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Reactogenicity and immunogenicity of the intradermal administration of BNT162b2 mRNA vaccine in healthy adults who were primed with an inactivated SARS-CoV-2 vaccine

Yutthapong Temtanakitpaisan [a,b], Suchaorn Saengnipanthkul [c,*], Nataporn Sarakosol [d], Sasinapa Maskasame [e], Siwawoot Mongkon [e], Benjaporn Buranrat [b], Sutthiwan Thammawat [b], Samadhi Patamatamkul [b], Pattaranit Nernsai [f]

[a] Division of Cardiology, Bangkok Hospital Khon Kaen, Khon Kaen, Thailand
[b] Faculty of Medicine, Mahasarakham University, Mahasarakham, Thailand
[c] Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[d] Ancillary Support Division, Bangkok Hospital Khon Kaen, Khon Kaen, Thailand
[e] Pharmacy Department, Bangkok Hospital Khon Kaen, Khon Kaen, Thailand
[f] Division of Infectious Diseases, Department of Internal Medicine, Khon Kaen Hospital, Thailand

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ABSTRACT

Because of the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), safe and effective vaccines are urgently required. The shortage of effective vaccines is a major challenge in many developing countries. We studied intradermal (ID) fractional dose BNT162b2 mRNA (Comirnaty®, Pfizer-BioNTech) as a booster dose in healthy adults who were previously immunized with an inactivated SARS-CoV-2 vaccine. This is a retrospective cohort study that included healthy adults who were immunized with two doses of inactivated SARS-CoV-2 vaccine and received a booster dose with ID fractional dose or intramuscular (IM) full-dose BNT162b2 mRNA between August 1 to August 15, 2021. The primary endpoint was safety that included local and systemic adverse reactions. The secondary endpoints were levels of SARS-CoV-2 spike protein receptor-binding domain IgG antibody (anti-S-RBD IgG) and neutralizing antibody activity against the Delta variant (B.1.617.2) using surrogate viral neutralization test (sVNT) 3 weeks after the booster dose. A total of 43 healthy adults (median age of 31 years) were included in the study; among them, 23 participants received ID fractional dose (6 μg) BNT162b2 mRNA, and 20 participants received IM full-dose (30 μg) BNT162b2 mRNA. No serious adverse reactions were observed. Local adverse reactions occurred more frequently in the ID group. No differences were observed in the baseline level of anti-S-RBD IgG (289 vs 286 AU/mL, $p > 0.9$, in the ID and IM groups, respectively). After booster, anti-S-RBD IgG titer increased to 13294 (9255–19573) AU/mL in the ID group and 23456 (16943–38539) AU/mL in the IM group. All participants in the IM group and 95.6 % of participants in the ID group had seroconversion evaluated by sVNT (≥68 % inhibition to the Delta variant). ID administration of BNT162b2 mRNA was safe and well-tolerated and generated a robust immune response. Therefore, ID delivery of the BNT162b2 mRNA vaccine has the potential for a dose-sparing strategy.

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 554 million with cumulative death>6.3 million since December 2019 [1]. Several viral mutations and genetic variants of SARS-CoV-2 have emerged during the pandemic. These variants have different receptor-binding domains that result in decreased neutralization by antibodies elicited by a previous infection or vaccine. The increase in viral transmissibility and disease severity is another concern of the variants [2,3]. According to the epidemiological update from the World Health Organization on July 13, 2022, 5 variants of concern (VOCs) have been identified: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [4]. Despite remarkable vaccine development and global efforts to distribute vaccines world-

* Corresponding author at: Division of Nutrition, Department of Pediatrics, Faculty of Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. 123 Mittraphap Road, Muang, Khon Kaen 40002, Thailand.
E-mail address: suchsa@kku.ac.th (S. Saengnipanthkul).

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wide, the emergence of new SARS-CoV-2 variants has raised a concern about reduced vaccine effectiveness [5].

CoronaVac® (Sinovac) is an inactivated whole-virion SARS-CoV-2 vaccine used in Thailand's mass vaccination program. Results of a phase 3 clinical trial of CoronaVac in Turkey showed 83.5 % efficacy in preventing symptomatic coronavirus disease of 2019 (COVID-19) infection with a reasonable safety profile [6]. A large national cohort in Chile reported that CoronaVac provided 65.9 % vaccine effectiveness for preventing symptomatic COVID-19, 87.5 % for preventing hospital admission, and 86.3 % for preventing mortality [7]. Published reports so far suggest that antibody responses to the COVID-19 vaccine and vaccine efficacy declined weeks to months after vaccination [8–10]. Moreover, Vacharathit et al. demonstrated that CoronaVac provided lower neutralizing activity than natural infection [11]. Thus, a heterologous booster dose was contemplated to enhance immunity and potentially induce a broader immune response to VOCs.

In Thailand, B1.617.2 (Delta) variant was the major variant in the second and third quarters of 2021 [12]. The Delta variant is notorious for increased transmissibility and reduced vaccine efficacy [11,13]. Therefore, the booster dose was considered for healthcare workers (HCWs). The mRNA vaccines provided high efficacy (95 % from the BNT162b2 mRNA vaccine [14] and 94.1 % from the mRNA-1273 vaccine [15]) and were well-tolerated. There are data to support the heterologous vaccination using the mRNA vaccine as a booster dose. Borobia et al. reported that the administration of BNT162b2 as a boosting dose in individuals who were primed with ChAdOx1-S provided a robust immune response [16]. Normark et al. demonstrated that heterologous boost with mRNA-1273 in a prime dose of ChAdOx1 provided superior protection against the B.1.351 variant compared to homologous ChAdOx1-S/ChAdOx1-S vaccination [17]. The authors believed that the mRNA-1273 vaccine stimulated the SARS-CoV-2-specific B-cell memory that was preemptively produced by the ChAdOx1-S vaccine. Regarding boosters with mRNA vaccine, Bar-On et al. showed that administration of a booster (third) dose of BNT162b2 mRNA vaccine significantly reduced the rates of COVID-19 infection and severe cases [18].

As vaccine shortage was a major challenge in Thailand, a booster dose with mRNA vaccine may not be available for every HCW. Recent data showed that intradermal (ID) administration of a fractional dose of mRNA-1273 vaccine provided a robust antibody response with reasonable toleration and safety [19]. Therefore, ID delivery could be considered a vaccine dose-sparing strategy. At our institution (Bangkok Hospital Khon Kaen, Khon Kaen, Thailand), BNT162b2 mRNA (Comirnaty®, Pfizer-BioNTech) was distributed by the Thai Ministry of Public Health as a booster dose for frontline HCWs. The vaccine is a multidose vial and is typically diluted before use. One vial contains five doses of 30 μg of BNT162b2 mRNA. If there is a residual volume in vials of BNT162b2 mRNA, it was given intradermally to volunteers who worked in the hospital but were not considered frontline HCWs. To assess the safety of ID administration of a fractional dose of BNT162b2 mRNA vaccine, local and systemic adverse reactions were assessed 30 min after injection and on days 1, 2, 3, 7, 14, and 21. All adverse reactions were recorded in a vaccine adverse event reporting form (VAERF). Immunogenicity was assessed by evaluating the titers of SARS-CoV-2 spike protein receptor-binding domain IgG antibody (anti-S-RBD IgG) and neutralizing antibody (NAb) activity against the Delta variant (B.1.617.2) before and after the booster. Hereby, we collected data regarding the safety and immunogenicity of the ID administration of BNT162b2 mRNA vaccine in healthy adults who had received two doses of inactivated SARS-CoV-2 vaccine.

Material and methods

This is a retrospective cohort study of all vaccinated individuals who received either ID fractional dose (6 μg) or intramuscular (IM) full-dose (30 μg) BNT162b2 mRNA (lot number 30125BA) as a booster between August 1 to August 15, 2021. Inclusion criteria included healthy adults aged 18–59 years who were previously immunized with two doses of inactivated SARS-CoV-2 vaccine and had results of anti-S-RBD IgG before and 3 weeks after receiving a booster. Demographic data, including age, sex, body weight, height, and date of first, second, and booster (third) doses, were obtained from the VAERF. The primary endpoint was safety that included local and systemic adverse reactions. The secondary endpoints were levels of anti-S-RBD IgG and NAb activity against the Delta variant before and 3 weeks after the booster dose.

Immunogenicity

Serum samples were collected within 1 week before and 3 weeks after the booster dose. All sera were tested for the presence of anti-S-RBD IgG using quantitative SARS-CoV-2 IgG QN chemiluminescent microparticle immunoassay on ARCHITECT SARS-CoV-2 IgG II Quant (Abbott Laboratories). The cutoff for seropositivity was 50 AU/mL. The seroconversion rate was defined as anti-RBD IgG titers $\geq$ 840 AU/mL, which was the definition of high-titer COVID-19 convalescent plasma suggested by the United States Federal Food and Drug Administration (US-FDA) [20].

Specific NAb titers to the Delta variant were measured using a surrogate virus neutralization test (sVNT, GenScript), which was approved by the US-FDA for Emergency Use Authorization. In brief, negative control, positive control, or sample was mixed with horseradish peroxidase receptor-binding domain solution with a volume ratio of 1:1 and incubated at 37 °C for 30 min. Afterward, 100 μL of mixture solution was pipetted into precoated 96-well microplates, plates were covered, incubated at 37 °C for 15 min, and washed several times with a washing buffer, a substrate solution (3,3′,5,5′-tetramethylbenzidine) was added in the dark at 20℃–25℃ for 15 min, and then, the reaction was stopped with a stop solution buffer. The optical density was read on a spectrophotometer at 450 nm. The cutoff for the presence of SARS-CoV-2 NAb was $\geq$ 30 % inhibition. The seroconversion rate was defined as $\geq$ 68 % inhibition, adopted from a definition of high-titer COVID-19 convalescent plasma according to the US-FDA statement [20].

Statistical analysis

Data analyses were performed using the R statistical software (version 4.1.0). Descriptive statistics were reported for categorical data using median and interquartile range (IQR). Categorical data were presented using frequencies and percentages. A comparison of anti-S-RBD IgG level and percentage of NAb activity among ID and IM groups was performed using the Mann–Whitney test, whereas Fisher's exact test was applied to compare the seroconversion rate between the two groups. Statistical significance was set at 0.05.

Ethical consideration

The study was conducted in accordance with the guidelines of the Declaration of Helsinki, Belmont Report. The study protocol was approved by the Mahasarakham University Ethics Committee for Research Involving Human Subjects (223–029/2022, Date of Approval June 24, 2022). Informed consent was waived by the ethics committee.

Results

All 247 vaccinated individuals who received the booster dose with BNT162b2 mRNA vaccine between August 1 and August 15, 2021, were initially reviewed for inclusion (184 and 63 HCWs received IM and ID, respectively). A total of 43 healthy adults with a median age of 31 (28–40) years met all inclusion criteria. Two-hundred and four participants were excluded because they did not have results of anti-S-RBD IgG before receiving a booster. Twenty-three participants received ID fractional dose BNT162b2 mRNA, and 20 participants received IM full-dose BNT162b2 mRNA. The duration between the second dose and booster dose was 75 (74–75) days. Table 1 shows the baseline demographic data of the participants.

Safety

In both groups, there were no serious adverse reactions that required medical attention. Fig. 1 shows an overview of both local and systemic adverse reactions. No acute adverse reactions occurred in the first 30 min. A total of six participants used antipyretic or pain medications to treat adverse reactions (one participant in the ID group and five participants in the IM group). Most of the systemic adverse reactions lasted for 1–3 days, and no local adverse reactions lasted longer than 8 days.

Local adverse reactions

The most common local adverse reactions in the ID group were local erythema and swelling (100 % and 87 %, respectively). The average wheal and erythema diameters in the ID group were 27 mm (SD 21; range 0–80 mm) and 54 mm (SD 22; range 0–100 mm), respectively. None reported severe erythema or swelling>10 cm in diameter. Both erythema and swelling lasted equal to or <8 days and were self-limiting and well-tolerated. Pain at the injection site was common in both ID (63 %) and IM (70 %) groups and was generally mild to moderate.

Systemic adverse reactions

Fatigue was common in both ID (39.1 %) and IM (40 %) groups. Myalgia occurred more frequently in the IM group (40 %) than in the ID group (4.3 %). None reported fever.

Immunogenicity

The anti-S-RBD IgG titers

No significant difference in baseline anti-S-RBD IgG titers was observed (289 vs 286 AU/mL, $p > 0.9$, in the ID and IM groups, respectively); 4.3 % of participants in the ID group and 10 % of participants in the IM group had high anti-S-RBD IgG titers (≥840 AU/mL). Anti-S-RBD igG titers (IQR) increased to 13294 (9255–19573) AU/mL in the ID group and 23456 (16943–38539) AU/mL in the IM group 3 weeks after receiving a booster with BNT162b2 mRNA vaccine. All participants in both ID and IM groups had seroconversion with anti-RBD IgG level ≥ 840 AU/mL.

Table 1
Characteristics of participants.

Demographic characteristics	ID (n = 23)	IM (n = 20)
Male, n (%)	16 (69.6 %)	4 (20.0 %)
Age, years		
Median	33	30
IQR	28–39	28–40
BMI, kg/m^2		
Median	22.8	21.6
IQR	20.4–25.1	20.0–23.6
Duration between the second and third dose (days)		
Median	75	75
IQR	75–75	74–85

ID: intradermal group; IM: intramuscular group; IQR: interquartile range.

SARS-CoV-2 NAb to Delta variant

The median of sVNT was 25.5 (19.2–34.8) %inhibition in the ID group and 35.0 (22.7–51.3) %inhibition in the IM group before booster. A high-titer of specific NAb to the Delta variant (≥68 % inhibition) was found in 4.3 % of the ID group and 6.2 % of the IM group. Furthermore, the median of sVNT increased to 97.2 (93.7–97.7) %inhibition in the ID group and 97.1 (96.3–97.5) %inhibition in the IM group 3 weeks after receiving a booster. All participants in the IM group and 95.6 % of the participants in the ID group had seroconversion with high titers of specific NAb to the Delta variant (≥68 % inhibition). Table 2 shows the details of anti-S-RBD IgG and specific NAb to the Delta variant.

Discussion

ID administration of a fractional dose was previously studied as a dose-sparing strategy for several vaccines and demonstrated noninferiority of immunogenicity in influenza (H1N1 and H2N3), rabies, and hepatitis B vaccines [21]. We reported the results of the retrospective cohort study and showed that ID administration of a 6 μg BNT162b2 mRNA SARS-CoV-2 vaccine dose as a booster in adults who were primed with a two-dose regimen of CoronaVac was safe and well-tolerated and induced a significant immune response. Swelling, erythema, pain, and itching at the injection sites were the most common local adverse reactions in the ID group. These local reactions were temporary and similar to those reported in prior studies after ID injection of the mRNA-1273 SARS-CoV-2 vaccine [19].

In this study, immune markers were used as a surrogate to predict vaccine effectiveness to prevent the SARS-CoV-2 infection. Anti-S-RBD IgG levels increased significantly in both ID and IM groups 3 weeks after receiving a booster with the BNT162b2 vaccine. Although the anti-S-RBD IgG titers were significantly higher in the IM group than those in the ID group (23456 vs 13294 AU/mL, $p < 0.001$), both titers were substantially higher than the cutoff for high-titer convalescent plasma (≥840 AU/mL). Moreover, none of the participants in either group failed to seroconvert after the booster dose. In this study, the immunogenicity was consistent with previous studies on ID administration of the COVID-19 vaccine. Intapiboon et al. demonstrated halved humoral immune response and less effective *T*-cell response in ID BNT162b2 mRNA vaccine booster compared with IM booster. However, no significant difference in NAb against the Delta variant was observed [22]. Nantanee et al. reported that ID administration of AZD1222 provided a high level of anti-S-RBD IgG and functional NAb on day 14. Nevertheless, a more rapid waning of NAb was observed in the ID group than that in the IM group at 3 months [23].

Age and gender are important associating factors of immune response to vaccination [24]. Women have a higher immune response to vaccination and more frequent local and systemic reactions than men [25,26]. In this study, there was inequality in gender between the ID and IM groups because most of the frontline HCWs, who received IM administration of the vaccine, were nurses. A high proportion of females in the IM group could be one of the contributing factors to a higher immune response to vaccination. However, no significant difference in antibody

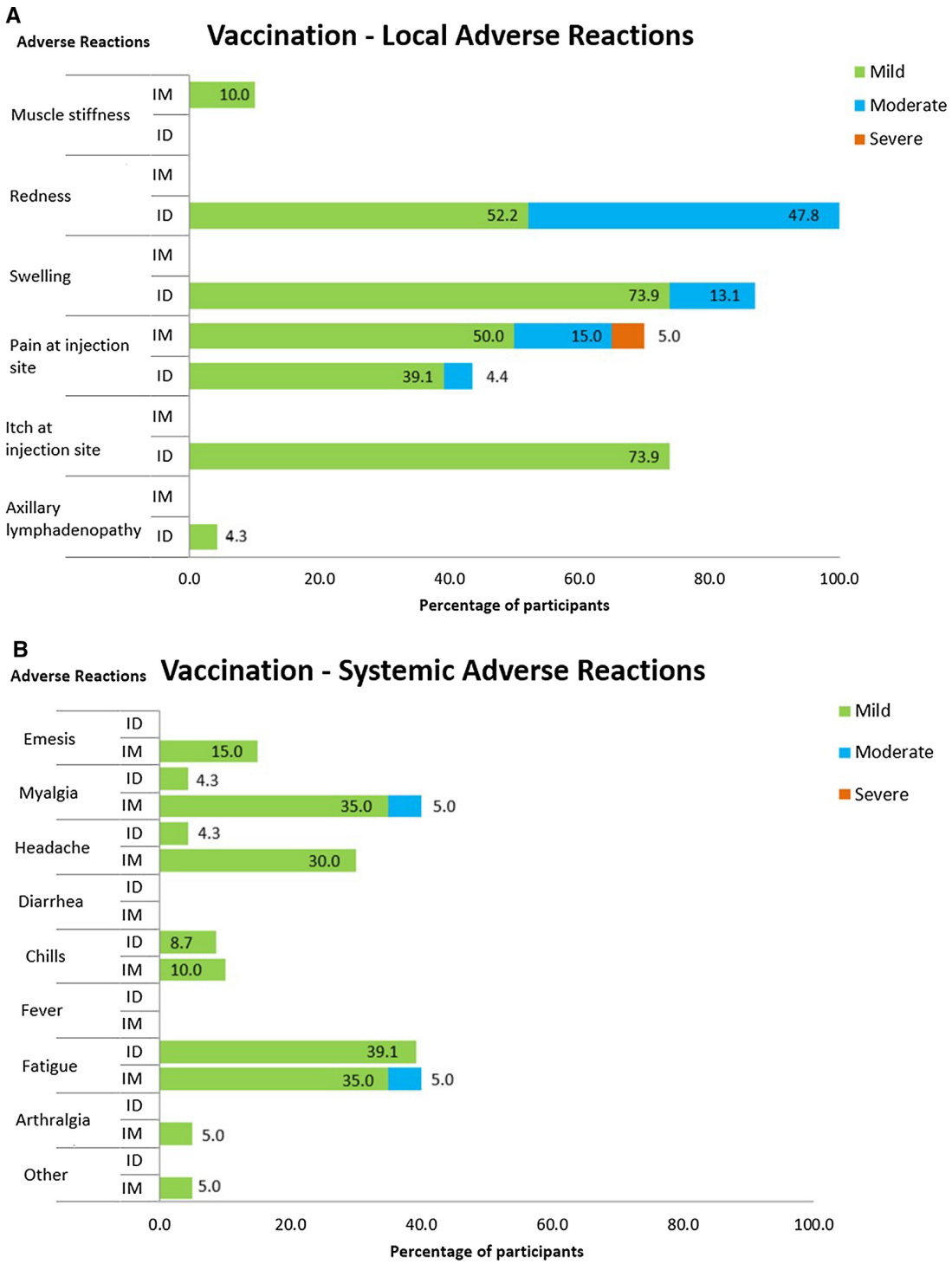

Fig. 1. Local and systemic adverse reactions associated with vaccination.

response after COVID-19 vaccination between males and females was observed in previous studies [10,27].

To evaluate immunogenicity from vaccination, antibodies that are elicited via natural infection should be differentiated. A sole assessment of antibodies against the spike (S) protein may be insufficient as these antibodies are present after natural infection and vaccination. To solve this issue, parallel measurement of S and nucleocapsid (N) antibodies may be applied. Nevertheless, its use was limited in this study, given that both antibodies can be detected in individuals vaccinated with an inactivated whole-virion SARS-CoV-2 vaccine [28]. Although all participants in this study did not report symptoms suggestive of COVID-19 infection before and after vaccination, asymptomatic SARS-CoV-2 infection cannot be entirely ruled out.

NAb titers are highly predictive of immune protection from SARS-CoV-2 infection and may be used to assist vaccine develop-

Table 2
Level of anti-S-RBD IgG and NAb activity against the Delta variant using sVNT.

	ID (n = 23)	IM (n = 20)	P-value
At baseline before booster (day 1)			
Anti-S-RBD IgG (AU/mL)	289 (205–494)	286 (200–597)	>0.9
Anti-S-RBD IgG ≥ 840 AU/mL (N (%))	1 (4.3 %)	2 (10 %)	0.6
SARS-CoV-2 NAb against the Delta variant (%inhibition)	25.5 (19.2–34.8)	35.0 (22.7–51.3)	0.14
%inhibition ≥ 68 % (N (%))	1 (4.3 %)	1 (6.2 %)*	>0.9
Day 21			
Anti-S-RBD IgG (AU/mL)	13294 (9255–19573)	23456 (16943–38539)	<0.001
Anti-S-RBD IgG ≥ 840 AU/mL (N (%))	23 (100 %)	20 (100 %)	>0.9
SARS-CoV-2 NAb against the Delta variant (%inhibition)	97.2 (93.7–97.7)	97.1 (96.3–97.5)	0.8
%inhibition ≥ 68 % (N (%))	22 (95.6 %)	20 (100 %)	>0.9

Anti-S-RBD IgG: SARS-CoV-2 spike protein receptor-binding domain IgG antibody; Nab: neutralizing antibody; sVNT: surrogate viral neutralization test.
*NAb activity against the Delta variant was available in 16 of 20 participants in the IM group.

ment [29]. sVNT showed a strong correlation with a conventional virus neutralization test, which is a current gold standard [30,31]. Moreover, there is a qualitative agreement between the concentrations of SARS-CoV-2 binding antibodies and the NAb percentage from sVNT [32,33]. Regarding specific NAb to the Delta variant in this study, there was a tremendous increase in %inhibition by sVNT after the booster in both groups with very high rates of seroconversion (≥68 %inhibition) (95.6 % vs 100 %, p > 0.9, in the ID and IM groups, respectively). Hammerschmidt et al. also reported better neutralization against the Delta variant in heterologous ChAdOx1-S/ BNT162b2 vaccination compared with homologous ChAdOx1-S/ChAdOx1-S regimen [34].

In summary, there was a robust immune response after receiving a booster with BNT162b2 mRNA SARS-CoV-2 vaccine via both IM and ID routes in participants who were primed with an inactivated SARS-CoV-2 vaccine. A dose-sparing strategy may be considered in the setting of vaccine shortage or in patients who previously experienced a serious systemic adverse reaction from IM administration due to concerns about the rapid waning of immune response in the ID group.

Limitations

As this is a retrospective cohort study, there was inequality in baseline characteristics, such as gender and risks for SARS-CoV-2 infection, between the IM and ID groups due to their roles in the hospital as mentioned above. Additionally, there was a limitation in the use of a combined assessment of anti-S and anti-N antibodies to discriminate between immune responses after natural infection and vaccination. Finally, there were no definitive cutoff levels of the anti-S-RBD IgG and the sVNT for protection against acute SARS-CoV-2 infection. Therefore, we adopted a definition of high-titer COVID-19 convalescent plasma according to the US-FDA statement (anti-S-RBD IgG level ≥ 840 AU/mL and sVNT ≥ 68 %inhibition) to implicate the protective immunity. Moreover, both surrogate markers for immune response to vaccination only represent a humoral immune response. To better understand overall vaccine-mediated immunity, further studies on cellular immune response are needed.

Conclusions

Our study highlighted two important topics regarding vaccination during the COVID-19 pandemic. First, ID administration of a fractional dose of BNT162b2 mRNA vaccine has the potential benefit of dose sparing. Second, heterologous vaccination and booster with mRNA vaccine elicited satisfactory immune response and inhibition to the Delta variant. Both topics merit further studies to better explore the most effective COVID-19 vaccination strategy.

CRediT authorship contribution statement

Yutthapong Temtanakitpaisan: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Suchaorn Seangnipanthkul:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Nataporn Sarakosol:** Conceptualization, Methodology, Project administration, Resources, Writing – review & editing. **Sasinapa Maskasem:** Conceptualization, Resources, Writing – review & editing. **Siwawoot Mongkon:** Conceptualization, Resources, Visualization, Writing – review & editing. **Benjaporn Buranrat:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Sutthiwan Thammawat:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Samadhi Patamatamkul:** Conceptualization, Methodology, Writing – review & editing. **Pattaranit Nernsai:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

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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