) was linked with higher log anti-SARS-CoV-2 IgG antibodies at pre-booster shot (Fig. 4b).

Local reactions were reported by 92% (N = 46) of the participants. Pain at the injection site was the most common symptom (88%, N = 44), followed by tenderness (22%, N = 11), and swelling (22%, N = 11). Itching, warmth, and bruising were minor local reactions that affected 6% to 8% of participants. Systemic reactions

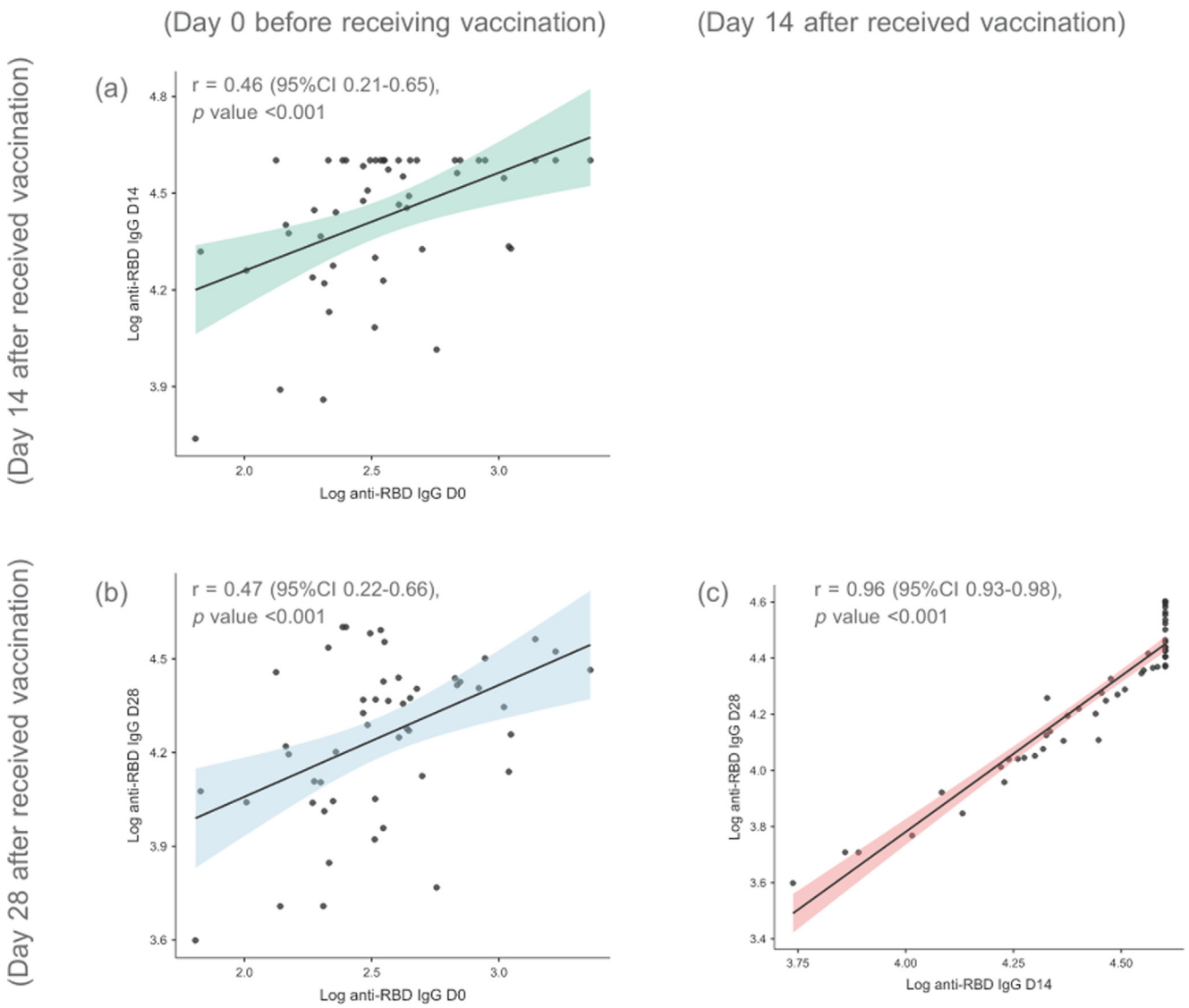


Fig. 2. Correlation of anti-SARS-CoV-2 IgG antibody levels by time point. $^{-SD}$ mean – SD, $^{\mu}$ mean, $^{+SD}$ mean + SD, * Estimated marginal means by multivariable linear regression models as presented in Table 3.

Table 3
Association between anti-SARS-CoV-2 IgG antibody levels at day 14 and individual characteristics, vaccination interval, and baseline anti-RBD IgG using a multivariable linear regression model.

Variables	β co-eff.	95% CI	*p* value
Age (years)	−196.4	−479.9 to 87.1	0.170
Male	−8,960.9	−14,600.5 to −3,321.3	0.003
BMI (kg/m^2)	437.3	−55.2 to 929.9	0.080
Days from last vaccination	178.2	71.95 to 284.4	0.002
Log anti-SARS-CoV-2 IgG antibodies at day 0	18,094.8	9,590.5 to 26,599.0	<0.001
Constant	−31,955.0	−64,942 to 1,030.8	0.057
		Adjusted R^2: 0.47	

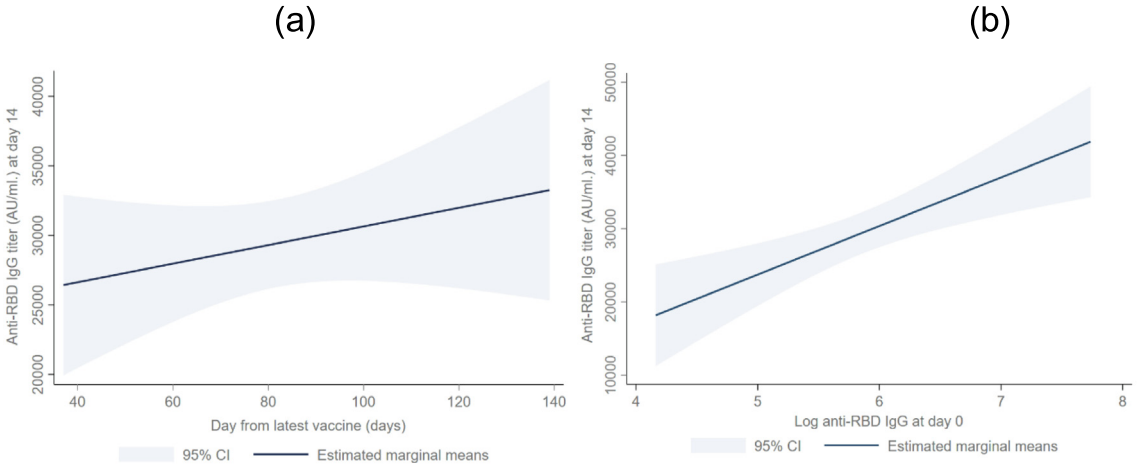
were reported by 85% (N = 30) of the participants. Feeling unwell after vaccination was the most common symptom (50%, n = 25), followed by fatigue (38%, n = 19), myalgia (36%, n = 18), chills (34%, n = 17), and headache (22%, n = 11). Only 6% (n = 3) reported no adverse reaction at all for 7 days after receiving the BNT162b2 booster (see Table 5).

4. Discussion

To the best of our knowledge, this is the first investigation evaluating the dynamic of anti-SARS-CoV-2 IgG antibody levels after a booster of BNT162b2 in Thai HCWs who previously completed two doses of CoronaVac. All participants had anti-SARS-CoV-2 IgG anti-

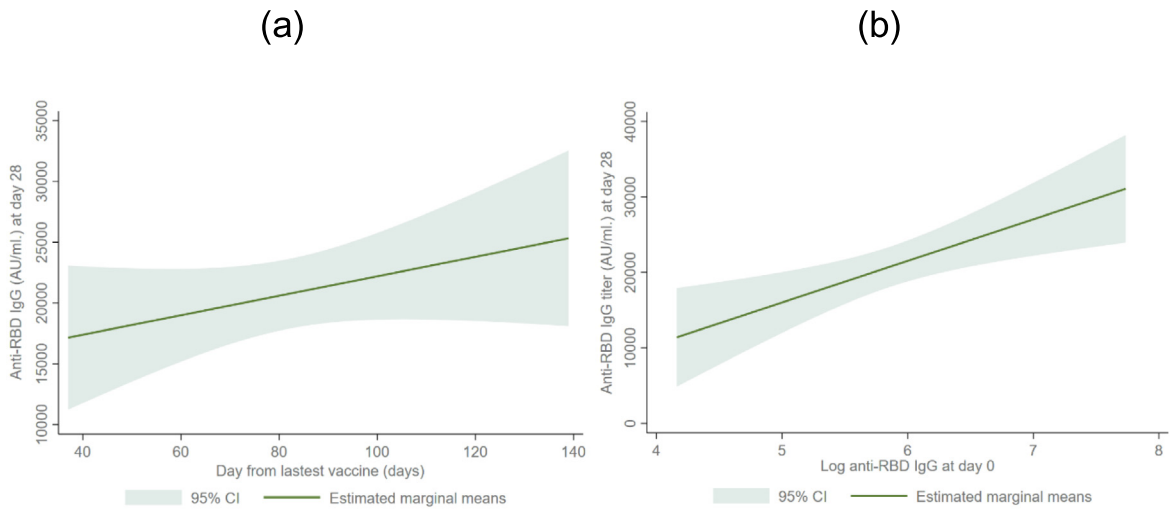
Table 4
Association between anti-SARS-CoV-2 IgG antibody levels at day 28 and individual characteristics, vaccination interval, and baseline anti-RBD IgG using a multivariable linear regression model.

Variables	β co-eff.	95% CI	*p* value
Age (years)	−162.52	−399.1 to 74.0	0.173
Male	−8,652.2	−13,358.2 to −3,946.3	<0.001
BMI (kg/m^2)	750.6	339.6 to 1,160.6	<0.001
Days from last vaccination	169.3	80.9 to 258.2	<0.001
Log anti-SARS-CoV-2 IgG antibodies at day 0	7,326.8	4,244.8 to 10,408.8	<0.001
Constant	−45,361.4	−72,887.1 to 17,835.7 Adjusted R^2: 0.61	0.002



Days from last vaccine	Marginal mean*	95% CI*	Log anti-SARS-CoV-2 IgG antibodies at day 0	Marginal mean*	95% CI*
56 $^{-SD}$	22,811.2	18,996.2 to 26,626.2	2.21 $^{-SD}$	21,255.5	17,701.7 to 24,809.4
82 $^{\mu}$	27,268.8	24,606.6 to 29,930.9	2.54 $^{\mu}$	27,268.8	24,606.6 to 29,930.9
107 $^{+SD}$	31,726.33	28,019.1 to 35,433.6	2.88 $^{+SD}$	33,282.0	29,096.5 to 37,467.5

Fig. 3. Estimated marginal mean of anti-SARS-CoV-2 IgG antibodies at day 14 by interval between 2nd dose of CoronaVac and 3rd dose of BNT162b2 vaccine. $^{-SD}$ mean – SD, $^{\mu}$ mean, $^{+SD}$ mean + SD, * Estimated marginal means by multivariable linear regression models as presented in Table 4.



Days from last vaccine	Marginal mean	95% CI	Log anti-SARS-CoV-2 IgG antibodies	Marginal mean	95% CI
56 -SD	22,811.2	18996.2 to 26,626.2	2.21 -SD	21,255.5	17,701.7 to 24,809.4
82 μ	27,268.8	24606.6 to 29,930.9	2.54 μ	27,268.8	24,606.6 to 29,930.9
107 +SD	31,726.33	28019.1 to 35,433.6	2.88 +SD	33,282.0	29,096.5 to 37,467.5

Fig. 4. Estimated marginal mean of anti-SARS-CoV-2 IgG antibodies at day 28 by interval between 2nd dose of CoronaVac and 3rd dose of BNT162b2 vaccine. $^{-SD}$ mean – SD, $^{\mu}$ mean, $^{+SD}$ mean + SD, * Estimated marginal means by multivariable linear regression models as presented in Table 4.

body levels greater than 50.0 AU/ml (assay cutoff) at 14 days and 28 days after receiving the heterologous booster with BNT162b2.

The baseline antibody level following complete vaccination highlights the necessity of the booster dose. The lowers the anti-SARS-CoV-2 IgG antibody level, the lower the protection against wild-type and variant types of SARS-CoV-2. In this study, the median anti-SARS-CoV-2 IgG antibody level was 335.5 AU/ml (IQR 213.7–499.7) an average of 82 days after a second dose of CoronaVac, which is similar to a study of anti-spike antibodies, which drop significantly by day 42 post immunization in Indonesian HCWs compared to day 14 post CoronaVac vaccination.[26] Vaccine effectiveness against COVID-19 infections also reduced after three to five months in Malaysian subjects who received full CoronaVac vaccination [6]. This seems to indicate that antibody levels following full CoronaVac vaccination drop significantly with time. For instance, a phase I/II clinical trial reported a median of 1,045.7 AU/ml, IQR 721.6–1,515.5, 28 days following full CoronaVac vaccination [27]. Similar findings were documented in Hong Kong healthcare workers, also measured 28 days after full vaccination (mean 1,005.2 AU/ml, 95% CI = 850.3–1,160.0) [16,27]. A comparison of the median antibody levels at day 28 of the Phase I/II clinical trial and day 82 of our study (1,045.7 AU/ml vs. 335.5 AU/ml) shows a 33.4% drop between those timepoints. This confirmed the need of a booster vaccination after a complete dose of CoronaVac.

Two and four weeks after receiving a booster dose of BNT162b2, the median anti-SARS-CoV-2 IgG antibody level in our participants was 31,613.5 AU/ml (IQR = 20,832–40,000) and 20,311.9 (IQR = 11,920.7–27,414.4), respectively. A trial in Turkey found that the median anti-RBD IgG level 28 days after a Pfizer booster among

Table 5
Self-reported reactions and adverse reactions after the BNT162b2 booster vaccination.

Self-reported side effects	*n*	(%)
Local reactions		
No local reaction	4	8.0
Pain	44	88.0
Tenderness	11	22.0
Swelling	11	22.0
Bruising	4	8.0
Itching	3	6.0
Warmth	3	6.0
Redness	0	–
Systemic reactions		
No systemic reaction	15	30.0
Fatigue	25	50.0
Myalgia	18	36.0
Fever/Chills	17	34.0
Headache	11	22.0
Dizziness	3	6.0
Diarrhea	3	6.0
High grade fever	2	4.0
Anorexia	1	2.0
Arthralgia	1	2.0
Nausea	1	2.0
Vomiting	0	–
Abdominal pain	0	–
Allergic reactions		
Rash	3	6.0
Angioedema	0	–
Dyspnea	0	–
Muscle weakness	0	–
No local nor systemic side effect	3	6.0

CoronaVac-prime subjects was 25,538 AU/ml, which was 46 times greater than the baseline level [28]. As compared to the Turkish study, our investigation indicated a lower level of anti-RBD IgG on 28 days (20,311.9 AU/ml) following booster [28]. This could be due to the fact that a lower level at baseline resulted in a lower level on day 28 after booster. When compared the immunogenicity of a third dose of SARS-CoV-2 vaccination among CoronaVac-prime participants, a booster with BNT162b2 displayed the highest level of anti RBD-IgG than a booster with other vaccines (AstraZeneca, CoronaVac, and BBIBP-CorV) [28–30]. As a result, a heterologous booster dose of BNT162b2 should be recommended over other vaccine platforms to persons who have completed two doses of CoronaVac in order to maintain high anti-RBD IgG levels throughout the COVID-19 VOCs outbreak.

According to the result of the Angkasek-winai et al study from AstraZeneca priming in Thailand, the immunogenicity of anti-RBD-IgG was highest among participants taking a booster dosage of Pfizer (2364 BAU/ml), followed by AstraZeneca (264.6 BAU/ml), and BBiBP-CorV (128.1 BAU/ml) at 14 days after the booster dose [30]. Pfizer, AstraZeneca, and BBiBP-CorV booster doses increased anti-RBD IgG geometric mean concentrations (GMCs) by 25.1, 2.3, and 1.2 folds, respectively [30]. A study from Munro et al (COV-BOOST) from the United Kingdom in the AstraZeneca priming group found that the anti RBD-IgG at 28 days after a booster dose was highest among participants taking a booster dosage of Moderna (31,111 ELU/ml, GMR 32.30) followed by Pfizer (20,517 ELU/ml, GMR 24.48), Novavax (6975 ELU/ml, GMR 8.75), Janssen (5517 ELU/ml, GMR 5.84), AstraZeneca (2457 ELU/ml, GMR 3.25) and Valneva (1835 ELU/ml, GMR 2.20) respectively [31]. As a result, mRNA-based COVID-19 vaccine should be considered as a booster dose in the AstraZeneca priming group. From the Atmar et al. in the United States of America, the GMC of SARS-CoV-2 anti-spike IgG at two weeks after booster dosage in Pfizer priming group was highest in Moderna (6155.0 BAU/ml, GMR 17.3) followed by Pfizer (3,409.1 BAU/ml, GMR 14.9) and Janssen (1904.7 BAU/ml, GMR 6.2) respectively. [32] Munro et al found that the anti RBD-IgG at 28 days after a booster dose in Pfizer priming group was highest among participants taking a booster dosage of Moderna (33,768 ELU/ml, GMR 11.49) followed by Pfizer (27,242 ELU/ml, GMR 8.11), Janssen (17,079 ELU/ml, GMR 5.63), Novavax (10,862 ELU/ml, GMR 4.78), AstraZeneca (13,424 ELU/ml, GMR 5.33) and Valneva (4204 ELU/ml, GMR 1.31) respectively [31]. From the Atmar et al. in the United States of America, the GMC of SARS-CoV-2 anti-spike IgG at two weeks following booster dosage in the Moderna-priming group was highest in Moderna (6799 BAU/ml, GMR 7.9), Pfizer (5195.6 BAU/ml, GMR 9.7), and Janssen (3,029.4 BAU/ml, GMR 4.7).[32] While these numbers cannot be directly compared, boosting with mRNA COVID-19 vaccine from Moderna or Pfizer among participants primed with inactivated, viral vector, and mRNA-based vaccine revealed the highest anti SARS-CoV-2 anti-RBD IgG level and GMR when compared to other vaccine platforms.

In our study, three factors were found to be significantly associated with higher levels of anti-SARS-CoV-2 IgG antibodies at both day 14 and day 28 after the booster vaccination. These included being female as opposed to male, higher log anti-SARS-CoV-2 IgG antibodies at day 0, and longer interval between the second shot of CoronaVac and the booster shot of BNT162B2. Higher anti-SARS-CoV-2 IgG antibodies after receiving vaccination among females was no surprise as the immune response is known to be more vigorous in females compared to males [33]. Our data also supports the role of estrogen in promoting a superior antibody response in women [34]. The finding that higher anti-SARS-CoV-2 IgG antibodies at baseline led to higher anti-SARS-CoV-2 IgG antibodies at day 14 and day 28 was also intuitive and self-explanatory. The last finding regarding the longer interval between the last shot of CoronaVac and the booster shot of BNT162B2 leading to higher anti-SARS-CoV-2 IgG antibody levels at 14 and 28 days after the booster shot was more important and had further implications. Due to the limited number of participants and follow-up time, it was difficult to pinpoint the exact ideal timing for the booster vaccination. Given the waning immune response following the second dose of CoronaVac, the interval for the booster dose should not be too short. We suggest administering the booster at least 3 months after completion of CoronaVac vaccination.

The booster dose of BNT162B2 rapidly promoted a humoral immune response in our study participants, implying that double vaccination of CoronaVac granted sufficient memory B cell albeit low antibody production. Although the observed anti-SARS-CoV-2 IgG antibody level at day 14 after BNT162B2 immunization was markedly increased, the antibody level gradually decreased at day 28 (Fig. 1). This phenomenon was formerly reported in both natural infection and mRNA vaccination [35,36]. The persistence of long-lived bone marrow plasma cells (BMPCs) is crucial in maintaining the antibody in serum [37]. Interleukin-21 is a key cytokine in maintaining the BMPCs and is considered for future vaccine development [38]. Considering the Delta variant's dominance as the circulating strain in Thailand, a booster dose of BNT162B2 vaccine for frontline HCWs and healthy people who have completed the primary series of CoronaVac at least 3–5 months after the second dose of CoronaVac should be considered.

Within 7 days of receiving a BNT162B2 booster shot, 94% of participants experienced either a local or systemic adverse event. However, none of participants had a severe adverse event. This study found a higher percentage of local (71.9%) and systemic (13.5%) side effects than in participants who received only one injection of the BNT162B2 vaccine [39]. Fatigue was the most common systemic adverse reaction of BNT162B2, regardless of whether the participant received a first or booster dose, while tenderness was more common among BNT162B2 individuals who got

a homogeneous prime/boost [39]. The percentage of people experiencing fever in our study was comparable to AstraZeneca/Pfizer, which was higher than the homologous prime/boost vaccine series [40]. These findings could reflect that a heterologous vaccination produced more local and systemic reactogenicity after a booster dose than a homologous dose. Participants who intend to get heterologous vaccination should be advised of the increased risk of experiencing adverse effects after receiving a heterologous booster dosage.

This study had several limitations. The sample size was small due to limitation of the funding. There was also a risk of selection bias as the potential participants knew about the study from advertisements through social media. We only observed immune response in healthy adults, therefore the antibody response may differ in people with other diseases that complicate immune status. Although the antibody level significantly increased, the RBD used in the Abbott kit is from the wild-type SARS-CoV-2. The actual neutralizing antibody should be further determined against SARS-CoV-2 variants. For future research, the participants in this study should be monitored to further assess the dynamic of SARS-CoV-2 anti-spike IgG levels after booster vaccination. Serum inflammatory factors and pro-inflammatory cytokine levels, such as IL-2, IL-6, TNF-alpha, and cytotoxic T cell, should also be measured to correlate them with humoral immune response.

5. Conclusion

A booster dose of BNT162B2 promoted a high level of anti-SARS-CoV-2 IgG antibodies. Being female, having higher log anti-SARS-CoV-2 IgG antibodies prior to booster vaccination, and a longer interval between the second shot of CoronaVac and the booster shot of BNT162B2 were found to be significantly associated with higher levels of anti-SARS-CoV-2 IgG antibodies. A third dose of BNT162B2 vaccine should be considered for frontline HCWs and patients with co-morbidities who have already completed CoronaVac. The time between the second CoronaVac shot and the booster shot should be at least three months.

CRediT authorship contribution statement

Amonrphat Kitro: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition, Resources. **Wachiranant Sirikul:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Weeraya Thongkum:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Suthinee Soponpong:** Formal analysis, Investigation. **Umpa Yasamut:** Formal analysis, Investigation. **Wuttipat Kiratipaisarl:** Writing – review & editing, Resources, Supervision. **Apiradee Kosai:** Formal analysis, Investigation. **Watchara Kasinrerk:** Writing – original draft. **Chatchai Tayapiwatana:** Conceptualization, Methodology, Writing – review & editing, Resources, Supervision. **Kriengkrai Srithanaviboonchai:** Conceptualization, Methodology, Writing – review & editing, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.020.

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