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Immunogenicity and Reactogenicity of Messenger RNA Coronavirus Disease 2019 Vaccine Booster Administered by Intradermal or Intramuscular Route in Thai Older Adults

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Background. Intradermal (ID) vaccination may alleviate COVID-19 vaccine shortages and vaccine hesitancy.

Methods. Persons aged ≥65 years who were vaccinated with 2-dose ChAdOx1 12–24 weeks earlier were randomized to receive a booster vaccination by either ID (20 μg mRNA-1273 or 10 μg BNT162b2) or intramuscular (IM) (100 μg mRNA-1273 or 30 μg BNT162b2) route. Anti–receptor-binding domain (RBD) immunoglobulin G (IgG), neutralizing antibody (NAb), and interferon gamma (IFN-γ)–producing cells were measured at 2–4 weeks following vaccination.

Results. Of 210 participants enrolled, 70.5% were female and median age was 77.5 (interquartile range, 71–84) years. Following booster dose, both ID vaccinations induced 37% lower levels of anti-RBD IgG compared with IM vaccination of the same vaccine. NAb titers against ancestral and Omicron BA.1 were highest following IM mRNA-1273 (geometric mean, 1718 and 617), followed by ID mRNA-1273 (1212 and 318), IM BNT162b2 (713 and 230), and ID BNT162b2 (587 and 148), respectively. Spike-specific IFN-γ responses were similar or higher in the ID groups compared with IM groups. ID route tended to have fewer systemic adverse events (AEs), although more local AEs were reported in the ID mRNA-1273 group.

Conclusions. Fractional ID vaccination induced lower humoral but comparable cellular immunity compared to IM and may be an alternative for older people.

Clinical Trials Registration. TCTR20220112002.

Keywords. COVID-19 booster vaccination; immune responses; intradermal; mRNA vaccines; older adults.

Coronavirus disease 2019 (COVID-19) booster vaccination has been found to improve protection against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, including the Omicron variants [1–4]. The booster vaccination has been recommended for older adults due to their aging immune system (immunosenescence) as well as the likelihood of having comorbidities that predispose them to severe COVID-19. However, the booster vaccine coverage among older Thai adults was reported recently at 44% (unpublished report by the Ministry of Public Health), which is relatively low but similar to other settings, which could partly be attributed to vaccine hesitancy regarding adverse effects following messenger RNA (mRNA) vaccination [2].

Intradermal (ID) vaccination of BCG and rabies vaccines have been given routinely in many settings. The dermis and epidermis layers are rich in antigen-presenting cells, and lower or fractional dosage of vaccine content are normally administered intradermally. ID administration for other vaccines such as inactivated polio, hepatitis B, and influenza vaccines given at fractional dose is found to induce equivalent (or higher) immunogenicity and similar safety profiles compared to intramuscular (IM) or subcutaneous (SC) vaccination [5, 6]. Hence, COVID-19 vaccination via the ID route may be considered as an alternative to IM vaccination. This would be particularly relevant in the context of limited COVID-19 vaccine supplies [7]. Moreover, this alternative route using lower amount of mRNA vaccine could reduce adverse effects and may increase acceptance of these vaccines.

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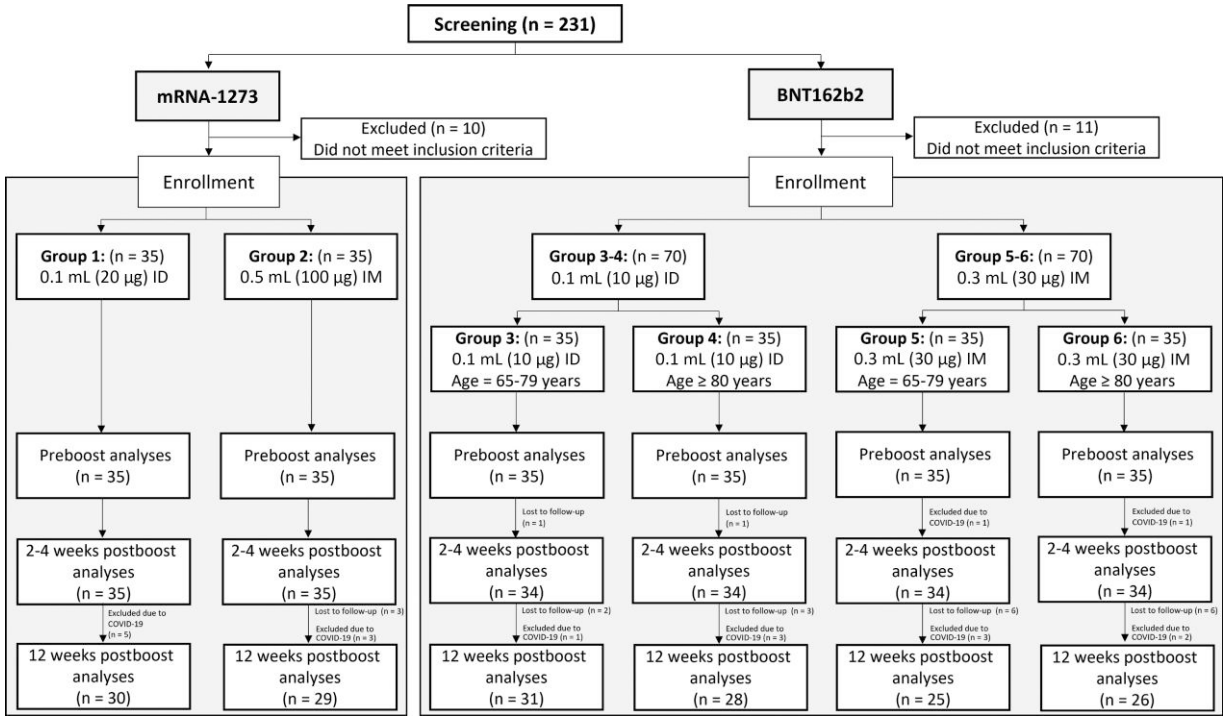

Figure 1. Consort flow diagram. Two hundred thirty-one participants were screened and 210 were deemed eligible for enrollment. Participants were randomized into 6 study arms (n = 35 each) and assessed prevaccination (preboost, 12–24 weeks after completing ChAdOx1 primary series), 2–4 weeks postboost, and 12 weeks postboost (after excluding participants lost to follow-up or anti-nucleoprotein positive at baseline). Abbreviations: COVID-19, coronavirus disease 2019; ID, intradermal; IM, intramuscular.

There are limited studies on COVID-19 vaccination given via the ID route. Most studies were conducted in healthy adults and found that ID vaccination induced similar or slightly lower immune responses than IM, but with fewer systemic adverse events (AEs) [8, 9]. Older adults have different immune composition under the skin and may respond to ID route differently. This study aims to compare the immunogenicity and reactogenicity of fractional-dose mRNA-1273 (Moderna) and BNT162b2 (Pfizer) booster vaccination given via ID route with standard-dose mRNA-1273 and BNT162b2 given via IM route in older adults previously vaccinated with 2 doses of ChAdOx1 (AstraZeneca).

MATERIALS AND METHODS

This open-label study was conducted at a single-center, tertiary hospital in Bangkok, Thailand, during the period of January–June 2022. Eligible subjects were individuals aged ≥65 years who have primarily received 2 doses of IM ChAdOx1 series 12–24 weeks earlier. Exclusion criteria included any previous infections of SARS-CoV-2, acute illness or inflammation, history of anaphylaxis to any vaccination or drugs, receipt of any vaccination within 2 previous weeks, and receipt of any immunosuppressants or in the state of immunosuppression. Patients and their caretakers were informed of the benefits granted by joining the study (ie, immunization as per national guidelines recommendation against COVID-19) as well as its risks (ie, novelty from current standards vaccination) before written informed consent was obtained.

The participants were randomized to 1 of the 4 vaccination groups: ID mRNA-1273 (20 µg; 0.1 mL; n = 35), IM mRNA-1273 (100 µg; 0.5 mL; n = 35), ID BNT162b2 (10 µg; 0.1 mL; n = 35 for each group of 65−79 and ≥80 years of age) or IM BNT162b2 (30 µg; 0.3 mL; n = 35 for each group of 65−79 and ≥80 years of age). The ID administration was given at the deltoid area using Mantoux technique. Wheals were measured post–ID vaccine administration to ensure correct technique (within range of 4–8 mm).

Blood samples were collected before and at 2–4 weeks after vaccination for immunogenicity evaluation of anti–SARS-CoV-2 receptor-binding domain immunoglobulin G (anti-RBD IgG) antibodies and pseudovirus neutralizing antibodies against ancestral Wuhan and Omicron variants (BA.1, BA.2, BA.4/5), as well as cellular immune response (by enzyme-linked immunosorbent spot assay [ELISpot]) assessment. Another blood sample was collected at 12 weeks after vaccination to evaluate anti-RBD IgG levels. Baseline blood samples were tested for anti–nucleoprotein antibody (anti-NP) and anti-RBD IgG using qualitative assay (Abbott, List No. 06R86) on the ARCHITECT I System to exclude prior

Table 1. Baseline Characteristics of Study Participants, by Route of Administration and Type of Coronavirus Disease 2019 Booster Vaccine

Baseline Characteristics	Type and Route of Booster Vaccine Administration							
				BNT162b2 (ID)		BNT162b2 (IM)		
	Total	mRNA-1273 (ID)	mRNA-1273 (IM)	65–79 y	≥80 y	65–79 y	≥80 y	*P* Value
No. (row %) of participants	210 (100.0)	35 (16.7)	35 (16.7)	35 (16.7)	35 (16.7)	35 (16.7)	35 (16.7)	
Male sex	62 (29.5)	7 (20.0)	9 (25.7)	15 (42.9)	11 (31.4)	8 (22.9)	12 (34.3)	.311
Age, y, median (IQR)								
All participants	77.5 (71.0–84.0)	75.0 (69.0–81.0)	73.0 (67.0–82.0)	71.0 (67.0–76.0)	86.0 (82.0–88.0)	72.0 (67.0–73.0)	85.0 (82.0–89.0)	<.001
65–79 y	71.0 (67.0–74.0)	71.0 (68.0–75.0)	69.0 (67.0–73.0)	71.0 (67.0–76.0)	…	72.0 (67.0–73.0)	…	.622
≥80 y	85.0 (82.0–88.0)	82.0 (81.0–87.0)	83.0 (82.0–84.5)	…	86.0 (82.0–88.0)	…	85.0 (82.0–89.0)	.341
Age category								
65–79 y	116 (55.2)	23 (65.7)	23 (65.7)	35 (100.0)	0 (0.00)	35 (100.0)	0 (0.00)	<.001
≥80 y	94 (44.8)	12 (34.3)	12 (34.3)	0 (0.00)	35 (100.0)	0 (0.00)	35 (100.0)	
BMI, kg/m^2, median (IQR)	24.1 (21.6–26.7)	24.1 (20.4–25.9)	25.5 (22.7–28.0)	22.7 (20.9–25.2)	23.9 (21.5–26.5)	24.6 (22.7–28.7)	23.7 (22.1–25.7)	.130
BMI category								
<18.5 kg/m^2	10 (4.8)	3 (8.6)	0 (0.00)	3 (8.6)	3 (8.6)	0 (0.00)	1 (2.9)	.210
≥18.5 kg/m^2	200 (95.2)	32 (91.4)	35 (100.0)	32 (91.4)	32 (91.4)	35 (100.0)	34 (97.1)	
Underlying diseases								
Hypertension	143 (68.4)	25 (71.4)	21 (60.0)	25 (71.4)	22 (64.7)	23 (65.7)	27 (77.1)	.698
Dyslipidemia	141 (67.5)	27 (77.1)	18 (51.4)	25 (71.4)	20 (58.8)	21 (60.0)	30 (85.7)	.222
Diabetes mellitus	48 (23.0)	5 (14.3)	9 (25.7)	12 (34.3)	8 (23.5)	9 (25.7)	5 (14.3)	.324
CCI, median (IQR)	4.0 (3.0–5.0)	3.0 (3.0–4.0)	4.0 (3.0–4.0)	3.0 (2.0–4.0)	5.0 (4.0–6.0)	3.0 (2.0–4.0)	5.0 (4.0–6.0)	.159
Interval between second dose and booster dose, wk, median (IQR)	18.1 (15.6–20.3)	15.6 (14.3–17.4)	15.6 (14.3–16.7)	18.9 (17.3–20.4)	20.0 (18.1–21.4)	19.3 (17.7–20.9)	19.7 (18.0–21.4)	<.001
		P = .656			*P* = .865			

Data are presented as No. (column %) unless otherwise indicated.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ID, intradermal; IM, intramuscular; IQR, interquartile range.

SARS-CoV-2 infection. Participants who were enrolled but later found to have positive anti-NP at baseline were excluded from the analysis.

Participants were observed for at least 30 minutes following vaccination for any immediate AEs. Participants and their caretakers (or person living together) were instructed to submit self-assessment report using an electronic diary (eDiary) in the Google Form for 7 days for any AEs. The solicited local AEs include pain, erythema, and swelling/induration at the injection site and localized axillary lymphadenopathy or swelling or tenderness ipsilateral to the injection arm. The solicited systemic AEs included headache, fatigue, myalgia, arthralgia, diarrhea, dizziness, nausea/vomiting, rash, fever, and chills. The severity of solicited AEs was graded using a numerical scale from 1 to 4 based on the Common Terminology Criteria for Adverse Events–Version 5.0 guided by the United States National Cancer Institute [10]. The submitted eDiarys were verified to ensure the accuracy and completeness of the AE data in every subject at the second visit, 2–4 weeks after vaccination.

The study protocol was registered at Thai Clinical Trial Registry (TCTR20220112002) and was approved by the Siriraj Institutional Review Board (Certificate of Approval No. Si 001/2022). Written informed consent was obtained from the study participants prior to any procedure.

Measurement of SARS-CoV-2 Anti-RBD

The anti-RBD IgG was measured using a chemiluminescent microparticle assay (SARS-CoV-2 IgG II Quant, Abbott, List No. 06S60). The level of antibodies was quantified in arbitrary units per milliliter (AU/mL) and then converted into binding antibody units per milliliter (BAU/mL) using the equation provided by the manufacturer (BAU/mL = 0.142 × AU/mL).

Measurement of Neutralizing Antibodies Against SARS-CoV-2 Variants

The pseudovirus neutralization test assay was carried out as previously published [11]. The 50% pseudovirus neutralizing antibody titer ($PVNT_{50}$) was defined as the highest test serum dilution that reduced the virus infectivity by 50% relative to the control wells with no serum. The minimum detection limit was 1:40; antibody titer of 1:20 was assigned to samples below the detection limit.

Measurement of Cellular Immune Response

Cellular immunity was determined by interferon gamma (IFN-γ) ELISpot (Mabtech, Nacka Strand, Sweden) to the ancestral strain on a subset of participants for each group (n = 20). Peripheral blood mononuclear cells were counted and stimulated with S-peptide consisting of 100 peptides from spike protein, and nucleoprotein–membrane protein–open reading

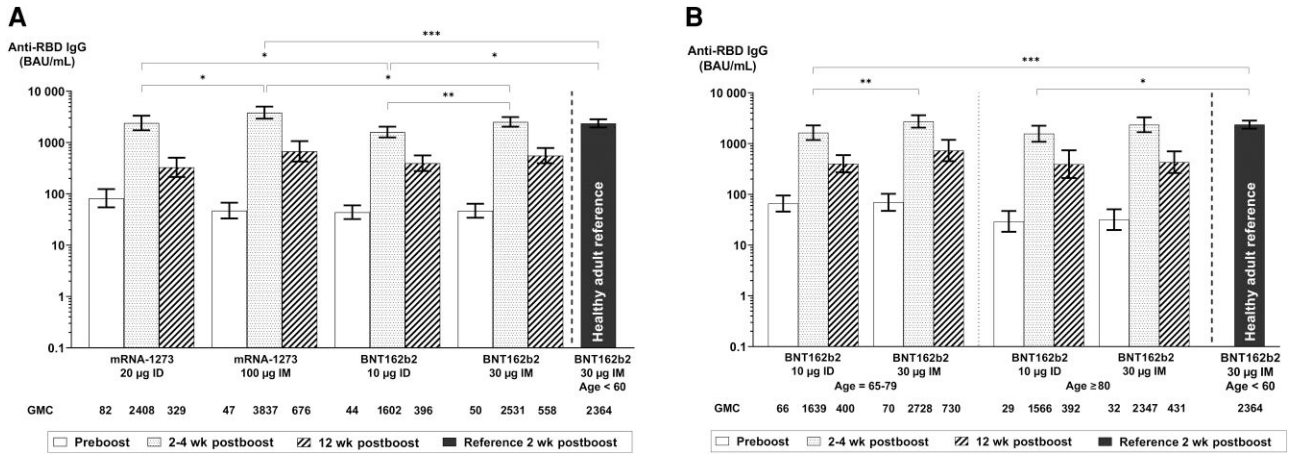

Figure 2. Anti–severe acute respiratory syndrome coronavirus 2 receptor-binding domain (RBD) immunoglobulin G (IgG) geometric mean concentrations (GMCs) at baseline and 2–4 weeks after intramuscular (IM) or intradermal (ID) booster administration stratified by vaccine type (mRNA-1273 or BNT162b2) (*A*) and age group (for BNT162b2 vaccine arms) (*B*). GMCs are displayed with 95% confidence intervals and were compared using unpaired Student *t* test. GMCs 2 weeks after booster administration in a previous study among healthy adults aged <60 years who received IM BNT162b2 boosters after 2-dose ChAdOx1 primary series were included as a reference [12]. Only statistically significant *P* values are displayed. **P* ≤ .05, ***P* ≤ .01, ****P* ≤ .001. Decimals are rounded to the nearest integer.

frame protein (NMO) peptide pools consisting of 101 peptides from nucleocapsid (N), membrane (M), open reading frame (ORF) 1, nonstructural protein 3, ORF-3a, ORF-7a, and ORF8 proteins. Negative controls contained only cell culture media, while positive controls contained anti-CD3 at a dilution of 1:1000. ELISpot plates were then incubated for 20 hours at 37°C and 5% carbon dioxide, washed, and developed using a conjugated secondary antibody that bound to membrane-captured IFN-γ. The plates were read using IRIS (Mabtech) and spots were analyzed using Apex software 1.1 (Mabtech) and converted to spot-forming units per million cells.

Statistical Analysis

The primary measured endpoint was humoral immunogenicity. The anti–SARS-CoV-2 RBD IgG and $PVNT_{50}$ titer were presented as geometric mean concentration (GMC) and geometric mean titer (GMT) with 95% confidence interval (CI) and were compared using unpaired *t* test between the groups. Using the results from our previous study [12], a sample size of 35 subjects per group provided 85% power to determine differences in antibody concentrations between ID and IM vaccination groups. Correlations between anti-RBD IgG and NAbs against the ancestral Wuhan strain and Omicron variants 2–4 weeks after booster administration were performed using Spearman correlation tests and coefficients. The AEs were the secondary endpoints presented as frequencies and compared using χ^2 test between the groups. GraphPad Prism 9 version 9.2.0 (GraphPad Software, San Diego, California) was used to perform all the statistical analyses except for the analysis of variance analysis of the anti-RBD IgG among different age groups, which was performed using Stata version 17 software (StataCorp, College Station, Texas).

RESULTS

Participants' Baseline Characteristics

A total of 231 participants were screened, and 210 were enrolled and randomized to 1 of the 4 vaccination groups; in the BNT162b2 groups, participants were recruited into 2 age groups (Figure 1). Among 210 participants included in the analysis, the majority (70.5%) were female, the median age was 77.5 years (interquartile range [IQR], 71.0–84.0 years), and the median body mass index was 24.1 kg/m^2 (IQR, 21.6–26.7 kg/m^2). The majority (81.9%) of the participants had at least 1 health condition, and the median Charlson Comorbidity Index was 4.0 (IQR, 3.0–5.0) (Table 1).

Anti-SARS-CoV-2 RBD IgG Responses

There were no statistical differences in anti-RBD IgG at baseline between the vaccine groups (Figure 2*A* and Supplementary Table 1). At 2–4 weeks after booster vaccination, the GMC increased 29.2, 81.1, 35.3, and 53.3 times from baseline for the ID mRNA-1273, IM mRNA-1273, ID BNT162b2, and IM BNT162b2 groups, respectively ($P < .001$) (Figure 1 and Supplementary Table 1). Overall, the anti-RBD IgG GMC following mRNA-1273 vaccinations was higher than for BNT162b2, regardless of administration routes. Participants who received IM mRNA-1273 had significantly higher anti-RBD IgG than IM BNT162b2 (GMC: 3837.12 vs 2530.58 BAU/mL, respectively; $P = .021$). ID vaccination of either mRNA-1273 or BNT162b2 had 37% lower anti-RBD IgG responses than IM vaccination of the respective vaccine ($P = .028$ and $P = .005$, respectively) (Figure 2*A* and Supplementary Table 1). Interestingly, when compared with healthy subjects <60 years of age who received BNT162b2

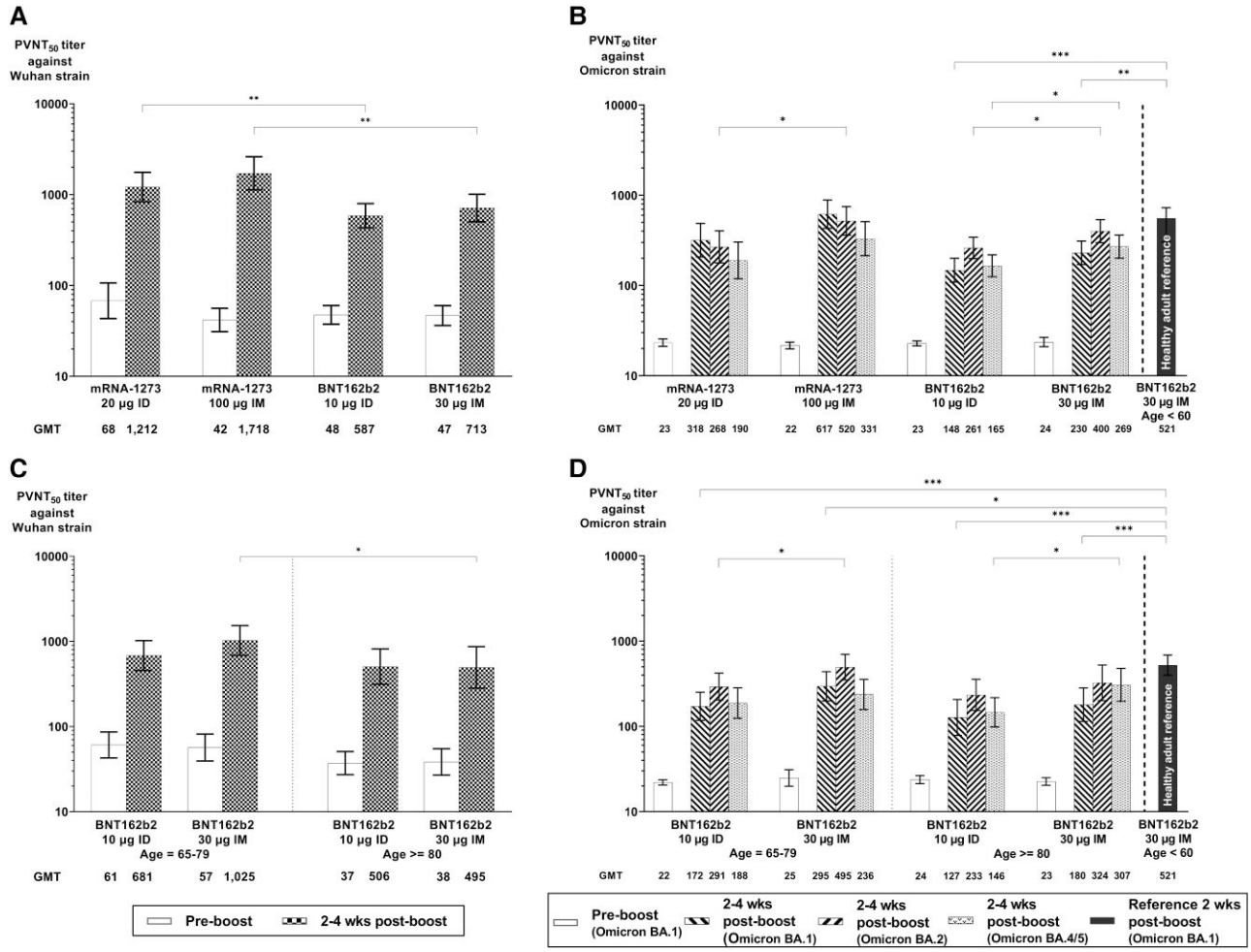

Figure 3. The 50% pseudovirus neutralizing antibody titers ($PVNT_{50}$) against severe acute respiratory syndrome coronavirus 2 ancestral Wuhan strain (*A*) and Omicron variants (*B*) at baseline and 2–4 weeks following intramuscular (IM) or intradermal (ID) booster vaccination using mRNA-1273 or BNT162b2 vaccine and in the BNT162-b2 vaccine groups stratified by age (*C* and *D*). Geometric mean titers (GMTs) with 95% confidence intervals were compared using unpaired Student *t* tests. $PVNT_{50}$ GMTs against Omicron BA.1 2 weeks after booster administration in a previous study among healthy adults age <60 years who received IM BNT162b2 boosters after 2-dose ChAdOx1 primary series were included as a reference [12]. Only statistically significant *P* values are displayed. $^{*}P \leq .05$, $^{**}P \leq .01$, $^{***}P \leq .001$. Decimals are rounded to the nearest integer.

IM booster vaccination from our previous study [12] (GMC: 2364 [95% CI, 2006–2786] BAU/mL), both mRNA-1273 and BNT162b2 IM vaccination as well as mRNA-1273 ID vaccination generated similar or higher anti-RBD IgG concentrations, but lower concentrations by BNT162b2 ID vaccination.

Among participants in the BNT162b2 groups, there were no significant differences in anti-RBD IgG responses between those aged 65–79 years and those ≥80 years who received the similar route. When compared with reference group of younger adults aged <60 years, similar anti-RBD IgG responses were found for IM vaccination regardless of age 65–79 years or ≥80 years, whereas significantly lower responses were found for ID vaccination (Figure 2*B* and Supplementary Table 2).

At 12 weeks following the booster vaccination, the overall anti-RBD IgG GMC declined by 4- to 7-fold of the levels at 2–4 weeks, but were still between 4- and 14-fold higher than at baseline. The rate of decline as measured by geometric mean ratios between 12 weeks and 2–4 weeks postbooster was similar between the ID and IM groups, as well as in the different age range in the BNT162b2 groups (Figure 2*A* and 2*B*).

Neutralizing Antibody Responses Against the SARS-CoV-2 Variants

At baseline, only 95 of 210 (45.2%) and 11 of 210 (5.2%) participants had neutralizing antibodies ($PVNT_{50}$) against Wuhan and Omicron BA.1. There was a significant increase in $PVNT_{50}$ against ancestral Wuhan and Omicron variants following ID or IM booster vaccination; all participants became seropositive for Wuhan and approximately 89%, 95%, and 88% of the study cohort was seropositive for Omicron BA.1, BA.2, and BA.4/5, respectively. There was a strong positive correlation between $PVNT_{50}$ titers for all tested strains and anti-RBD IgG ($r = 0.6–0.8$, $P < .001$; Supplementary

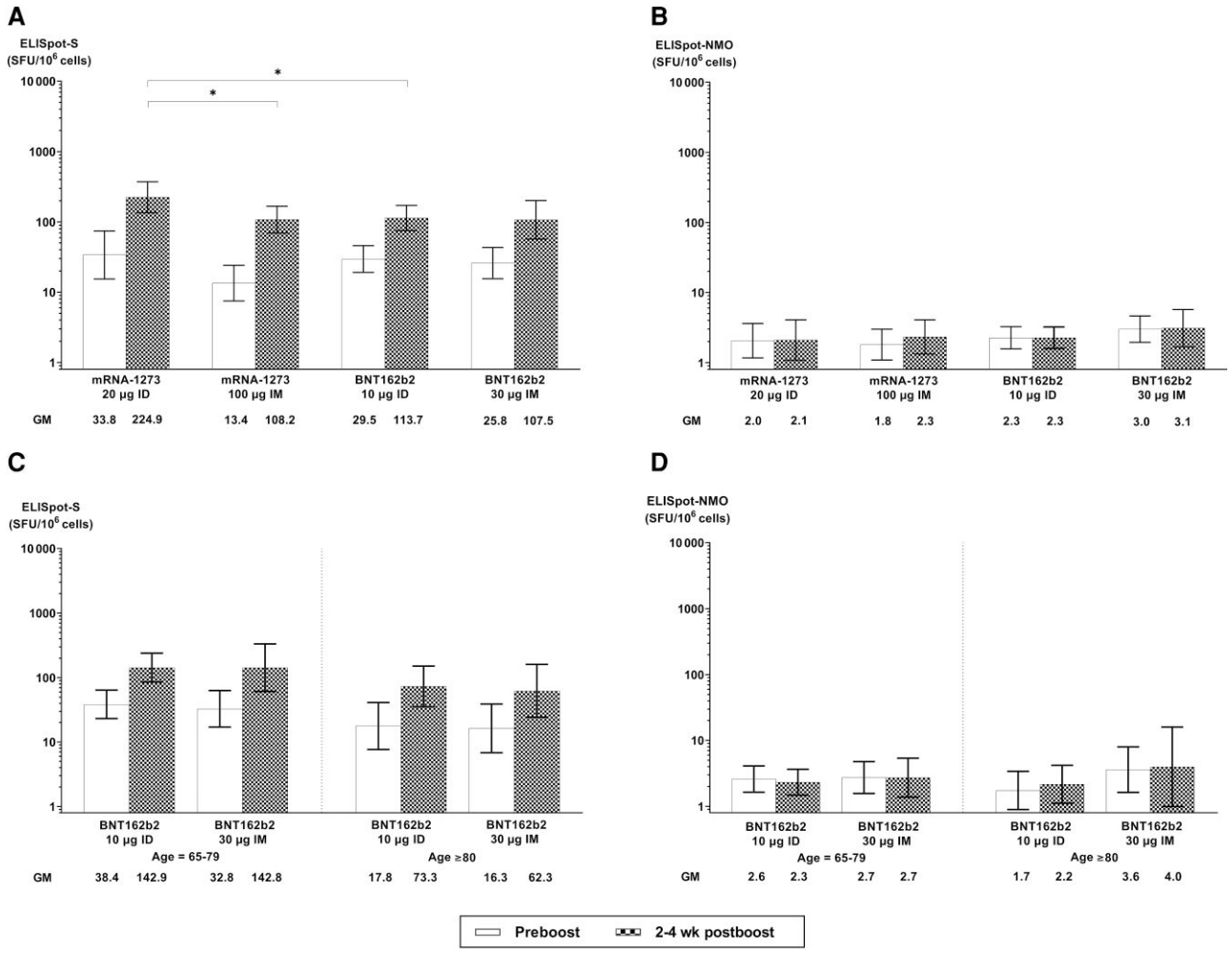

Figure 4. Severe acute respiratory syndrome coronavirus 2 spike-specific interferon gamma (IFN-γ)–producing cell responses (*A*) and nucleoprotein–membrane protein–open reading frame protein-specific IFN-γ–producing cell responses (*B*) at baseline and 2–4 weeks following intramuscular or intradermal booster vaccination using mRNA-1273 or BNT162b2 vaccine and in the BNT162b2 vaccine groups stratified by age (*C* and *D*). Geometric means of spot-forming units/10^6 cells with 95% confidence intervals were compared using unpaired Student *t* tests. Only statistically significant *P* values are displayed. $^*P \leq .05$. Abbreviations: ELISpot, enzyme-linked immunosorbent spot assay; GM, geometric mean; ID, intradermal; IM, intramuscular; NMO, nucleoprotein–membrane protein–open reading frame protein; SFU, spot-forming units.

Figure 1). Unlike what was seen for anti-RBD IgG, there was no statistical differences in $PVNT_{50}$ against Wuhan strain between ID or IM of either vaccine (mRNA-1273: 1212 [95% CI, 835–1759] for ID vs 1718 [95% CI, 1130–2612] for IM, $P = .210$; for BNT162b2: 587 [95% CI, 432–798] for ID vs 713 [95% CI, 502–1009] for IM, $P = .407$). However, both mRNA-1273 and BNT162b2 ID groups induced significantly lower $PVNT_{50}$ for Omicron variants than IM of the same vaccine. In general, both mRNA-1273 ID or IM vaccination generated higher $PVNT_{50}$ against Wuhan than ID or IM vaccination of BNT162b2 ($P < .005$ for the comparisons of the same route), and ID mRNA-1273 had similar GMT to IM BNT162b2 ($P = .577$). When compared with the reference range for $PVNT_{50}$ against Omicron BA.1 in younger adults (aged <60 years) who received BNT162b2 IM booster from our previous study, there were no significant differences for older people who received mRNA-1273 either by ID or IM, while significantly lower $PVNT_{50}$ was observed for the BNT162b2 groups (GMTs: ID, 147.8 or IM, 230.1 vs 521.2; $P < .001$ and $P = .005$, respectively) (Figure 3*A* and 3*B* and Supplementary Table 3).

When stratified by participants aged 65–79 years and ≥80 years among the BNT162b2 groups following either route, the younger group generally had higher $PVNT_{50}$ and proportion seropositive against all strains, although this was only statistically significant for the $PVNT_{50}$ against Wuhan following the IM route (GMT: 1025.3 vs 495.2, $P = .036$) (Figure 3*C* and 3*D* and Supplementary Table 4).

Cellular Immune Responses Against Ancestral Wuhan Strain

Following the booster dose, all ID or IM vaccination groups generated significant increase in IFN-γ–producing cell responses against the spike protein from baseline (Figure 4*A*

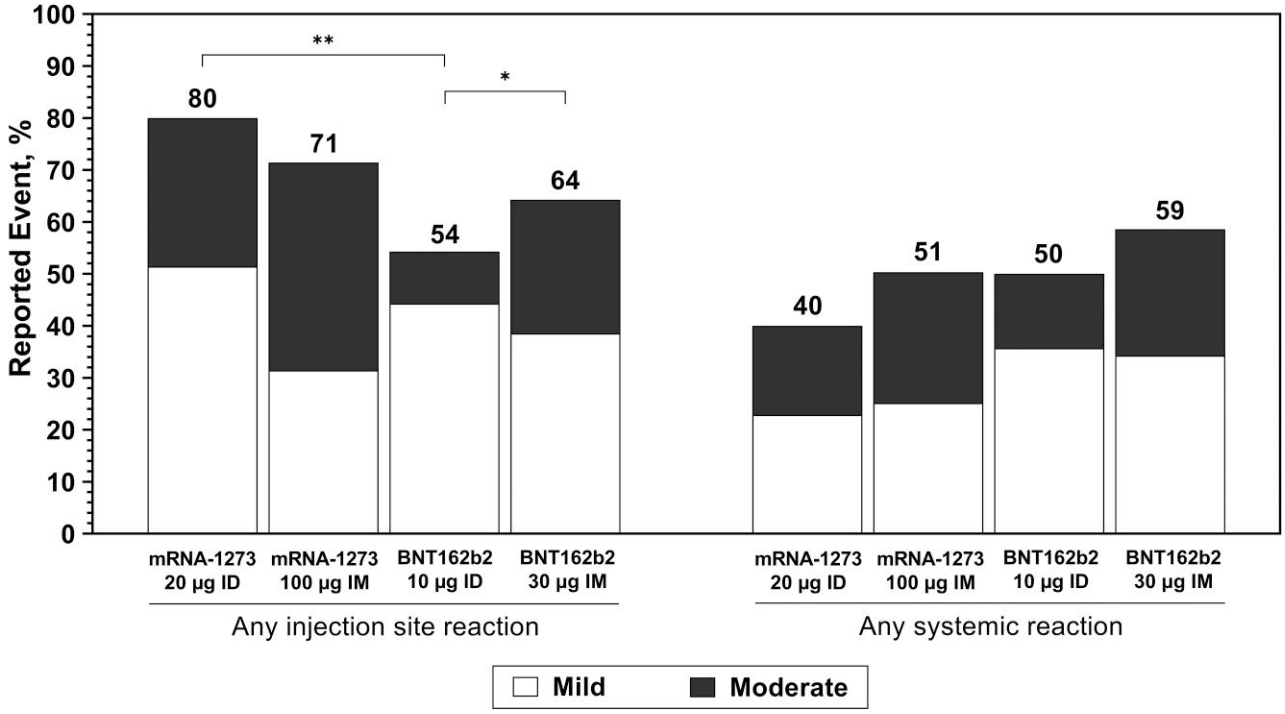

Figure 5. Local and systemic adverse events reported 7 days after intramuscular (IM) or intradermal (ID) vaccination across the 4 mRNA-1273 or BNT162b2 regimens. Only statistically significant *P* values are displayed. $^{*}P \leq .05$, $^{**}P \leq .01$.

and Supplementary Table 5). Participants who received ID vaccination had higher IFN-γ responses than the respective IM route, but this was statistically significant only in mRNA-1273 vaccine ($P = .026$). Interestingly, the ID mRNA-1273 group had significantly higher spike-specific IFN-γ responses than the ID BNT162b2 groups ($P = .047$). There were no statistical differences in IFN-γ response against NMO proteins between baseline and postbooster for either mRNA-1273 and BNT162b2, nor between ID and IM of either vaccine (Figure 4*B* and Supplementary Table 5).

When stratified by participants aged 65–79 years and ≥80 years among the BNT162b2 groups, similar IFN-γ responses against spike protein were found between ID and IM vaccination within each age group. Between participants aged 65–79 years and participants aged ≥80 years, higher but not statistically significant IFN-γ responses against the spike protein were observed (Figure 4*C* and Supplementary Table 6). There were no statistical differences in IFN-γ response against NMO proteins between ID and IM vaccination within each age group and vaccination route between each age group (Figure 4*D* and Supplementary Table 6).

Adverse Events

All AEs reported were mild (grade 1) to moderate (grade 2) and all participants recovered within 2–3 days (Figure 5 and Supplementary Tables 7 and 8). No serious AEs were found in this study. The systemic AEs were not statistically different between the groups, although IM groups tended to have a higher rate of AEs than ID (51% vs 40% for mRNA-1273, and 59% vs 50% for BNT162b2). Myalgia was more common with IM vaccination for both mRNA-1273 and BNT162b2 compared with ID vaccination (Supplementary Table 7 and Supplementary Figure 2). In contrast, the ID route tended to have more frequent local AEs than IM for mRNA-1273 (80% vs 71%), whereas this was the opposite for BNT162b2 (54% vs 64%). mRNA-1273 in general induced more local reactions than BNT162b2 ($P = .009$; Figure 5).

DISCUSSION

To our knowledge, this is the first study to compare the immunogenicity and reactogenicity of fractional-dose ID administration of mRNA vaccines as the booster vaccination in older adults with the standard-dose mRNA vaccines given IM. We found that fractional dosing (0.1 mL) of mRNA-1273 or BNT162b2 induced humoral and cellular immunes responses, with mRNA-1273 mounting higher responses than BNT162b2. While lower antibody responses were observed between ID and IM vaccination of either mRNA-1273 and BNT162b2, fractional-dose mRNA-1273 ID vaccination generally induced similar or higher antibody and cellular responses as those induced by standard-dose BNT162b2 IM vaccination.

In addition, the anti-RBD antibody responses induced by ID and IM vaccinations appear to wane at a similar rate, reflecting the similar decline of neutralizing antibody at 12 weeks post–booster administration. Local AEs were reportedly more common following ID vaccination than IM vaccination, but the systemic AEs were less frequent following ID vaccination. Overall, fractional ID vaccination of mRNA vaccine may be considered as an alternative to standard IM vaccination for older adults, particularly in settings where there are vaccine shortages (eg, new COVID-19 vaccines) and/or vaccine hesitancy due to high reactogenicity.

Older adults are the primary target for COVID-19 vaccination as they have increased risk of severe COVID-19 due to immunosenescence and likely have comorbidities. Previous studies of COVID-19 booster vaccination in older adults given via IM route were found to be highly effective against COVID-19, with >80% against any COVID-19–related symptoms and >90% against hospitalization and death, prior to the emergence of SARS-CoV-2 Omicron variants [13–15]. Neutralizing antibodies are thought to be the primary mechanism of protection against SARS-CoV-2 infection [16], while cellular immune responses are thought to be more important against severe COVID-19 [17]. In our study, despite the lower antibody response and similar or higher cellular immune responses found following ID administration when compared with respective IM administration of the same vaccine, the clinical relevance is unknown. Applying the immune correlate with protective efficacy at day 29 following vaccination reported by Gilbert et al [18], where the $PVNT_{50}$ of 100 correlated with estimate protective efficacy of 93%, the $PVNT_{50}$ against Omicron of 200–300 induced by both vaccines, either ID or IM route, in this study would imply similarly high protective efficacy. It is possible that ID administration may offer similar protection as with IM administration. ID injection may be less familiar to many vaccinators than IM injection; however, we have extensive experience with using ID administration as part of routine BCG and rabies vaccination. For this study, we ensured that the technique was correct by monitoring the wheal size that appeared following each injection. The higher immunogenicity following mRNA-1273 IM vaccination than BNT162b2 IM vaccination is consistent with previous studies [19–21]. A higher antigen amount in mRNA-1273 than in BNT162b2 is likely to account for this finding. However, it is important to note that the amount of vaccine content used in the ID administration of fractional mRNA-1273 dose is less than half of the current recommended IM administration dose (50 μg). Whether the immune responses induced by fractional dose given via ID route induced a similar immune memory cell response as standard-dose IM delivery remains to be determined.

We observed marginally lower neutralizing antibodies and cellular immune responses among adults aged ≥80 years compared with adults aged 65–79 years. This is consistent with previous studies of BNT162b2 that found lower neutralizing antibody responses in older adults compared with younger adults [22, 23]. This underscores the importance of choice of vaccine in older adults. Nevertheless, our findings suggest that older adults can mount robust immunity following a booster dose, even with ID administration of fractional dosage.

Consistent with our findings from previous studies on ID administration, we found a tendency of fewer systemic AEs but higher local AEs with ID route when compared with IM delivery. Because a common reason for COVID-19 vaccine hesitancy in older people is the concern of vaccine AEs [24], reducing systemic AEs following mRNA vaccination may lead to lower vaccine hesitancy. Of note, we found the proportions of AEs reported following ID route in this study were lower than that reported in adults aged <60 years (54%–80% vs 91% for local AEs, and 40%–50% vs 69% for systemic AEs) [9]. This is consistent with other studies that found lower reactogenicity in older people [25].

There are some limitations in this study. First, as the sample size was small, we were unable to make reliable comparisons between males and females. Given that sex-disaggregated responses to vaccines are uncertain [26, 27], further studies are needed that specifically address this question. Second, this was an open-label study since the administration route cannot be concealed, which may introduce bias on reporting of AEs, although this is unlikely to affect our immunogenicity findings. Third, data from younger adults were based on another study cohort, which may not be directly comparable. However, the study was conducted under similar settings and the data were generated using the same testing methods by the same laboratory, minimizing variability. Fourth, we are not able to determine whether the lower immunogenicity of ID groups in this study was from the route of administration or from the fractional dosing. Last, our data may not be generalizable to other COVID-19 vaccines and other populations such as those with other comorbidities.

Despite the lower level of antibody response compared to standard IM vaccination, but with comparable cellular immune response, we can conclude that fractional ID mRNA-1273 or BNT162b2 booster regimens were immunogenic and likely to provide comparable protective efficacy. ID route could be considered an alternative option for older people, particularly in resource-limited settings. Further investigation of vaccine efficacy of ID vaccination using the bivalent vaccine is warranted.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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