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Immunological responses and adverse reactions of the heterologous second booster dose of BNT162b2 after two-dose CoronaVac for COVID-19 vaccination in healthcare workers of Faculty of Medicine, Naresuan University



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ABSTRACT

Background: The first COVID-19 vaccination campaign in Thailand began in April 2020, with healthcare workers receiving two doses of inactivated COVID-19 vaccine (CoronaVac). However, the emergence of the delta and omicron variants raised concerns about vaccine effectiveness. The Thai Ministry of Public Health provided the first booster dose (third dose) and second booster dose (fourth dose) of the mRNA vaccine (BNT162b2) for healthcare workers. This study investigated the immunity and adverse reactions elicited by a heterologous second booster dose of BNT162b2 after a two-dose CoronaVac vaccination for COVID-19 in healthcare workers of the Faculty of Medicine, Naresuan University.

Methods: IgG titres against the SARS-CoV-2-spike protein were measured four and 24 weeks after the second booster dose of BNT162b2 in the study participants. Adverse reactions were recorded during the first three days, four weeks and 24 weeks after the second booster dose of BNT162b2.

Results: IgG against the SARS-CoV-2-spike protein was positive (>10 U/ml) in 246 of 247 participants (99.6 %) at both four and 24 weeks after the second booster dose of BNT162b2. The median specific IgG titres at four and 24 weeks after the second booster dose of BNT162b2 were 299 U/ml (min: 2, max: 29,161) and 104 U/ml (min: 1, max: 17,920), respectively. The median IgG level declined significantly 24 weeks after the second booster dose of the BNT162b2 vaccine. Of the 247 participants, 179 (72.5 %) experienced adverse reactions in the first three days after the second booster dose of BNT162b2. Myalgia, fever, headache, injection site pain and fatigue were the most common adverse reactions.

Conclusion: This study demonstrated that a heterologous second booster dose of BNT162b2 after two doses of CoronaVac induced elevated IgG against the SARS-CoV-2-spike protein and caused minor adverse reactions in healthcare workers of the Faculty of Medicine, Naresuan University.

This study was registered as Thailand Clinical Trials No. TCTR20221112001.

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1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), which spread rapidly and caused a global pandemic. By October 2022,

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there were more than 620 million cumulative cases and over six million cumulative deaths worldwide, with a mortality rate of 2 % [1]. Several COVID-19 vaccines have been approved under the emergency use listing (EUL) by the World Health Organization (WHO) since June 2021, including an mRNA vaccine, viral vector vaccine and an inactivated viral vaccine.

CoronaVac is an inactivated whole-virion SARS-CoV-2 vaccine produced by Sinovac Biotechnology. In the early stages of the pandemic, CoronaVac had an efficacy of 51-83.5 % in preventing

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COVID-19, 86.3–100 % against severe COVID-19, and 87.5–100 % against hospitalisation, starting 14 days after receiving the second dose, with minor adverse reactions such as injection site pain, headache, fatigue and myalgia [2–4]. BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine encoding a prefusion-stabilised, membrane-anchored, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). BNT162b2 had an efficacy of 95 % in preventing COVID-19 7 days after the second dose, with minor adverse reactions such as pain at the injection site, fatigue and headache [5].

In Thailand, there were more than 250,000 cumulative COVID-19 cases and over 2,000 cumulative deaths as of October 2022 [6]. The first COVID-19 vaccination campaign in Thailand started in April 2020. The Thai Ministry of Public Health provided COVID-19 vaccinations for healthcare workers with an inactivated COVID-19 vaccine (CoronaVac) at two doses (the first and second doses were four weeks apart). In August 2021, the B.1.617.2 (delta) variant spread rapidly and resulted in increasing numbers of breakthrough COVID-19 infections worldwide, even in fully vaccinated persons [7–9]. The emergence of the delta variant and the waning immunity of vaccines over time caused many countries to implement the use of the booster vaccine [10–12]. At the time of the emergence of the delta strain, the Thai Ministry of Public Health provided the first booster dose (third dose) of heterologous mRNA vaccine (BNT162b2) to healthcare workers fully vaccinated with CoronaVac. However, the delta wave was rapidly followed by the B.1.1.529 (omicron) strain in December 2021. The Thai Ministry of Public Health then provided a second booster dose (fourth dose) of the mRNA vaccine (BNT162b2) to healthcare workers in January and February 2022, due to concerns over the waning immunity provided by vaccines and the evasion of vaccine protection by the omicron variant. Few studies have shown a consistently lower vaccine effectiveness against the omicron variant than against the delta variant [13–15]. There have been a few studies on the heterologous vaccination with CoronaVac plus the first booster dose (third dose) of the BNT162b2 vaccine [16-21].

There is limited knowledge available on the benefits and adverse reactions of heterogeneous vaccination with CoronaVac plus a second booster dose (fourth dose) of BNT162b2. Therefore, the present study aimed to assess the immunological responses and adverse reactions elicited by a second heterologous booster dose of BNT162b2 after a two-dose CoronaVac vaccination for COVID-19 in Thai healthcare workers.

2. Methods

2.1. Study design and participants

We performed a longitudinal prospective descriptive study by recruiting 340 volunteers among healthcare workers from the Faculty of Medicine, Naresuan University, Thailand, who received a heterologous second booster dose of BNT162b2 for COVID-19 vaccination after a two-dose regimen of CoronaVac. The study participants received two doses of CoronaVac between April 2021 and July 2021 (the first and second doses were four weeks apart), followed by the first booster dose of BNT162b2 three months after the second dose of CoronaVac, i.e. between August 2021 and September 2021. These participants received a second booster dose of BNT162b2 five to six months after the first booster dose of BNT162b2, between January 2022 and February 2022. All of the vaccine doses were provided by the Thai Ministry of Public Health.

Eligible participants were 20 years of age and older and had never had prior clinical symptoms of SARS-CoV-2 infection. To ensure rapid enrolment in the study, we did not screen participants for laboratory evidence of SARS-CoV-2 infection, but identified a history of COVID-19 infection and other severe infections during the screening visit. Exclusion criteria were immunocompromised individuals, those receiving immunosuppressive drugs, those receiving blood products, pregnant women, those with other severe infections, and those that had COVID-19 infection within 14 days before blood sampling. Clinical data, including the age, sex, vital signs and adverse reactions, were collected during all visits. We collected data on adverse reactions that occurred during the first three days, four weeks and 24 weeks after the second booster dose of BNT162b2. Blood samples were collected at four and 24 weeks after the second booster dose of BNT162b2. The study protocol was approved by the Naresuan Institutional Review Board (COA No. 396/2021) and written informed consent was obtained from all participants.

2.2. Antibody measurement

Six millilitres of venous blood were collected into an EDTA tube. The blood samples were centrifuged at 1500 rpm for 10 min to obtain serum samples, which were then stored at -20 °C until antibody analysis. Specific antibody (IgG) titres against the SARS-CoV-2-spike protein were measured using a fluoroenzyme immunoassay (EliA SARS-CoV-2-Sp1 IgG, Thermo Fisher Scientific, Waltham, MA, USA) (negative: < 7 U/ml, equivocal range 7–10 U/ml, positive: > 10 U/ml). A titre > 10 U/ml was considered positive for an antibody against the SARS-CoV-2-spike protein. According to the Department of Medical Sciences of the Thai Ministry of Public Health, this test has a diagnostic sensitivity of 98 % and specificity of 100 % (analysis no. CV93). In addition, previous studies demonstrated that this test has a diagnostic sensitivity and specificity of 96.9–100 % and 99.4–100 %, respectively [22–25].

2.3. Statistical analysis

Continuous data on immunological responses were analysed using the Shapiro–Wilk W test. When comparing the groups, the Mann–Whitney *U* test was used to analyse the median (min– max) or median (Q1-Q3). Categorical data and adverse reactions are presented as frequencies and percentages. Statistical significance was set at P < 0.05. All statistical analyses were performed using the STATA software (version 12.0; StataCorp, College Station, TX, USA).

3. Results

3.1. Participants and adverse reactions

A total of 340 participants were enrolled in this study. Only 247 participants were included in the analysis, due to the withdrawal of 93 participants from the study during the 24-week follow-up period (Fig. 1). Eight participants were excluded as they had confirmed COVID-19 infection within 14 days prior to blood sampling. Hence, the cohort of eligible participants included 205 female (83 %) and 42 male (17 %) participants. The median age was 35.91 ± 7 . 44 years (range, 23–59 years). Of the 247 participants, 179 (72.5 %) experienced adverse reactions in the first three days after the second booster dose of BNT162b2. Myalgia, fever, headache, injection site pain and fatigue were the most common adverse reactions. No serious adverse reactions or need for hospitalisation were reported. Participants' demographic characteristics are presented in Table 1. Adverse reactions are presented in Table 2. The adverse reactions were further stratified by sex and age, as presented in Table 3. Participants in the 30-39 year-old age group had the most adverse reactions, and those aged 50 years or older had fewer adverse reac-

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Fig. 1. Composition of study participants, healthcare workers from the Faculty of Medicine, Naresuan University.

Table 1

Participants' demographic details at the time of receiving the second booster dose of BNT162b2.

Parameters	Overall	Female	Male
Gender, n (%)	247	205 (82.996 %)	42 (17.004 %)
Age, Mean ± SD.	35.91 ± 7.44	35.65 ± 7.09	37.21 ± 8.90
(Min: Max)	(23: 59)	(23: 59)	(23: 58)

Table 2

Participants' adverse reactions after receiving the second booster dose of BNT162b2.

Adverse reactions	At First 3 days n (%)	At 4 weeks n (%)	At 24 weeks n (%)
Myalgia	153 (62.2)	4 (1.6)	0 (0.0)
Fever	83 (33.6)	1 (0.4)	0 (0.0)
Headache	62 (25.1)	5 (2.0)	0 (0.0)
Pain at injection site	49 (19.8)	1 (0.4)	0 (0.0)
Fatigue	47 (19.0)	0 (0.0)	0 (0.0)
Diarrhea	9 (3.6)	0 (0.0)	0 (0.0)
Rash	6 (2.4)	0 (0.0)	0 (0.0)
Nausea	5 (2.0)	1 (0.4)	0 (0.0)
Vomiting	2 (0.8)	0 (0.0)	0 (0.0)
Others	2 (0.8)	1 (0.4)	0 (0.0)
Serious adverse reactions	0 (0.0)	0 (0.0)	0 (0.0)
Need for hospitalization	0 (0.0)	0 (0.0)	0 (0.0)

tions, in the first three days after the second booster dose of BNT162b2.

3.2. Immunological responses

IgG against the SARS-CoV-2-spike protein was positive (>10 U/ ml) in 246 of 247 participants (99.6 %) at both four and 24 weeks after the second booster dose of BNT162b2. The median IgG against the SARS-CoV-2-spike protein level at four weeks after the second booster dose of BNT162b2 was 299 U/ml (min:2, max:29,161). The median IgG against the SARS-CoV-2-spike protein level at 24 weeks

after the second booster dose of BNT162b2 was 104 U/ml (min: 1, max: 17,920). The median IgG level declined significantly 24 weeks after the second booster dose of the BNT162b2 vaccine (Fig. 2).

IgG titres against the SARS-CoV-2-spike protein were further stratified by sex, age group and history of confirmed COVID-19 infection (Figs. 3–5, Table 4). In females, IgG titres significantly decreased 24 weeks after the second booster dose of BNT162b2. For all age groups, the IgG titres also decreased significantly, except for those aged 50 years or older and among participants with confirmed COVID-19 infection during the 24-week follow-up period. Participants aged 50 years or older produced the lowest antibody titres compared to the other age groups within the 23–59 age range.

At 24 weeks after the second booster dose of BNT162b2, 93 of the 247 participants (37.7 %) had a confirmed COVID-19 infection. COVID-19 infections were confirmed by RT-PCR and rapid antigen test kits in seven (7.5 %) and 86 (92.5 %) of the 93 participants, respectively. Thus, this regimen of two heterologous doses of CoronaVac plus the second booster dose of BNT162b2 had an efficacy of 62.3 % (95 %CI, 56.0–68.4 %) in preventing COVID-19 infection in this study. In total, 91 of the 93 participants (97.8 %) experienced mild symptoms. There was no instances of severe disease, hospitalization, admission to ICU or death.

4. Discussion

Our study described the immune response and adverse reactions of heterologous COVID-19 vaccination with two doses of CoronaVac plus a second booster dose (fourth dose) of BNT162b2 in healthcare workers of the Faculty of Medicine, Naresuan University. We found that this aforementioned regimen induced elevated IgG against the SARS-CoV-2-spike protein in 99.6 % of the study participants. Our present study supported previous studies' findings that the IgG titres decreased significantly after 3-4 months [13.14.21]. The insignificant decline in IgG titres in males might be due to the small number of male participants. Participants aged 50 years or older tended to produce the lowest antibody titres compared to the other age groups. However, since there were only nine participants falling into the age group of 50 years old or older, a comparison with the other age groups was not done. This finding suggests that the immune response decreased substantially within a few months.

During the 24-week follow-up period, 93 participants (37.7 %) were confirmed as having COVID-19. In this group, the IgG titre at 24 weeks was comparable to that at four weeks after the second dose of BNT162b2. The relatively constant IgG titre may be associated with natural COVID-19 infection-induced immunity.

Our study suggests that the heterologous two doses of Corona-Vac plus the second booster dose of BNT162b2 had an efficacy of 62.3 % (95 %CI, 56.0–68.4) in preventing COVID-19 infection, and was highly effective in preventing hospitalisations, admissions to ICU and deaths. Our results corroborate other studies' findings that the vaccine effectiveness against the omicron variant is consistently lower than that against the delta variant [13–15]. In a previous study in Hong Kong, the vaccine effectiveness was 50.9 % in participants that received two doses of CoronaVac with a BNT162b2 booster [15].

Adverse reactions were most likely to occur within three days of the second booster dose of BNT162b2. Myalgia, fever, headache, injection site pain and fatigue were the most common adverse reactions. No serious adverse reactions or the need for hospitalisation were reported. In our study, participants of the 30–39 year-old age group often had adverse reactions, and participants aged 50 years or older had fewer adverse reactions. Our results on adverse reactions corroborates previous studies of the heterolo-

Table 3

Partici	oants'	adverse	reactions	after	receiving	the second	booster	dose of	BNT162b2	stratified	bv sex	(and	age	groui	DS.
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Parameters	n	At First 3 days n (%)	At 4 weeks n (%)	At 24 weeks n (%)
Overall	247	179 (72.5)	9 (3.6)	0 (0.0)
Sex				
Male	42	28 (11.3)	3 (1.2)	0 (0.0)
Female	205	151 (61.2)	6 (2.4)	0 (0.0)
p-value		0.355	0.184	_ `
Âge				
<30	51	41 (16.6)	1 (0.4)	0 (0.0)
30-39	118	92 (37.3)	2 (0.8)	0 (0.0)
40-49	69	44 (17.8)	4 (1.6)	0 (0.0)
≥50	9	2 (0.8)	2 (0.8)	0 (0.0)
p-value		0.001*	0.025*	_

*The p-value < 0.05 were considered significant.



Fig. 2. Comparison of the IgG against the SARS-CoV-2-spike protein at four and 24 weeks after the second booster dose of BNT162b2 in the cohort of 247 participants. The median and p-value were tested using the Mann-Whitney U test (STATA 12.0 software).



Fig. 3. Comparison of the IgG against the SARS-CoV-2-spike protein at four and 24 weeks after the second booster dose of BNT162b2, stratified by sex (male and female). The median and p-value were tested using the Mann-Whitney U test (STATA 12.0 software).

gous CoronaVac plus BNT162b2 booster vaccination, which found that the adverse reactions mostly occurred within the first week, and were mild to moderate and self-limiting [16,19–21].



Fig. 4. Comparison of the IgG against the SARS-CoV-2-spike protein at four and 24 weeks after the second booster dose of BNT162b2, stratified by age groups (<30 years old, 30–39 years old, 40–49 years old, \geq 50 years old). The median and p-value were tested using the Mann-Whitney *U* test (STATA 12.0 software).



Fig. 5. Comparison of the IgG against the SARS-CoV-2-spike protein at four and 24 weeks after the second booster dose of BNT162b2, stratified by history of confirmed COVID-19 (no; no history of confirmed COVID-19, yes; had history of confirmed COVID-19). The median and p-value were tested using the Mann-Whitney *U* test (STATA 12.0 software).

There have been few studies on the homologous second booster doses (fourth dose) of mRNA vaccines. These studies suggest that the homologous second booster dose (fourth dose) of mRNA vaccines increases immunogenicity and vaccine effectiveness compared

Table 4

The IgG against the SARS-CoV-2-spike protein at four and 24 weeks after the second booster dose of BNT162b2 vaccine, stratified by sex, age groups and history of confirmed COVID-19 infection during the 24-week follow-up period.

Parameter	n	EliA SARS-CoV-2Sp1 lgG (U/ml) at 4 weeks after the second doses of BNT162b2 vaccine					EliA SARS-CoV-2Sp1 lgG (U/ml) at 24 weeks after the second doses of BNT162b2 vaccine				
		Median	Q1	Q3	min	max	Median	Q1	Q3	min	max
Overall *	247	299	181	480	2	29,161	104	57	267	1	17,920
Sex											
Male	42	317.5	208	434	2	4,386	115	59	414	1	8,722
Female*	205	287	179	487	49	29,161	100	57	246	10	17,920
Age											
<30 *	51	269	163	513	51	25,605	104	56	254	28	1,318
30-39 *	118	325	196	496	80	29,161	103	59	246	18	17,920
40-49 *	69	277	179	374	2	26,840	89	50	303	1	17,127
\geq 50	9	234	182	460	151	27,677	274	120	795	55	2,792
Had COVID-19 infection in the period of 24 weeks follow-up											
Yes	93	291	162	432	51	25,605	267	155	484	49	17,920
No*	154	302.5	188	509	2	29,161	65	45	108	1	16,856

*The Mann-Whitney *U* test median (Q1-Q3) significant < 0.05.

to those who received three vaccine doses [26-34]. The rationale for the heterologous COVID-19 booster vaccines is considered where there are supply challenges for the same vaccine and to reducing reactogenicity, increasing immunogenicity and enhancing vaccine effectiveness [35]. The studies on the heterologous vaccination of CoronaVac plus a first booster dose of BNT162b2 suggest that the heterologous vaccination may provide superior immunogenicity to homologous vaccination [16-21]. However, there is limited data available on heterologous second booster doses of COVID-19 vaccine [36]. We only found one previous study of the vaccine effectiveness of the heterologous second booster doses with BNT162b2 in adults receiving two doses of CoronaVac in Thailand [37]. This study suggests that the fourth vaccination dose has a vaccine effectiveness of 75 % (95 % Cl, 71-80 %) during the omicron-predominant period, and a very high probability of preventing death and severe COVID-19. Our results corroborate the findings of this study, i.e. that the heterologous second booster doses prevented severe disease, hospitalisation, admission to ICU and death, with minor adverse reactions.

Our study has several limitations. Firstly, this was not a randomised controlled study. This study was not designed to compare different booster regimens. Secondly, the sample size was relatively small and the demographic characteristics were not representative of the Thai population. Thirdly, the study participants were not tested for SARS-CoV-2 at the start of the study. Therefore, we could not rule out asymptomatic COVID-19 infections that may have affected the immunological response and the vaccine efficacy in this study. Fourthly, we did not measure neutralising antibody titres, which are highly predictive parameters of immune protection against SARS-CoV-2 infection [38]. Lastly, the follow-up period may not have been sufficient to identify long-term adverse reactions. Large-scale, multicentre, prospective and longitudinal studies are therefore needed to determine the immunological responses and adverse reactions to heterologous second booster doses of COVID-19 vaccines.

5. Conclusions

This study demonstrated that a heterologous second booster dose of BNT162b2 after two doses of CoronaVac induces elevated IgG against the SARS-CoV-2-spike protein and causes minor adverse reactions in health care workers of Faculty of Medicine, Naresuan university.

Authors contributions

Supawadee Makanut, Apirath Wangteeraprasert, Wittawat Jitpewngam and Sutatip Pongcharoen designed the study. Supawadee Makanut and Sutatip Pongcharoen wrote the manuscript. Wangteeraprasert, Jitpewngam and Ngoenkam discussed the results.

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Institutional review board statement

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of the HKSH Medical Group (REC-2021-14).

Informed consent statement

Written informed consent was obtained from all of the patients to publish this paper.

Data availability statement

The data used to support the findings of this study are included in the article.

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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References

- World Health Organization. Coronavirus disease (COVID-19) dashboard. https://covid19.who.int. accessed on June 30th, 2022.
- [2] Palacios R, Patiño EG, de Oliveira Piorelli R, et al. Double-blind, randomized, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of treating healthcare professionals with the adsorbed COVID-19 (inactivated) vaccine manufactured by Sinovac - PROFISCOV: A structured summary of a study protocol for a randomised controlled trial. Trials 2020;21(1):853. https://doi.org/10.1186/s13063-020-04775-4. Published 2020 Oct 15.
- [3] Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a doubleblind, randomised, placebo-controlled, phase 3 trial in Turkey [published correction appears in Lancet. 2022 Jan 29;399(10323):436]. Lancet. 2021;398 (10296):213-22. http://doi.org/10.1016/S0140-6736(21)01429-X
- [4] Jara A, Undurraga EA, González C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385(10):875–84. <u>https://doi.org/ 10.1056/NEIMoa2107715</u>.
- [5] Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15. <u>https://doi.org/ 10.1056/NEIMoa2034577</u>.
- [6] World Health Organization. Coronavirus disease (COVID-19) dashboard. https://covid19.who.int/region/searo/country/th. Accessed on October 26th, 2022.
- [7] Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(31):1059-1062. Published 2021 Aug 6. http://doi. org/10.15585/mmwr.mm7031e2.
- [8] Rosenberg ES, Dorabawila V, Easton D, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med 2022;386(2):116–27. <u>https://doi.org/10.1056/ NEJMoa2116063</u>.
- [9] Pilishvili T, Gierke R, Fleming-Dutra KE, et al. Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel. N Engl J Med 2021;385(25):e90. <u>https://doi.org/10.1056/NEJMoa2106599</u>.
- [10] Naaber P, Tserel L, Kangro K, et al. Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. Lancet Reg Health Eur 2021;10:. <u>https://doi.org/10.1016/j. lanepe.2021.100208</u>100208.
- [11] Pegu A, O'Connell SE, Schmidt SD, et al. Durability of mRNA-1273 vaccineinduced antibodies against SARS-CoV-2 variants. Science 2021;373 (6561):1372–7. <u>https://doi.org/10.1126/science.abj4176</u>.
- [12] Goldberg Y, Mandel M, Bar-On YM, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. N Engl J Med 2021;385(24):e85.
- [13] Accorsi EK, Britton A, Shang N, et al. Effectiveness of homologous and heterologous covid-19 boosters against omicron. N Engl J Med 2022;386 (25):2433–5. <u>https://doi.org/10.1056/NEIMc2203165</u>.
- [14] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386(16):1532-46. <u>https:// doi.org/10.1056/NEIMoa2119451</u>.
- [15] Tsang NNY, So HC, Cowling BJ, Leung GM, Ip DKM. Effectiveness of BNT162b2 and CoronaVac COVID-19 vaccination against asymptomatic and symptomatic infection of SARS-CoV-2 omicron BA.2 in Hong Kong: a prospective cohort study. Lancet Infect Dis 2023;23(4):421–34. <u>https://doi.org/10.1016/S1473-3099(22)00732-0</u>.
- [16] Moghnieh R, Mekdashi R, El-Hassan S, et al. Immunogenicity and reactogenicity of BNT162b2 booster in BBIBP-CorV-vaccinated individuals compared with homologous BNT162b2 vaccination: Results of a pilot prospective cohort study from Lebanon. Vaccine 2021;39(46):6713–9. https://doi.org/10.1016/j.vaccine.2021.10.007.
- [17] Pérez-Then E, Lucas C, Monteiro VS, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. Nat Med 2022;28(3):481–5. <u>https://doi.org/10.1038/s41591-022-01705-6</u>.
- [18] 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. <u>https://doi.org/ 10.1002/imv.27350</u>.
- [19] Kanokudom S, Assawakosri S, Suntronwong N, et al. Safety and Immunogenicity of the Third Booster Dose with Inactivated, Viral Vector, and mRNA COVID-19 Vaccines in Fully Immunized Healthy Adults with Inactivated Vaccines (Basel) 2022;10(1):86. <u>https://doi.org/10.3390/</u> vaccines10010086. Published 2022 Jan 6.
- [20] Costa Clemens SA, Weckx L, Clemens R, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority,

single blind, randomised study. Lancet 2022;399(10324):521-9. <u>https://doi.org/10.1016/S0140-6736(22)00094-0</u>.

- [21] Lai KT, Lai Wan Loong EY, Fung TL, et al. Safety and immunogenicity of a booster vaccination by CoronaVac or BNT162b2 in previously two-dose inactivated virus vaccinated individuals with negative neutralizing antibody. Vaccines (Basel) 2022;10(4):556. <u>https://doi.org/10.3390/vaccines10040556</u>. Published 2022 Apr 3.
- [22] Wiwe EF, Carlsson ER, Rasmussen CL, et al. Long-term comparison of 7 SARS-CoV-2 antibody assays in the North Zealand covid-19 cohort. J Appl Lab Med 2022;7(3):711–26. <u>https://doi.org/10.1093/jalm/jfab173</u>.
- [23] Schulte-Pelkum J, Comment on Favresse, et al. Persistence of anti-SARS-CoV-2 antibodies depends on the analytical kit: A report for up to 10 months after infection. Microorganisms 2021, 9, 556. Microorganisms. 2021;9(8):1786. https://doi.org/10.3390/microorganisms9081786. Published 2021 Aug.
- [24] Solastie A, Virta C, Haveri A, et al. A highly sensitive and specific SARS-CoV-2 spike- and nucleoprotein-based fluorescent multiplex immunoassay (FMIA) to measure IgG, IgA, and IgM class antibodies. Microbiol Spectr 2021;9(3): e0113121.
- [25] Lin YC, Lee YL, Cheng CY, et al. Multicenter evaluation of four immunoassays for the performance of early diagnosis of COVID-19 and assessment of antibody responses of patients with pneumonia in Taiwan. J Microbiol Immunol Infect 2021;54(5):816–29. <u>https://doi.org/10.1016/i. imii.2021.02.003</u>.
- [26] Bar-On YM, Goldberg Y, Mandel M, et al. Protection by a fourth dose of BNT162b2 against Omicron in Israel. N Engl J Med 2022;386(18):1712–20. https://doi.org/10.1056/NEIMoa2201570.
- [27] Magen O, Waxman JG, Makov-Assif M, et al. Fourth dose of BNT162b2 mRNA covid-19 vaccine in a nationwide setting. N Engl J Med 2022;386(17):1603–14. https://doi.org/10.1056/NEJMoa2201688.
- [28] Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T. Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study. BMJ. 2022;377:. <u>https://doi.org/10.1136/bmj-2022-071113</u>. Published 2022 May 24e071113.
- [29] Arbel R, Sergienko R, Friger M, et al. Effectiveness of a second BNT162b2 booster vaccine against hospitalization and death from COVID-19 in adults aged over 60 years. Nat Med 2022;28(7):1486-90. <u>https://doi.org/10.1038/ s41591-022-01832-0</u>.
- [30] Regev-Yochay G, Gonen T, Gilboa M, et al. Efficacy of a fourth dose of covid-19 mRNA vaccine against omicron. N Engl J Med 2022;386(14):1377-80. <u>https:// doi.org/10.1056/NEIMc2202542</u>.
- [31] Muhsen K, Maimon N, Mizrahi AY, et al. Association of receipt of the fourth BNT162b2 dose with omicron infection and COVID-19 hospitalizations among residents of long-term care facilities. JAMA Intern Med 2022;182(8):859–67. https://doi.org/10.1001/jamainternmed.2022.2658.
- [32] Cohen MJ, Oster Y, Moses AE, Spitzer A, Benenson S. Israeli-Hospitals 4th Vaccine Working Group. Association of Receiving a Fourth Dose of the BNT162b Vaccine With SARS-CoV-2 Infection Among Health Care Workers in Israel. JAMA Netw Open. 2022;5(8):. <u>https://doi.org/10.1001/jamanetworkopen.2022.24657</u>.
 [33] Grewal R, Kitchen SA, Nguyen L, et al. Effectiveness of a fourth dose of covid-19
- [33] Grewal R, Kitchen SA, Nguyen L, et al. Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: test negative design study. BMJ. 2022;378:. <u>https://doi.org/ 10.1136/bmj-2022-071502</u>. Published 2022 Jul 6e071502.
- [34] Link-Gelles R, Levy ME, Gaglani M, et al. Effectiveness of 2, 3, and 4 COVID-19 mRNA vaccine doses among immunocompetent adults during periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 sublineages predominated -VISION network, 10 States, December 2021-June 2022. MMWR Morb Mortal Wkly Rep. 2022;71(29):931-9. <u>https://doi.org/10.15585/mmwr.mm7129e1</u>. Published 2022 Jul 22. . http://doi.org/.
- [35] Interim recommendations for heterologous COVID-19 vaccination schedules. Geneva: World Health Organization; 2021. https://www.who.int/publications/ i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-heterologousschedules, accessed 6 August 2022.
- [36] Good practice statement on the use of second booster doses for COVID-19 vaccines. World Health Organization; 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-good-practice-statement-second-booster, accessed on 18 August 2022.
 [37] Intawong K, Chariyalertsak S, Chalom K, et al. Effectiveness of heterologous
- [37] Intawong K, Chariyalertsak S, Chalom K, et al. Effectiveness of heterologous third and fourth dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand: a test-negative, casecontrol study. Lancet Reg Health Southeast Asia 2023;10:. <u>https://doi.org/ 10.1016/j.lansea.2022.100121</u>100121.
- [38] Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205–11. <u>https://doi.org/10.1038/s41591-021-01377-8</u>.