นิพนธ์ต้นฉบับ

การตอบสนองทางภูมิคุ้มกัน 1 เดือน หลังได้รับวัคซีนเข็มกระตุ้นระหว่าง BNT162b2 และ ChAdOx1 nCoV-19 ในบุคลากรทางการแพทย์สุขภาพดี ที่เคยรับ Sinovac-CoronaVac มาก่อน 2 เข็ม

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บทคัดย่อ

บุคลากรทางการแพทย์เป็นกลุ่มแรกๆที่ได้รับการฉีดวัคซีนป้องกันไวรัสโควิด-19 ตั้งแต่เริ่มการระบาดของไวรัสโควิด-19 จากนั้นได้แนะนำให้ฉีดเข็มกระตุ้น ซึ่งไม่มีการประเมินผลการตอบสนองของวัคซีนเข็มกระตุ้นในระยะเวลาที่ทำการศึกษา

วัตถุประสงค์: เพื่อศึกษาระดับการตอบสนองทางภูมิคุ้มกัน 1 เดือน หลังได้รับการฉีดวัคซีนเข็มกระตุ้นระหว่าง BNT162b2 และ ChAdOx1 nCoV-19 ในบุคลากรทางการแพทย์สุขภาพดีที่เคยรับ Sinovac-CoronaVac มาก่อน 2 เข็ม

วิธีการศึกษา: การศึกษาแบบไปข้างหน้า ในโรงพยาบาลนครพิงค์ช่วงเดือนสิงหาคม พ.ศ. 2564 – พ.ศ. 2565 ในบุคลากรทางการแพทย์ที่มีสุขภาพดี ที่เคยได้รับวัคซีน Sinovac-CoronaVac จำนวน 2 เข็ม อาสาสมัครได้รับการตรวจเลือดที่ระยะ 1 เดือนหลังได้รับวัคซีนเข็มกระตุ้นด้วย BNT162b2(Pfizer-BioNTech) หรือ ChAdOx1 nCoV-19 (AstraZeneca) การตรวจวัดระดับภูมิคุ้มกันด้วยเครื่อง Elecsys® Anti-SARS-CoV-2 S version 2 (ECLIA, Roche) เปรียบเทียบระดับภูมิคุ้มกันระหว่าง BNT162b2 และ ChAdOx1 nCoV-19 ด้วยสถิติ multivariable linear regression

ผลการศึกษา: อาสาสมัครทั้งหมด 168 คน โดย 86 คนได้รับเข็มกระตุ้นด้วย ChAdOx1 nCoV-19 และ 82 คนได้รับเข็มกระตุ้นด้วย BNT162b2 ค่าเฉลี่ยและค่ามัธยฐานของระดับภูมิคุ้มกันในกลุ่ม ChAdOx1 nCoV-19 มีค่า 4,677.01 U/mL (±4,081.54) และ 4,266.24 U/mL (IQR 5,875.59) และกลุ่ม BNT162b2 มีค่า 17,085.76 U/mL (± 10,723.3) และ 15,104.69 U/mL (IQR 11,597.86) ตามลำดับ ระดับภูมิคุ้มกันหลังได้รับเข็มกระตุ้นในระยะเวลา 1 เดือนในกลุ่ม BNT162b2 มีค่าสูงกว่ากลุ่ม ChAdOx1 nCoV-19 อย่างมีนัยสำคัญทางสถิติเท่ากับ 12,408.74 (95% CI;9, 958.70-14, 858.78, p<0.001) อย่างไรก็ตามทั้งสองกลุ่มไม่พบเหตุการณ์ไม่พึงประสงค์ร้ายแรงและไม่มีรายงานการติดเชื้อไวรัสโควิด-19 ในระหว่างการศึกษา

สรุปผลการศึกษา: ในบุคลากรทางการแพทย์สุขภาพดีที่เคยรับวัคซีน Sinovac มาก่อน พบว่าระดับภูมิคุ้มกันต่อไวรัสโควิด-19 หลังได้รับเข็มกระตุ้น 1 เดือน ด้วย BNT162b2 สูงกว่าได้รับ ChAdOx1 nCoV-19 อย่างมีนัยสำคัญ ข้อมูลนี้อาจจะนำไปใช้เป็นแนวทางในการพิจารณาเชิงนโยบายในการให้วัคซีนเพื่อกระตุ้นภูมิคุ้มกันในบุคลากรทางการแพทย์ในอนาคตหากเกิดสถานการณ์ที่คล้ายคลึงกับการระบาดของโรคโควิด-19

คำสำคัญ: ไวรัสโควิด-19, Sinovac, วัคซีน, BNT162b2, ChAdOx1 nCoV-19, เข็มกระตุ้นเข็ม 3, บุคลากรทางการแพทย์, Anti-SARS-CoV-2 spike RBD antibodie

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Original Article

Pattern of Antibody Response After either BNT162b2 or ChAdOx1 nCoV-19 as a Booster Shot Following Two Shots of Sinovac-CoronaVac among Healthcare Workers

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ABSTRACT

Background: Two shots of Sinovac-Coronavac vaccine were provided to healthcare workers in Thailand during the early outbreak of SARS-CoV-2 infection. BNT162b2 or ChAdOx1 nCoV-19 has been used as a booster dose. However, at the time of this study conducted data of immunogenic response after boosting with BNT162b2 or ChAdOx1 nCoV-19 is limited.

Methods: The objective of our study was to measure the antibody response at one month after receiving BNT162b2 (Pfizer-BioNTech) or ChAdOx1 nCoV-19 (AstraZeneca) as the booster dose in healthcare worker who had fully vaccinated with two doses of Sinovac during August 2021 to 2022. Exclusion criteria were; diabetes mellitus, chronic kidney disease, immunodeficiency syndrome, cancer, BMI more than 35 kg per m2, BW more than 100 kg, pregnancy, lactation, postpartum, history of SARS-CoV-2 infection and currently taking immunosuppressive agent or prednisolone at least 20 mg per day within one month before receiving the third dose of vaccine. All participants' blood samples were drawn at one month after the booster dose. Anti SARS- CoV-2 spike RBD antibodies were measured by Elecsys® Anti-SARS-CoV-2 S version 2 (ECLIA, Roche), an immunoassay.

Results: A total of 168 participants were enrolled, 86 received ChAdOx1 nCoV-19 and 82 received BNT162b2. Mean and median of anti SARS-CoV-2 spike RBD level in BNT162b2 group was 17,085.76 U/mL (±10,723.3) and 15,104.69 U/mL (IQR 11,597.86) respectively, whereas mean and median of anti SARS-CoV-2 spike RBD level in ChAdOx1 nCoV-19 group was 4,677.01 U/mL (±4,081.54) and 4,266.24 U/mL (IQR 5,875.59) respectively. Anti SARS-CoV-2 spike RBD antibodies level at one month after the booster vaccine was significantly higher in participants who received BNT162b2, mean difference 12,408.74 (95% CI; 9,958.70-14,858.78, p<0.001). Participants in neither BNT162b2 group nor ChAdOx1 nCoV-19 group has serious adverse event and incidence of SARS-CoV-2 infection within one month after the booster dose.

Conclusions: Anti-SARS-CoV-2 spike RBD antibodies level at one-month post-vaccination in population who received BNT162b2 as the third dose after fully vaccinated with Sinovac were higher compared to those who received ChAdOx1 nCoV-19 as the third dose. Additional data may be necessary to fully elucidate the long-term response.

Keywords: SARS-CoV-2, Sinovac, BNT162b2, ChAdOx1 nCoV-19, immunogenicity, third dose, booster dose, healthcare worker, Anti-SARS-CoV-2 spike RBD antibodies

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Introduction

Severe acute respiratory syndrome coronavirus 2[1] outbreak has started since December 2019. The SARS-CoV-2 pandemic caused widespread morbidity and mortality. Therefore, rapid vaccine development occurred extensively across the world. Immunity to SARS-CoV-2 has been shown to reduce the risk of severe disease or even protect against reinfection.[2] Nevertheless, primary immune responses from recovered individuals decline over time.[3-4] Hence, potential vaccines against SARS-CoV-2 were encouraged for all people. At the initial of the SARS-CoV-2 pandemic, the vaccine supply was limited.

Thailand is one of many countries which had limited access to mRNA and viral-vector vaccines. The inactivated vaccine of Sinovac was shown to be effective without any serious adverse events in phase-3 randomized, placebo-controlled trials.[5] Sinovac vaccine was administered for many Thai populations during the early phase of the SARS-CoV-2 pandemic. Adults who received two doses of the Sinovac vaccine have been demonstrated to have high antibody responses[6-7]; although, 3-6 months after administration of the Sinovac vaccine, the antibodies against SARS-CoV-2 continued to decline.[8-9] Consequently, a booster dose is necessary for those who received two shots of Sinovac vaccine.[10]

Giving BNT162b2 as a third dose in adults who received two doses of Sinovac vaccine showed higher immunologic response than giving Sinovac vaccine as a booster dose [11] Meanwhile, administration of ChAdOx1 nCoV-19 as a booster shot following two Sinovac doses in healthcare workers showed significant immunity improvement one month after vaccination.[12]

Notwithstanding, the data that compares the immunogenic response between BNT162b2 and ChAdOx1 nCoV- 19 as a third dose following two doses of the Sinovac vaccine was scarce. To determine the antibody response pattern, we provided either BNT162b2 or ChAdOx1 nCoV-19 as a booster shot among healthy volunteers. At the time that this study was conducted, we needed the evidence base medicine as basic information for medical personnel living in northern region who were at risk of infection.

Methods

Study Design and Population

Our study was a prospective cohort, single-center study. From August 2021 to August 2022, we recruited 168 healthy healthcare workers in Nakornping Hospital who had already received two doses of Sinovac vaccine and after that received either BNT162b2 or ChAdOx1 nCoV-19 as the third dose. Exclusion criteria were participants who might have difficulty on immune response after vaccination as the following: diabetes mellitus, chronic kidney disease, immunodeficiency syndrome, cancer, BMI more than 35 kg per m^2, BW more than 100 kg, pregnancy, lactation, postpartum not more than three months, history of SARS-CoV-2 infection and currently taking immunosuppressive agent or prednisolone at least 20 mg per day within one month before receiving the third

dose of vaccine. This trial was designed to determine the antibody response pattern after the third dose of the SARS-CoV-2 vaccine among healthy volunteers.

Sample size estimation

According to the previous pooled randomized trial reported the median of SARS-CoV-2 anti-spike IgG responses from Covid-19 ChAdOx1 nCoV-19 (AstraZeneca) prime-boost interval between <6 weeks vs. ≥12 weeks as 23,173 [IQR: 11,665-43,633], and 51,291[IQR: 28,597-93,521], respectively[13], we calculated sample size based on the matched paired Wilcoxon signed-rank test using the G*Power 3.1.9.7 program. Standard deviations were estimated by the formula of SD=IQR/1.35.[14] Prespecified power of analysis was 80% and alpha error was 0.05. Twenty-one participants were at least required for two-time intervals assessment. We finally added 15% of sample needed, therefore the total recruited subjects were 25. Type I error was set at 0.05 for all the analyses.

The sample size was aimed to enroll to 30 participants for each age group of age 30-<40 years, 40-<50 years and 50-<60 years and then enroll sex at ratio 1:1 into each age group if eligible sex was not achievable then enroll any eligible participants to meet minimum target number of 21.

Data collection

Baseline characteristics, along with the history of Sinovac vaccination, were collected using a case record form on the day of recruitment. After providing informed consent, participants were classified into 2 groups (one group will boost with BNT162b2 (PZ) and the other will boost with ChAdOx1 (AZ) nCoV-19 as the third dose). Participants were equally recruited in each group. A number of participants in each group was also equally divided according to each age range (30 to less than 40 years, 40 to less than 50 years, and 50 to less than 60 years). Males and females were also divided by a 1:1 ratio in each group. Blood samples 3 to 5 ml were collected one month after the third dose of vaccination for complete blood count and anti-spike RBD antibodies.

All participants had been informed and gave consent for the use of their data and clinical sample before starting recruitment. The trial ethical consideration was reviewed and granted for approval by local ethics committee on 13 August 2021. Clinical trial registration ID was TCTR20210831002. The trial was funded by Nakornping Hospital for laboratory cost.

Serologic Analysis for Determination of Immune Responses

Anti-SARS-CoV-2 spike RBD antibodies were measured by Elecsys® Anti-SARS-CoV-2 S version 2 (ECLIA, Roche), May 2021, an immunoassay for the in vitro quantitative determination of total antibodies to the SARS-CoV-2 S protein RBD in human serum. The assay uses a recombinant RBD protein in a double-antigen sandwich assay format, which favors the quantitative determination of high-affinity antibodies against SARS-CoV-2. The test was intended as an aid to assess the adaptive humoral immune response, including neutralizing antibodies, to the SARS-CoV-2 S protein after natural infection with SARS-CoV-2 or in vaccine recipients.

The antibody level, which is equal to or more than 0.8 units per ml (U/mL), was defined as positive for immunity against SARS-CoV-2. Besides, the antibody level that was equal to or more than 15 U/mL indicated the detection of inhibitory antibodies compared to other neutralization assays as the following: plaque reduction neutralization test (PRNT) with percent inhibition 50% or more, whole virus neutralization test (NT) with percent inhibition 80% or more, and surrogate NT with percent inhibition 20% or more. Moreover, for the antibody level, which was equal to or more than 132 U/mL in participants who had prior SARS-CoV-2 natural infection, convalescent plasma donation was permitted.

Study End Points

The primary study endpoint was to compare the antibody level at one month after receiving BNT162b2 or ChAdOx1 nCoV-19 as a third dose following two doses of the Sinovac vaccine. The secondary end point included serious adverse events at one month after administration of BNT162b2 or ChAdOx1 nCoV-19 and the incidence of SARS-CoV-2 infection following the third dose of vaccine.

Statistical Analysis

Baseline characteristics were presented with descriptive statistics. Categorical data were presented as numbers and percentages, and continuous data were presented as mean and median with p values. To compare difference of two continuous data, independent t-test was used for normal distributed data and rank sum test for non-normal distributed data. Fisher's exact test was used to compare two different proportions. Multivariable linear regression was performed to compare two different mean adjusted for confounding factors presenting with adjusted beta coefficient (95% confidence interval, CI).

In addition, subgroup analyses were prespecified comparing 1) AZ<15 U/mL vs ≥ 15 U/mL vs PZ ≥ 15 U/mL, 2) AZ<132 U/mL vs ≥132 U/mL vs PZ ≥132 U/mL, 3) AZ<132 U/mL vs ≥132 U/mL. ANOVA was used to compare three groups mean, meanwhile Kruskal-Wallis was used for median comparison. Statistical analysis was done using STATA version 16. P value < 0.05 was determined as statistically significant.

Results

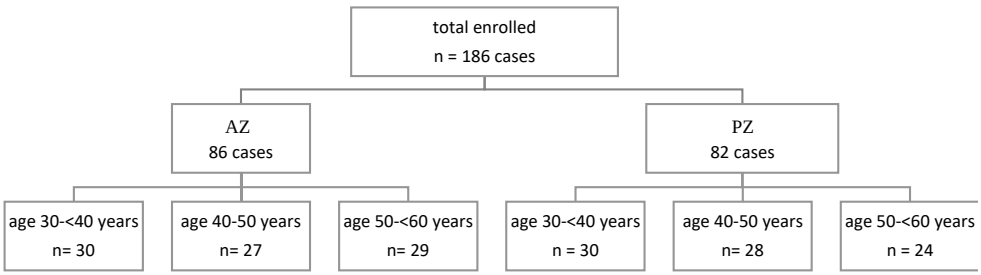

Figure 1 Study flow diagram for recruiting the participants

Characteristics of Participants

We enrolled 168 healthy healthcare workers who had received two shots of the Sinovac vaccine in this prospective cohort study (Figure 1). Participants received either BNT162b2 or ChAdOx1 nCoV-19 as the third dose. Of 168 participants, 93 (55.4%) were female, median age was 43 years old (categorized into three age groups: 35.7% were 30 – 39 years old, 32.7% were 40-49 years old, and 31.6% were 50-59 years old. There were 88 (52.4%) participants who had underlying diseases (hypothyroid, hypertension, dyspepsia, dyslipidemia, allergic rhinitis, hepatitis B, asthma, migraine, and renal calculi). The two groups had no significant differences according to baseline characteristics. The factors that found statistically significant were the duration from second dose vaccine which was longer in the PZ group, and having any underlying diseases which the AZ group showed higher proportions (Table 1).

Humoral Immunogenicity

Anti SARS-CoV-2 spike RBD antibodies were measured in all participants one month after receiving either ChAdOx1 nCoV-19 or BNT162b2 as the third dose. The mean and median of anti-SARS-CoV-2 spike RBD level in the ChAdOx1 nCoV-19 group were 4,677.01 U/mL and 4,266.24 U/mL, respectively. Meanwhile, the mean and median of anti-SARS-CoV-2 spike RBD level in the BNT162b2 group was 17,085.76 U/mL and 15,104.69 U/mL, respectively.

Table 1. Baseline Characteristics comparison between the AZ and the PZ group

	Total (n=168)	AZ (n=86)	PZ (n=82)	p-value
Sex, n (%)				0.165[a]
Male	75 (44.6)	43 (50)	32 (39)	
Female	93 (55.4)	43 (50)	50 (61)	
Age(year), mean (SD)	44.0 (8.7)	44.4 (8.5)	43.6 (8.9)	0.546[b]
Age gr 30-<40 y, n (%)	60 (35.7)	30 (34.9)	30 (36.6)	0.839[a]
Age gr 40-<50 y, n (%)	55 (32.7)	27 (31.4)	28 (34.1)	
Age gr 50-<60 y, n (%)	53 (31.6)	29 (33.7)	24 (29.3)	
BMI(Kg/m^2), mean (SD)	23.6 (3.9)	23.9 (3.7)	23.4 (4.1)	0.429[b]
Having any underlying diseases, n (%)	88 (52.4)	51 (59.3)	37 (45.1)	0.046[a]
Duration from second dose vaccine(days), mean (SD)	107.4 (25.0)	97.9 (23.5)	117.3 (22.7)	< 0.001[b]
WBC(cells/mm^3), median (IQR) min-max	6.4 (2) 3.7-14.1	6.35 (1.9) 4.3-9.9	6.6 (1.9) 3.7-14.1	0.273[c]
Lymphocyte(cells/mm^3), mean (SD)	2.2 (0.6)	2.3 (0.5)	2.2 (0.6)	0.311[b]

[a]Fisher's exact test, [b]Independent t-test, [c]Rank sum test

BMI denotes Body Mass Index, and WBC White Blood Cell, AZ represents ChAdOx1 nCoV-19, PZ represents BNT162b2

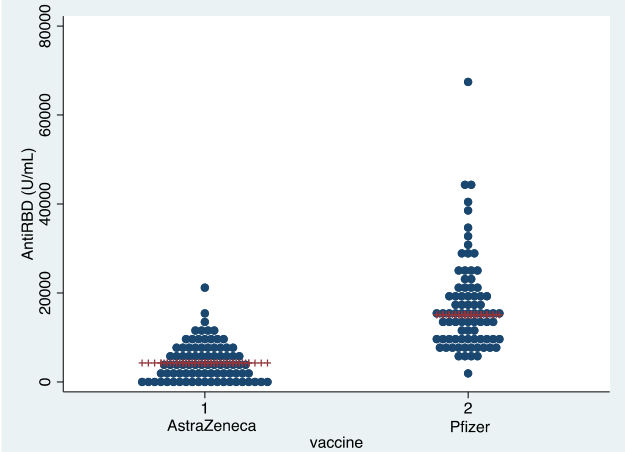

Figure 2 The box plot illustrates the median of anti-SARS-CoV-2 spike RBD antibody level between BNT162b2 group and ChAdOx1 group.

The mean difference of anti-SARS-CoV-2 spike RBD antibody response after being vaccinated with either BNT162b2 or ChAdOx1 nCoV-19 as the third dose following the Sinovac vaccine were compared. Anti-SARS-CoV-2 spike RBD antibodies, which were measured one month after the third dose of vaccine, had been shown as U/mL. Crude beta coefficient was analyzed using univariable linear regression. The result showed that anti-SARS-CoV-2 spike RBD antibodies from PZ was significant higher than AZ group, 12,408.74 (95% CI;9,958.70-14,858.78, p<0.001). After controlling for underlying disease using multivariable linear regression, anti-SARS-CoV-2 spike RBD antibodies from PZ was significant higher than AZ group, adjusted beta coefficient 11,075.51(95% CI;8,428.28-13,721.74, p<0.001).(Figure 2)

Subgroup analysis based on anti-SARS-CoV-2 spike RBD antibodies level after receiving the third dose vaccine for 1 month, with a cut-off of equal to or more than 15 U/mL, indicated the detection of inhibitory antibodies compared to other neutralization assays as described above. There were 2 participants in AZ group whose anti SARS-CoV-2 spike RBD antibodies level less than 15 U/mL. Meanwhile, anti SARS-CoV-2 spike RBD antibodies level of 84 and 82 participants were more than 15 U/mL in AZ and PZ group respectively. Duration before receiving the third dose vaccine was significantly different among AZ group which anti SARS-CoV-2 spike RBD antibodies level less than 15 U/mL, AZ group which anti SARS-CoV-2 spike RBD antibodies level equal to or more than 15 U/mL and PZ group which anti SARS-CoV-2 spike RBD antibodies level equal to or more than 15 U/mL ($p < 0.001$). (Table 2) On the other hand, sex, age, age group, BMI, having any underlying diseases, white blood cell count and lymphocyte count were not significantly associated with anti SARS-CoV-2 spike RBD antibodies response at a cut-off of level of equal to or more than 15 U/mL.

Table. 2 Factors associated with anti SARS-CoV-2 spike RBD antibodies response at the cut-off point at 15 U/mL

Factors	AZ (n=86)		PZ (n=82)	p-value
	< 15 U/mL (n=2)	≥ 15 U/mL (n=84)	≥ 15 U/mL (n=82)	
Sex, n (%)				0.292
Male	1 (50)	42 (50)	32 (39.0)	
Female	1 (50)	42 (50)	50 (61.0)	
Age(year), mean (SD)	44.5 (6.4)	44.1 (8.6)	43.6 (9.2)	0.911
Age gr 30-<40 y, n (%)	0 (0)	30 (35.7)	29 (35.4)	0.589
Age gr 40-<50 y, n (%)	2 (100)	26 (31.0)	28 (34.2)	
Age gr 50-<60 y, n (%)	0 (0)	28 (33.3)	25 (30.4)	
BMI(Kg/m2), mean (SD)	29.8 (3.4)	23.7 (3.6)	23.4 (4.1)	0.065
Having any underlying diseases, n (%)	2 (100)	50 (59.5)	48 (58.5)	0.723
Duration from second dose vaccine(days), mean(SD)	82 (7.1)	97.9 (23.6)	117.3 (22.7)	<0.001
WBC(cells/mm^3), median (IQR) min-max	8.3 (1.6) 7.5-9.1	6.3 (1.9) 4.3-9.9	6.6 (1.9) 3.7-14.1	0.150
Lymphocyte(cells/mm^3), mean (SD)	2.9 (0.4)	2.3 (0.5)	2.2 (0.6)	0.166

Table. 3 Factors associated with anti SARS-CoV-2 spike RBD antibodies response at the cut-off point at 132 U/mL

anti SARS-CoV-2 spike RBD antibodies level	AZ (n=86)		PZ (n=82)	p-value
	< 132 U/mL (n=15)	≥ 132 U/mL (n=71)	≥ 132 U/mL (n=82)	
Sex, n (%)				0.268
Male	9 (60)	34 (47.9)	32 (39.0)	
Female	6 (40)	37 (52.1)	50 (61.0)	
Age(year), mean (SD)	45.2 (8.7)	43.9 (8.5)	43.6 (9.2)	0.804
Age gr 30-<40 y, n (%)	2 (13.3)	28 (39.4)	29 (35.4)	0.165
Age gr 40-<50 y, n (%)	9 (60)	19 (26.8)	28 (34.1)	
Age gr 50-<60 y, n (%)	4 (26.7)	24 (33.8)	25 (30.5)	
BMI(Kg/m^2), mean (SD)	25.6 (4.2)	23.5 (3.4)	23.4 (4.1)	0.102
Having any underlying disease, n (%)	11 (73.3)	41 (57.8)	48 (58.5)	0.552
Duration from second dose vaccine(days), mean (SD)	91.2 (25.9)	98.9 (22.9)	117.3 (22.7)	<0.001
WBC(cells/mm^3), median (IQR) min-max	7 (2.7) 5.1-9.4	6.3 (1.8) 4.3-9.9	6.6 (1.9) 3.7-14.1	0.202
Lymphocyte(cells/mm^3), mean(SD)	2.5 (0.5)	2.2 (0.5)	2.2 (0.6)	0.124

Additionally, subgroup analysis bases on anti SARS-CoV-2 spike RBD antibodies level after receiving the third dose vaccine for one month, with a cut-off of was equal to or more than 132 U/mL. There were 15 participants in the AZ group whose anti-SARS-CoV-2 spike RBD antibodies level was less than 132 U/mL. Notwithstanding, anti SARS- CoV-2 spike RBD antibodies level of 71 and 82 participants were more than 132 U/mL in AZ and PZ group respectively. As before, the duration before receiving the third dose vaccine was significantly different among AZ group which anti SARS-CoV-2 spike RBD antibodies level less than 132 U/mL, AZ group which anti SARS-CoV-2 spike RBD antibodies level equal to or more than 132 U/mL and PZ group which anti SARS-CoV-2 spike RBD antibodies level equal to or more than 15 U/mL ($p < 0.001$). (Table 3) Howbeit, sex, age, age group, BMI, having any underlying diseases, white blood cell count and lymphocyte count were not significantly associated with anti SARS-CoV-2 spike RBD antibodies response at a cut-off of level of equal to or more than 132 U/mL.

Moreover, participants in the age group 40 years to less than 50 years in the AZ group, which anti-SARS-CoV-2 spike RBD antibodies levels of less than 132 U/mL were significantly different than participants in the AZ group, which anti-SARS- CoV-2 spike RBD antibodies levels equal to or more than than 132 U/mL ($p = 0.039$). Mean BMI in AZ group which anti SARS-CoV-2 spike RBD antibodies level less than 132 U/mL was 25.6 kg/m^2, significantly higher than in AZ group which anti SARS-CoV-2 spike RBD antibodies level equal to or more than than 132 U/mL ($p = 0.036$). (Table 4)

Serious adverse events were not found in either group. Additionally, there was no incidence of SARS-CoV-2 infection within one month after the booster shot in either group.

Table. 4 Factors associated with anti SARS-CoV-2 spike RBD antibodies response at the cut-off point at 132 U/mL of the AZ group

Factors	AZ (n=86)		p-value
	< 132 U/mL (n=15)	≥ 132 U/mL (n=71)	
Sex, n (%)			0.571
Male	9 (60)	34 (47.9)	
Female	6 (40)	37 (52.1)	
Age(year), mean (SD)	45.2 (8.7)	43.9 (8.5)	0.603
Age gr 30-<40 y, n (%)	2 (13.3)	28 (39.4)	0.039
Age gr 40-<50 y, n (%)	9 (60)	19 (26.8)	
Age gr 50-<60 y, n (%)	4 (26.7)	24 (33.8)	
BMI(Kg/m^2), mean (SD)	25.6 (4.2)	23.5 (3.4)	0.036
Having any underlying disease, n (%)	11 (73.3)	41 (57.8)	0.385
Duration from second dose vaccine(days), mean (SD)	91.2 (25.9)	98.9 (22.9)	0.253

Table. 4 Factors associated with anti SARS-CoV-2 spike RBD antibodies response at the cut-off point at 132 U/mL of the AZ group (Cont.)

Factors	AZ (n=86)		p-value
	< 132 U/mL (n=15)	≥ 132 U/mL (n=71)	
WBC(cells/mm^3), mean (SD)	7.14 (1.4)	6.4 (1.3)	0.065
Lymphocyte(cells/mm^3), mean (SD)	2.5 (0.5)	2.2 (0.5)	0.056

Discussion

This prospective cohort study evaluated anti-SARS-CoV-2 spike RBD antibody level of both ChAdOx1 nCoV-19 and BNT162b2 as the third dose vaccination in healthcare workers who had previously received two doses of Sinovac vaccine. The mean and median levels of anti-SARS-CoV-2 spike RBD antibodies in the BNT162b2 group appeared notably higher compared to those in the ChAdOx1 nCoV-19 group. In our study, baseline anti-SARS-CoV-2 spike RBD antibody level after two doses of the Sinovac vaccine was not measured. However, according to previous studies, mean anti-spike IgG level was comparable to other studies in Thailand; mean anti-spike IgG level measured 3 months after the two-dose vaccination of Sinovac was 92.9 Binding Antibody Units (BAU)/mL (median age 30 years, IQR 25-37, female 83.2%, n = 185)[8], 84.88 BAU/mL (median age 45 years, IQR 35-52, female 81.81%, n = 170, measured at four months) [12], 115 BAU/mL (median age 45.8 years, female 60.2%, n = 88, measured at two months)[15] and 94.8 BAU/mL (median age 35 years, IQR 29-44, female 84.2%, n = 180, measured at four weeks).[1] Our study investigated the immunogenicity response of either ChAdOx1 nCoV-19 or BNT162b2 as the booster shot.

There was an observational study that showed that a booster shot by BNT162b2 had higher immunogenicity for humoral immune response than a booster by Sinovac-CoronaVac in healthcare workers who have received two doses of Sinovac[11]. While one prospective cohort study showed significant improvement for both humoral and cellular immunity one month after vaccination by ChAdOx1 nCoV-19 in healthcare workers who had two shots of Sinovac[12]. Nonetheless, there was no study that compared the immune response after booster with BNT162b2 and ChAdOx1 nCoV-19 in healthcare workers.

There were many reasons that could make the antibody level higher in the BNT162b2 group. Firstly, BNT162b2 and ChAdOx1 nCoV-19 use different vaccine platforms. BNT162b2 was an mRNA-based vaccine, while ChAdOx1 nCoV-19 was a viral vector vaccine. These differing platforms trigger distinct immune responses due to variations in how they delivered the genetic material to the body's cells, which could impact the resulting antibody levels. mRNA-based vaccine induced long-lasting protective antibody (Ab) responses from activated B-cells[16] while adenovirus viral vector led to the production of new adenovirus viral proteins that generate

immunological response.[17] Secondly, previous studies had demonstrated that booster shots with different vaccine platforms could elicit stronger immune responses than homologous booster doses. This implied that heterologous boosting might enhance antibody response in individuals receiving a different booster vaccine than homologous boosting. For instance, homologous booster dose by Sinovac in healthcare workers showed lower immunogenicity for humoral immunity than heterozygous booster by BNT162b2 [(11)]. Moreover, a randomized controlled trial reported a poor immune response in three homologous doses of ChAdOx1 nCoV-19, while heterogeneous ChAdOx1 nCoV-19 as the third booster dose in participants who received two shots of BNT162b2 showed a better immune response.[18]

In the subgroup analysis of our study, even duration before receiving the third dose vaccine was significantly longer in PZ group but anti SARS-CoV-2 spike RBD antibodies level of all participants at one month equal to or more than 15 and equal to or more than 132 U/mL which the result was different in AZ group. According to the large surveillance study, the result showed the highest IgG seropositivity average at 77.4% at three weeks after the second dose of Sinovac and after that declined to 64.5% at 3 to 16 weeks following the second shot.[19] This implied that BNT162b2 induced stronger immune response than ChAdOx1 nCoV-19.

Additionally, factors associated with anti-SARS-CoV-2 spike RBD antibodies response equal to or more than 132 U/mL in the AZ group were age group and BMI. Sixty percent of participants with anti-SARS-CoV-2 spike RBD antibodies response less than 132 U/mL was in the age group 40 to less than 50 years. However, the highest proportion of participants with anti-SARS-CoV-2 spike RBD antibodies response equal to or more than 132 U/mL was in the age group 30 to less than 40 years. A systematic review and meta-analysis revealed that the immune effect of young people after being vaccinated with COVID-19 vaccines was better than that of the elderly (age equal or more than 55 years).[20] Participants with higher BMI resulted in poorer immune responses. A meta-analysis showed that obesity was significantly associated with a decreased antibody response to COVID-19 vaccines compared to people of normal weight.[21]

This study was the first prospective cohort study on healthy healthcare workers who had been fully vaccinated with Sinovac and received the third dose of the vaccine, either BNT162b2 or ChAdOx1 nCoV-19. There was also no missing data. Additionally, participants who attended this study were high-risk populations. Nevertheless, our limitations were as follows: we did not measure baseline anti-SARS-CoV-2 spike RBD antibodies, and there was no data on antibody response and incidence of infection at three months post-vaccination.

In summary, this study showed that the anti-SARS-CoV-2 spike RBD antibodies level at one month post-vaccination in the population who received BNT162b2 as the

third dose after fully vaccinated with Sinovac was higher compared to those who received ChAdOx1 nCoV-19 as the third dose. However, there was no incidence of SARS-CoV-2 infection within one month in both groups.

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References

1. Angkasekwinai N, Sewatanon J, Niyomnaitham S, Phumiamorn S, Sukapirom K, Sapsutthipas S, et al. Safety and immunogenicity of CoronaVac and ChAdOx1 against the SARS-CoV-2 circulating variants of concern (Alpha, Delta, Beta) in Thai healthcare workers. MedRxiv. medRxiv 2021.10.03.21264451. doi: https://doi.org/10.1101/2021.10.03.21264451
2. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody status and incidence of SARS- CoV-2 infection in health care workers. N Engl J Med. 2021;384(6):533-40. doi: 10.1056/NEJMoa2034545.
3. Wheatley AK, Juno JA, Wang JJ, Selva KJ, Reynaldi A, Tan HX, et al. Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19. Nat Commun. 2021;12(1):1162. doi: 10.1038/s41467-021-21444-5.
4. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature. 2021;591(7851):639-44. doi: 10.1038/s41586-021-03207-w.
5. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22. doi: 10.1016/S0140-6736(21)01429-X.
6. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181-92. doi: 10.1016/S1473-3099(20)30843-4.
7. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(6):803-12. doi: 10.1016/S1473-3099(20)30987-7.

8. Benjamanukul S, Traiyan S, Yorsaeng R, Vichaiwattana P, Sudhinaraset N, Wanlapakorn N, et al. Safety and immunogenicity of inactivated COVID-19 vaccine in health care workers. J Med Virol. 2022;94(4):1442-9. doi: 10.1002/jmv.27458.
9. Mok CKP, Cohen CA, Cheng SMS, Chen C, Kwok KO, Yiu K, et al. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. Respirology. 2022;27(4):301-10. doi: 10.1111/resp.14191.
10. Yigit M, Ozkaya-Parlakay A, Cosgun Y, Ince YE, Bulut YE, Senel E. Should a third booster dose be scheduled after two doses of CoronaVac? A single-center experience. J Med Virol. 2022;94(1):287-90. doi: 10.1002/jmv.27318.
11. Keskin AU, Bolukcu S, Ciragil P, Topkaya AE. SARS-CoV-2 specific antibody responses after third CoronaVac or BNT162b2 vaccine following two-dose CoronaVac vaccine regimen. J Med Virol. 2022;94(1):39-41. doi: 10.1002/jmv.27350.
12. Prasithsirikul W, Pongpirul K, Nopsopon T, Phutrakool P, Pongpirul W, Samuthpongtorn C, et al. Immunogenicity of ChAdOx1 nCoV-19 booster vaccination following two CoronaVac shots in healthcare workers. Vaccines (Basel). 2022;10(2):217. doi: 10.3390/vaccines10020217.
13. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-91. doi: 10.1016/S0140-6736(21)00432-3.
14. Medians and interquartile ranges. In: Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. England: A John Wiley & Sons; 2011. Available from: https://handbook-5-1.cochrane.org/chapter_7/7_7_3_5_mediansand_interquartile_ranges.htm
15. Ongkittikul S, Rompho P. SARS-CoV-2 IgG antibody response after immunization of healthcare workers with inactivated COVID-19 vaccine (CoronaVac) at Phyathai 3 hospital. The Bangkok Medical Journal. 2021;17(2):100-3. [In Thai]
16. Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol. 2010;17(7):1055-65. doi: 10.1128/CVI.00131-10.
17. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021;184(4):861-80. doi: 10.1016/j.cell.2021.01.007.
18. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021;398(10318):2258-76. doi: 10.1016/S0140-6736(21)02717-3.

19. Sauré D, O'Ryan M, Torres JP, Zuniga M, Santelices E, Basso LJ. Dynamic IgG seropositivity after rollout of CoronaVac and BNT162b2 COVID-19 vaccines in Chile: a sentinel surveillance study. Lancet Infect Dis. 2022;22(1):56-63. doi: 10.1016/S1473-3099(21)00479-5.
20. Wang J, Tong Y, Li D, Li J, Li Y. The impact of age difference on the efficacy and safety of COVID-19 vaccines: a systematic review and meta-analysis. Front Immunol. 2021;12:758294. doi: 10.3389/fimmu.2021.758294.
21. Ou X, Jiang J, Lin B, Liu Q, Lin W, Chen G, et al. Antibody responses to COVID-19 vaccination in people with obesity: A systematic review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13078. doi: 10.1111/irv.13078.