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Original article

Intradermal delivery of the third dose of the mRNA-1273 SARS-CoV-2 vaccine: safety and immunogenicity of a fractional booster dose

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ABSTRACT

Objectives: The aim of this study was to assess the safety and immunogenicity of a dose-sparing fractional intradermal (ID) booster strategy with the mRNA-1273 COVID-19 vaccine.
Methods: COVID-19 naive adults aged 18–30 years were recruited from a previous study on primary vaccination regimens that compared 20 μg ID vaccinations with 100 μg intramuscular (IM) vaccinations with mRNA-1273 as the primary vaccination series. Participants previously immunized with ID regimens were randomly assigned (1:1) to receive a fractional ID booster dose (20 μg) or the standard-of-care intramuscular (IM) booster dose (50 μg) of the mRNA-1273 vaccine, 6 months after completing their primary series (ID-ID and ID-IM group, respectively). Participants that had received a full dose IM regimen as the primary series, received the IM standard-of-care booster dose (IM-IM group). In addition, COVID-19 naive individuals aged 18–40 years who had received an IM mRNA vaccine as the primary series were recruited from the general population to receive a fractional ID booster dose (IM-ID group). Immunogenicity was assessed using IgG anti-spike antibody responses and neutralizing capacity against SARS-CoV-2. Cellular immune responses were measured in a sub-group. Safety and tolerability were monitored.
Results: In January 2022, 129 participants were included in the study. Fractional ID boosting was safe and well tolerated, with fewer systemic adverse events compared with IM boosting. At day 28 post-booster, anti-spike S1 IgG geometric mean concentrations were 9106 (95% CI, 7150–11 597) binding antibody units (BAU)/mL in the IM-IM group and 4357 (3003–6322) BAU/mL; 6629 (4913–8946) BAU/mL; and 5264 (4032–6873) BAU/mL in the ID-IM, ID-ID, and IM-ID groups, respectively.
Discussion: Intradermal boosting provides robust immune responses and is a viable dose-sparing strategy for mRNA COVID-19 vaccines. The favourable side-effect profile supports its potential to reduce vaccine hesitancy. Fractional dosing strategies should be considered early in the clinical development of future mRNA vaccines to enhance vaccine availability and pandemic preparedness. **Geert V.T. Roozen, Clin Microbiol Infect 2024;30:930**

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Introduction

The swift development and widespread distribution of SARS-CoV-2 vaccines have proven highly effective in mitigating the severe consequences of COVID-19 [1]. The mRNA-1273 vaccine demonstrated a protective efficacy of 93% after two intramuscular (IM) doses of 100 μg as a primary series, after a median follow-up of 5.3 months [2]. A booster dose of mRNA-1273 with 50 μg IM led to 1.7-fold (95% CI, 1.5–1.9) higher neutralizing antibody titers than those at 28 days after the second injection of the primary series [3].

Although many countries have already performed multiple booster rounds, a major disparity in booster administration between high-income, low-income, and middle-income countries remains. One of the causes are the high vaccine costs [4]. Fractional dosing strategies could be a cost-effective method to increase vaccine coverage [5], and may contribute to vaccine uptake in populations with fear of side effects as a reason for vaccine hesitancy [6,7].

Given the higher density of antigen-presenting cells in the dermis as compared with muscle tissue, the skin is an obvious site for fractional dose delivery. Previously, we have shown that two fractional intradermal (ID) doses of 20 μg mRNA-1273 as a primary series were safe and highly immunogenic [8,9]. To evaluate whether this strategy is also suitable for the mRNA-1273 booster, we extended the trial and administered a booster dose 6 months after the primary ID or IM series. We measured the immune responses elicited by a fractional (20 μg) ID booster or a full dose (50 μg) IM booster after either a fractional ID primary series or a regular (100 μg) IM primary series.

Methods

Study design and population

This open-label, partly randomized controlled clinical trial was performed at the Leiden University Medical Centre, a tertiary health care facility in The Netherlands. This is a follow-up study of a previous trial comparing safety and immunogenicity in healthy SARS-CoV-2-naive adults who were randomly assigned to primary vaccination with either two fractional doses of 20 μg of mRNA-1273 (Spikevax) through the ID route or the standard regimen with two doses of 100 μg of mRNA-1273 vaccine through the IM route (EU Clinical Trials Register: EUCTR2021-000454-26-NL). The vaccine was manufactured in Switzerland.

Participants of the original trial (aged 18–30 years) received a booster (third) dose 6 months after completing the primary vaccination series. In the original trial, two methods of ID administration were assessed: ID delivery according to the Mantoux technique and perpendicular ID administration using an ultra-short Bella-mu 1.4 microneedle (U-Needle BV, Enschede, The Netherlands). Because both methods yielded similar antibody responses, participants were grouped in the current trial and randomly assigned (1:1) to receive either a standard IM booster dose of 50 μg mRNA-1273 (ID-IM group) or a fractional ID booster dose of 20 μg mRNA-1273 (ID-ID group). Participants who had initially received two IM doses of 100 μg mRNA-1273 were assigned to the standard IM booster dose of 50 μg mRNA-1273 (IM-IM group).

For comparison, a fourth group of healthy adults (ages 18–40 years) was included, having received a primary series with two IM doses of either 100 μg mRNA-1273 or 30 μg of BNT16b2 (Comirnaty) through the Dutch Municipal Health Service 4–8 months earlier. This fourth group received a fractional ID booster dose of 20 μg mRNA-1273 (IM-ID group).

Participants with a history of COVID-19 or immunodeficiency were excluded from the study. All participants were screened for recent or current SARS-CoV-2 infection before enrolment and at every on-site visit by anti-SARS-CoV-2-nucleocapsid (anti-N) antibodies and SARS-CoV-2 PCR of a mid-turbinate or throat swab, and they were asked for positive COVID-19 antigen self-tests of PCRs at the municipal health care centre. Participants were excluded when tested positive.

Written informed consent was obtained from all participants. The trial was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was reviewed and approved by the Medical Ethics Committee of Leiden, The Hague, Delft (NL 76702.058.21).

Randomization and blinding

Randomization of ID-primed participants (block sizes of four) was done using sealed envelopes. Clinical investigators and participants were unblinded to the administration route. Laboratory personnel remained blinded for the study groups.

Vaccination procedure

Vaccine was prepared according to the manufacturer's instructions. A single dose of 50 μg mRNA-1273 vaccine was administered to participants in the IM-IM and ID-IM group as a 0.25 mL IM injection in the deltoid muscle. The participants in the ID-ID group and the IM-ID group received a single dose of 20 μg mRNA-1273 vaccine as a 0.1 mL ID injection in the skin of the deltoid region. Participants in the IM-ID group were vaccinated intradermally with a Becton Dickinson U-100 Micro-Fine insulin syringe with integrated 29G needle, using the Mantoux technique. Participants in the ID-ID group were vaccinated using the Bella-mu 1.4 mm microneedle. A clearly visible wheal was indicative of a successful ID injection, with a minimally required diameter of 6 mm.

Monitoring of tolerability and safety

Participants were asked to record solicited and unsolicited adverse events (AEs) for 14 days following vaccination (Supplements 1). The severity of AEs was graded according to a standard grading scale (Supplements 1). Solicited AEs included local and systemic reactions.

Immunogenicity analysis

Blood samples for immunological analyses were taken before booster vaccine administration, 28 days after vaccination and 6 months (25–27 weeks) after vaccination.

Binding IgG antibody responses against the receptor binding domain (RBD) and to the S1 subunit of the spike protein and the nucleocapsid (N) of SARS-CoV-2 were measured in serum as previously described [8]. Concentrations were expressed as international binding antibody units per mL (BAU/mL). Anti-N IgG concentrations >14.3 BAU/mL were considered as proof of a convalescent SARS-CoV-2 infection.

The presence of antibodies with neutralizing capacity against SARS-CoV-2 was measured using a microneutralization assay as previously described [10]. Serum dilutions ranging from 1:10 to 1:10 240 were tested, and the first dilution that resulted in zero plaque formation was reported as PRNT 100.

In the original trial, a subset of 25 participants of each group was selected to assess cellular immune responses. From those who remained in the booster study (13 in the IM-IM group, four in the ID-IM group, and six in the ID-ID group), peripheral blood mononuclear cells were isolated. SARS-CoV-2 spike-specific B-cell and T-cell

responses were measured before and 28 days after vaccination, as described previously [9] and in Supplements 4 and 5.

Statistical analysis and sample size

No formal power calculation was performed as all participants of the original trial were eligible to participate in the current study. The sample size of the IM-ID group of 40 was based on the expected group size of the other groups.

All participants that received a booster vaccination were included in the intention-to-treat population. The per protocol (PP) population comprised all participants who received a booster vaccination with a negative SARS-CoV-2 PCR at the day of vaccination (PCR results became available on the day after vaccine administration). Safety was assessed in the intention-to-treat population and immunogenicity in the PP population.

Primary outcome was defined as the S1 and RBD binding antibody concentrations at day 28 post-vaccination. Neutralizing capacity was a secondary outcome measure. The ID-IM, ID-ID and IM-ID groups were compared pairwise to the IM-IM control group. No adjustments for antibody concentrations before booster were made because the objective was to assess the entire vaccination regimen (primary series + booster). Binding antibody concentrations were reported in geometric mean concentrations (GMCs) with two-sided 95% CI and neutralizing antibodies were reported in geometric mean titers (GMTs) with two-sided 95% CI. Geometric mean fold rises with two-sided 95% CI were used to report the changes in antibody concentrations and titers during follow-up. At every time point, the four groups were compared with each other using a nonparametric test that adjusts for multiple comparison (Dunn's multiple comparison test).

The study protocol specified a non-inferiority analysis as primary outcome for the original trial. Because the sample size was not powered for the booster part of the trial and there were no non-inferiority criteria pre-defined for this part of the study, no non-inferiority analysis was performed.

All statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp). A $p < 0.05$ was considered significant.

Results

Participants

Details on the recruitment and loss to follow-up are shown in Fig. 1. In January 2022, a total of 129 participants received a booster: 31 in the IM-IM group, 27 in the ID-IM group, 28 in the ID-ID group and 43 in the IM-ID group. Two participants in the ID-IM group and three participants in the IM-ID group were excluded from the PP population because of a positive PCR for SARS-CoV-2 on the day of the booster. At the primary endpoint 28 days after the booster, 94/124 (75.8%) of the participants in the PP population were still in the trial. COVID-19 was the main reason for exclusion during the trial, which was balanced among the groups (Fig. 1).

Baseline characteristics of the participants are reported in Table 1. The IM-ID group contained relatively more females and was

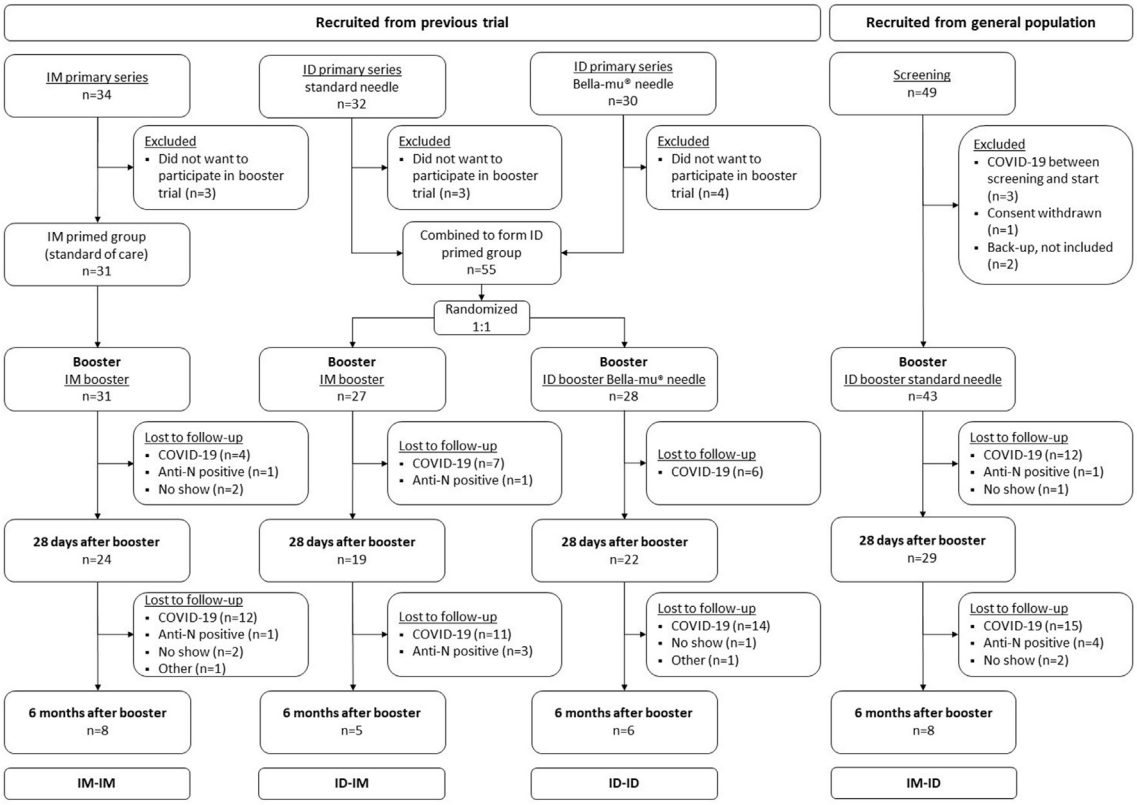

Fig. 1. Flowchart of inclusions, exclusions, and loss to follow-up of study participants. The current trial is a continuation of a previous trial that compared the safety and immunogenicity of two intradermally administered fractional doses of 20 μg of mRNA-1273 to the standard immunization regimen with two intramuscular doses of 100 μg of mRNA-1273 vaccine (EU Clinical Trials Register: EUCTR2021-000454-26-NL). Participants who received IM vaccinations in the primary series in the previous trial, were recruited to receive a 50 μg IM booster (IM-IM group, standard of care). Participants who received a fractional ID vaccination in the primary series in the previous trial, were recruited to receive a 50 μg IM booster (ID-IM group) or a 20 μg ID booster (ID-ID group). A fourth group was recruited from the general population to receive a fractional ID booster dose of 20 μg mRNA-1273 (IM-ID group). Anti-N, anti-nucleocapsid; ID, intradermal; IM, intramuscular.

Table 1
Characteristics of participants at inclusion (intention-to-treat population)

	Primary series 100 μg IM booster 50 μg IM IM-IM	Primary series 20 μg ID booster 50 μg IM ID-IM	Primary series 20 μg ID booster 20 μg ID Bella-mu ID-ID	Primary series 100 μg IM* booster 20 μg ID standard needle IM-ID
n	31	27	28	43
Female, n (%)	14 (45.2)	11 (40.7)	11 (39.3)	25 (58.1)
Age (y), mean ± SD	24.1 ± 3.5	23.1 ± 3.4	23.0 ± 3.2	26.8 ± 5.7
BMI in kg/m^2, mean ± SD	24.2 ± 4.1	24.9 ± 4.3	23.8 ± 5.0	23.4 ± 3.2
Primary series with BNT162b2, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	38 (88.4)
Time between primary series and booster in days, mean ± SD	176 ± 3	176 ± 3	177 ± 3	176 ± 17

All primary series and booster vaccinations were with mRNA-1273, except 30 μg in the case of a primary series with BNT162b2. BMI, body mass index; ID, intradermal; IM, intramuscular; SD, standard deviation.

slightly older compared with the other groups. In the IM-ID group 88.4% of the participants had received a regimen with the BNT126b2 vaccine in the primary immunization series, whereas the other groups had only received the mRNA-1273 vaccine.

Serological immunogenicity

Details on antibody concentrations and neutralizing capacity can be found in Fig. 2 and Table 2.

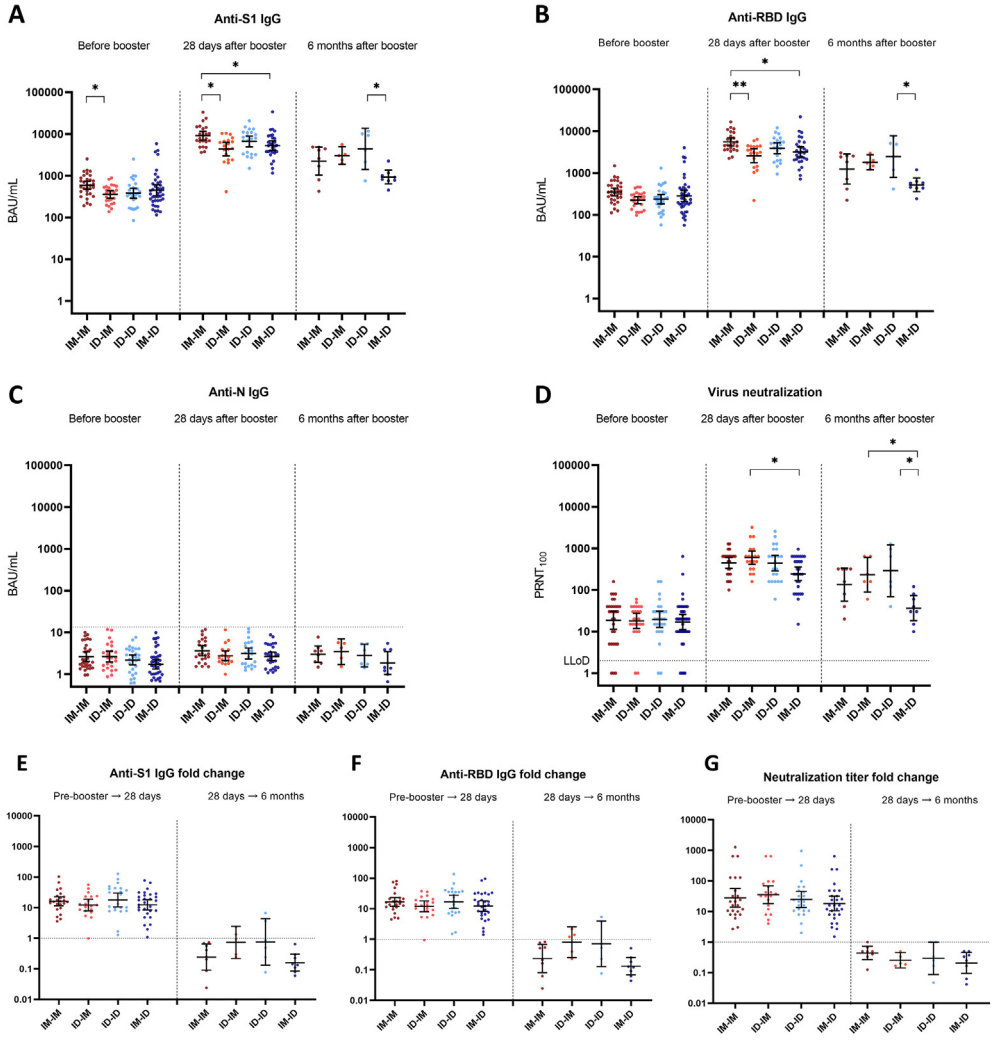

Fig. 2. Antibody responses. Every dot represents the result of a single participant at that time point. Error bars represent geometric means with a two-sided 95% CI. A single asterisk represents a significant difference with a $p < 0.05$, a double asterisk a $p < 0.01$ (Dunn's multiple comparison test). IM-IM stands for IM primary series and IM booster, ID-IM stands for ID primary series and IM booster, etc. A Anti-S1 IgG antibody concentrations in BAU/mL. B Anti-RBD IgG concentrations in BAU/mL. C Anti-N IgG titers in BAU/mL. Horizontal dotted line represents the cut-off for seropositivity (14.3 BAU/mL). D Virus neutralization titers. Horizontal dotted line represents the lower limit of detection. Results below the limit of detection were arbitrarily set to 1. E Anti-S1 IgG fold change. Horizontal dotted line represents a fold change of 1 (no increase and no decrease). F Anti-RBD IgG fold change. Horizontal dotted line represents a fold change of 1 (no increase and no decrease). G Neutralization titer fold change. Horizontal dotted line represents a fold change of 1 (no increase and no decrease). BAU, binding antibody units; CI, confidence interval; ID, intradermal; IgG, immunoglobulin G; IM, intramuscular; PRNT, plaque reduction neutralization test; RBD, receptor binding domain.

Table 2
Antibody concentrations reported in GMCs (IgG) and GMTs (neutralization) and fold change reported in GMFR (per protocol population)

	IM-IM	ID-IM	ID-ID	IM-ID
Pre-booster				
N	31	25	28	40
Anti-S1 IgG, BAU/mL (95% CI)	588 (471–743)	359 (291–442)	383 (291–505)	453 (334–613)
Anti-RBD IgG, BAU/mL (95% CI)	352 (283–437)	224 (186–272)	237 (183–306)	285 (209–387)
Neutralization, $PRNT_{100}$ (95% CI)	19 (11–30)	18 (12–27)	20 (13–30)	18 (12–26)
Booster + 28 d				
n	24	19	22	29
Anti-S1 IgG, BAU/mL (95% CI)	9106 (7150–11 597)	4357 (3003–6322)	6629 (4913–8946)	5264 (4032–6873)
Anti-S1 IgG, GMFR (95% CI)[a]	16.1 (11.5–22.7)	12.1 (7.8–18.7)	17.8 (10.5–30.0)	12.3 (8.4–18.2)
Anti-RBD IgG, BAU/mL (95% CI)	5535 (4430–6916)	2588 (1761–3804)	3900 (2903–5239)	3192 (2404–4239)
Anti-RBD IgG, GMFR (95% CI)[a]	16.6 (11.9–23.2)	11.9 (7.9–17.9)	16.7 (10.2–27.4)	12.7 (2.8–18.1)
Neutralization, $PRNT_{100}$ (95% CI)	445 (331–598)	598 (415–863)	440 (287–674)	234 (168–355)
Neutralization, GMFR (95% CI)[a]	26.8 (13.1–54.8)	34.1 (17.5–66.4)	23.3 (12.4–43.9)	17.0 (10.2–28.4)
Booster + 6 m				
n	8	5	6	8
Anti-S1 IgG, BAU/mL (95% CI)	2242 (1037–4845)	3055 (1873–4984)	4398 (1418–13 645)	929 (636–1358)
Anti-S1 IgG, GMFR (95% CI)[b]	0.2 (0.1–0.7)	0.7 (0.2–2.5)	0.7 (0.1–4.3)	0.2 (0.1–0.3)
Anti-RBD IgG, BAU/mL (95% CI)	1248 (544–2862)	1795 (1190–2707)	2466 (787–7733)	520 (357–757)
Anti-RBD IgG, GMFR (95% CI)[b]	0.2 (0.1–0.7)	0.8 (0.3–2.6)	0.7 (0.1–4.0)	0.1 (0.1–0.3)
Neutralization, $PRNT_{100}$ (95% CI)	135 (54–336)	230 (89–601)	291 (69–1218)	36 (18–73)
Neutralization, GMFR (95% CI)[b]	0.4 (0.2–0.7)	0.3 (0.1–0.5)	0.3 (0.1–0.5)	0.2 (0.1–0.5)

BAU, binding antibody units; GMC, geometric mean concentration; GMFR, geometric mean fold rise; GMT, geometric mean titer; ID, intradermal; IgG, immunoglobulin G; IM, intramuscular; PRNT, plaque reduction neutralization test; RBD, receptor binding domain.
[a] GMFR, geometric mean (booster + 28 days)/geometric mean (pre-booster).
[b] GMFR, geometric mean (booster + 6 months)/geometric mean (booster + 28 days).

At 28 days after booster administrations, the anti-S1 GMC of the IM-IM group (9106 [95% CI, 7150–11 597]) was significantly higher than that of the ID-IM (4357 [3003–6322]); $p = 0.01$) and the IM-ID group (5264 [4032–6873]); $p = 0.02$). The geometric mean fold rises (booster +28 days/pre-booster) for anti-S1 IgG did not differ between groups. Neutralization GMTs at 28 days after booster vaccination were 445 (331–598) in the IM-IM group, 598 (415–863) in the ID-IM group, 440 (287–674) in the ID-ID group, and 234 (168–355) in the IM-ID group. Neutralization titers in the ID-IM group were significantly higher than in the IM-ID group at this time point ($p = 0.02$).

Six months after booster vaccination, all 27 remaining participants had detectable antibody levels, and anti-S1 GMCs were significantly higher for the ID-ID group compared with the IM-ID group ($p = 0.045$). Neutralization of GMTs 6 months after booster were lower for IM-ID group compared with the ID-IM group ($p = 0.04$) and the ID-ID group ($p = 0.02$).

Cellular immunogenicity

The frequencies of spike-specific CD4+ and CD8+ T-cell responses, and B-cell responses before and after booster were comparable between the ID-ID, the IM-IM, and the ID-IM groups (Supplements 4; Fig. S1 for T-cells and Supplements 5; Fig. S2 for B-cells). Percentages of IgG positive SARS-CoV-2 specific B-cells correlated with the anti-S1 IgG antibody titers before booster, whereas no correlation was found 28 days after boosting (Fig. S2 [C]).

Safety and tolerability

No acute or serious adverse reactions and no grade 4 AEs occurred after vaccine administration. Mild and moderate pain at the injection site was the most prevalent AE (Fig. 3). Local muscle stiffness was more severe and more prevalent in IM boosted groups whereas itch at the injection site did occur more in ID boosted groups. Systemic AEs were more prevalent in IM boosted groups. This was especially true for nausea and vomiting, headache, chills, and fever.

One of the participants in the ID-IM group developed hyperpigmentation on her left hand and arm and face 2 days after the IM booster (Supplements 3; Fig. S3), which fully resolved within a week. Relatedness with vaccine administration was unclear.

Discussion

In this study, we compared the safety, tolerability, and immunogenicity of a fractional ID booster dose (20 μg mRNA-1273 COVID-19 vaccine) to the standard of care (50 μg IM dose), in both ID and IM primed, COVID-19 naive healthy persons. Fractional ID boosting was safe and well tolerated, with fewer systemic AEs compared with IM boosting. Although regimens that contained one or two fractional ID vaccine doses exhibit slightly lower immunogenicity, all participants had anti-S1 IgG concentrations >300 BAU/L, which has, been previously associated with 90% (77%–94%) protective efficacy against SARS-CoV-2 infection [11].

Other studies with ID boosting of COVID-19 vaccines have been performed [12–18], but to our knowledge, this is the first to assess an ID primary-booster regimen consisting solely of mRNA COVID-19 vaccines. Moreover, it is the first to evaluate the booster response in individuals who have received ID vaccinations as their primary series. We demonstrate that these ID-primed individuals reached high antibody concentrations and that their fold change in SARS-CoV-2 spike-specific B-cells did not differ compared with the controls, which suggest a good memory response. This is an important finding for future pandemics as in the acute stages of an epidemic, rapidly immunizing a larger number of people can yield greater benefits in preventing mortality than inducing higher antibody concentrations in a smaller group [19,20]. The excellent boost ability of individuals primed with a fractional ID dose, emphasizes the need to incorporate fractional dosing regimens early in the clinical development of future mRNA vaccines to improve vaccine availability and pandemic preparedness [21].

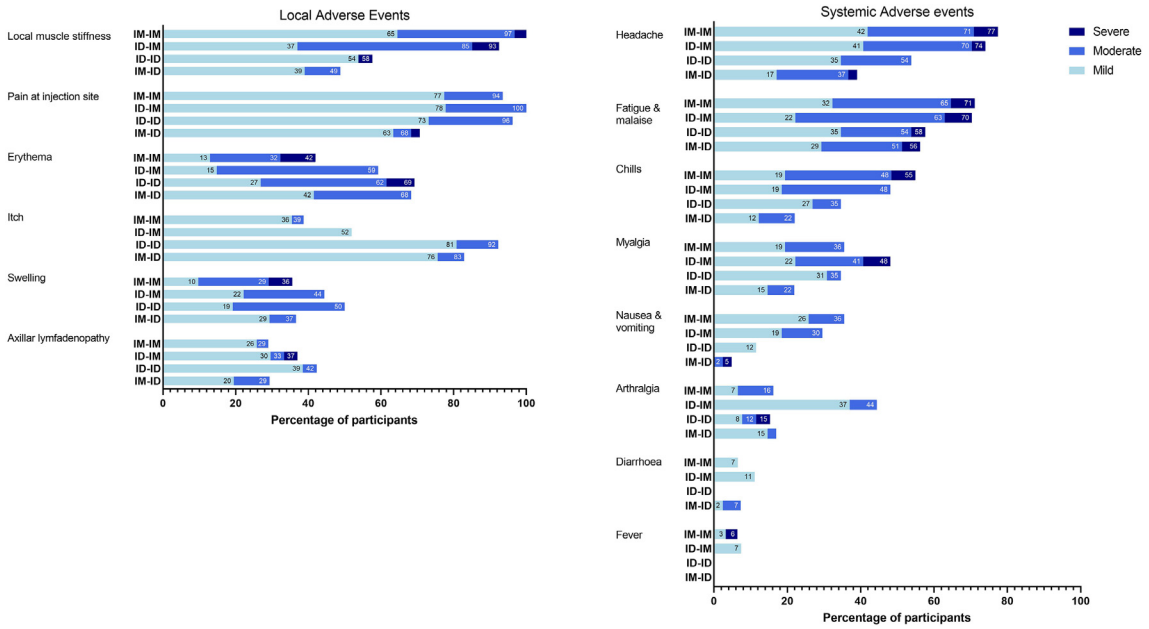

Fig. 3. Local and systemic adverse events after booster vaccination. Solicited adverse events related to vaccination reported for 28 days following administration. IM-IM stands for IM primary series and IM booster, ID-IM stands for ID primary series and IM booster, etc. ID, intradermal; IM, intramuscular.

Participants that received an ID booster reported less systemic AEs than IM boosted participants monitored in the first 2 weeks after the booster, which is in accordance with other studies assessing ID boosting with COVID-19 vaccines [12–14,17,18]. When recruiting the participants for the IM-ID group, we noted increased interest among individuals hesitant to receive another full dose. Although there is a multitude of reasons why people are reluctant to getting a COVID-19 vaccination, an important concern is side effects [22–26]. Given its favourable systemic AE profile compared with IM vaccination, ID vaccination may thus be a method to decrease vaccine hesitancy.

This study has some limitations. First, the findings in a relatively young and healthy population may not apply to older populations or those with co-morbidities, necessitating further study in older persons. In addition, the IM-ID group was recruited from the general population, with nearly 90% having received BNT162b2 as their primary series, which was the preferred vaccine for adults in The Netherlands. This disparity hampers direct comparison with the other groups and may also explain the observed lower binding and neutralizing antibody responses. Previous research shows that on average, a BNT162-mRNA-1273 prime-booster combination leads to circa 15% lower antibody concentrations and circa 30% lower neutralizing antibody titers compared with a prime-booster regimen solely comprising mRNA-1273 [27]. Finally, the high exclusion rate during the study due to COVID-19 has led to relatively small groups that may not have sufficient power to identify subtle differences in immunogenicity or side effects. This factor also limits the ability to draw conclusions on long-term immunogenicity because a rather small number of participants remained in the study up to 6 months post-booster. Exclusions due to COVID-19 may also have introduced a survival bias.

In conclusion, we have demonstrated that a fractional ID booster of the mRNA-1273 vaccine elicits a robust immune response, which supports ID administration as a dose-sparing strategy for mRNA vaccines in a future epidemic or when a new more virulent variant of concern arises.

Author contributions

AHER is the principal investigator. LGV and AHER designed the study. FRR advised on the design of the study. GVTR, MLMP, CPr, JJJ, JPRK, and OACL were responsible for the site work including recruitment, follow-up, and data collection. RSvB, GdH, and MKu, generated binding antibody data. MKi, SKM, and HLMdG generated the neutralizing antibody data. SPJ, MHMH, CRP, and WH generated the data regarding the B-cell and T-cell analysis. GVTR, WH, and CRP analysed the data. GVTR, AHER, and LGV wrote the manuscript. MLMP, CP, JJJ, HLMdG, CRP, WH, JPRK, OACL, MKu, SKM, RSvB, GdH, MHMH, SPJ, MCWF, MKi, FRR, and MR revised the manuscript.

Transparency declaration

All authors declare no conflict of interest. The trial was funded by the Bill and Melinda Gates Foundation. The supply of the Bellamu 1.4 mm microneedle was done by U-Needle.

Data availability

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.03.028.

References

[1] Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis 2022;22:1293–302. https://doi:10.1016/S1473-3099(22)00320-6.

[2] El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385:1774–85. https://doi:10.1056/NEJMoa2113017.

[3] Chu L, Vrbicky K, Montefiori D, Huang W, Nestorova B, Chang Y, et al. Immune response to SARS-CoV-2 after a booster of mRNA-1273: an open-label phase 2 trial. Nat Med 2022;28:104249. https://doi:10.1038/s41591-022-01739-w.

[4] Privor-Dumm L, Excler JL, Gilbert S, Abdool Karim SS, Hotez PJ, Thompson D, et al. Vaccine access, equity and justice: COVID-19 vaccines and vaccination. BMJ Glob Health 2023;8:e011881. https://doi:10.1136/bmjgh-2023-011881.

[5] Mungmunpuntipantip R, Wiwanitkit V. Cost-utility-safety analysis of alternative intradermal versus classical intramuscular COVID-19 vaccination. Int J Physiol Pathophysiol Pharmacol 2022;14:129–33.

[6] Solis Arce JS, Warren SS, Meriggi NF, Scacco A, McMurry N, Voors M, et al. COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries. Nat Med 2021;27:1385–94. https://doi:10.1038/s41591-021-01454-y.

[7] Dube E, MacDonald NE. COVID-19 vaccine hesitancy. Nat Rev Nephrol 2022;18:409–10. https://doi:10.1038/s41581-022-00571-2.

[8] Roozen GVT, Prins MLM, van Binnendijk R, den Hartog G, Kuiper VP, Prins C, et al. Safety and immunogenicity of intradermal fractional dose administration of the mRNA-1273 vaccine: a proof-of-concept study. Ann Intern Med 2022;175:1771–4. https://doi:10.7326/M22-2089.

[9] Prins MLM, Roozen GVT, Pothast CR, Huisman W, van Binnendijk R, den Hartog G, et al. Immunogenicity and reactogenicity of intradermal mRNA-1273 SARS-CoV-2 vaccination: a non-inferiority, randomized-controlled trial. npj Vaccines 2024;9:1. https://doi:10.1038/s41541-023-00785-w.

[10] Bewley KR, Coombes NS, Gagnon L, McInroy L, Baker N, Shaik I, et al. Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays. Nat Protoc 2021;16:3114–40. https://doi:10.1038/s41596-021-00536-y.

[11] Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science 2022;375:43–50. https://doi:10.1126/science.abm3425.

[12] Intapiboon P, Seepathomnarong P, Ongarj J, Surasombatpattana S, Uppanisakorn S, Mahasirimongkol S, et al. Immunogenicity and safety of an intradermal BNT162b2 mRNA vaccine booster after two doses of inactivated SARS-CoV-2 vaccine in healthy population. Vaccines-Basel. 2021;9. https://doi:10.3390/vaccines9121375.

[13] Assantachai P, Niyomnaitham S, Chatthanawaree W, Intalapaporn S, Muangpaisan W, Phannarus H, et al. Immunogenicity and reactogenicity of messenger RNA Coronavirus Disease 2019 vaccine booster administered by intradermal or intramuscular route in Thai Older adults. J Infect Dis 2023;228:868–77. https://doi.org/10.1093/infdis/jiad133.

[14] Nantanee R, Aikphaibul P, Jaru-Ampornpan P, Sodsai P, Himananto O, Theerawit T, et al. Immunogenicity and reactogenicity after booster dose with AZD1222 via intradermal route among adult who had received CoronaVac. Vaccine 2022;40:3320–9. https://doi:10.1016/j.vaccine.2022.04.067.

[15] Niyomnaitham S, Chatsiricharoenkul S, Toh ZQ, Senawong S, Pheerapanyawaranun C, Phumiamorn S, et al. Evaluation of the safety and immunogenicity of fractional intradermal COVID-19 vaccines as a booster: a pilot study. Vaccines (Basel) 2022;10. https://doi:10.3390/vaccines10091497.

[16] Temtanakitpaisan Y, Saengnipanthkul S, Sarakosol N, Maskasame S, Mongkon S, Buranrat B, et al. Reactogenicity and immunogenicity of the intradermal administration of BNT162b2 mRNA vaccine in healthy adults who were primed with an inactivated SARS-CoV-2 vaccine. Vaccine X 2022;12:100242. https://doi:10.1016/j.jvacx.2022.100242.

[17] Tawinprai K, Siripongboonsitti T, Porntharukchareon T, Wittayasak K, Thonwirak N, Soonklang K, et al. Immunogenicity and safety of an intradermal fractional third dose of ChAdOx1 nCoV-19/AZD1222 vaccine compared with those of a standard intramuscular third dose in volunteers who previously received two doses of CoronaVac: a randomized controlled trial. Vaccine 2022;40:1761–7. https://doi:10.1016/j.vaccine.2022.02.019.

[18] Pinpathomrat N, Intapiboon P, Seepathomnarong P, Ongarj J, Sophonmanee R, Hengprakop J, et al. Immunogenicity and safety of an intradermal ChAdOx1 nCoV-19 boost in a healthy population. NPJ Vaccines 2022;7:52. https://doi:10.1038/s41541-022-00475-z.

[19] Wiecek W, Ahuja A, Chaudhuri E, Kremer M, Simoes Gomes A, Snyder CM, et al. Testing fractional doses of COVID-19 vaccines. Proc Natl Acad Sci U S A 2022;119. https://doi:10.1073/pnas.2116932119.

[20] Cowling BJ, Lim WW, Cobey S. Fractionation of COVID-19 vaccine doses could extend limited supplies and reduce mortality. Nat Med 2021;27:1321–3. https://doi:10.1038/s41591-021-01440-4.

[21] Roozen GVT, Roukens AHE, Roestenberg M. COVID-19 vaccine dose sparing: strategies to improve vaccine equity and pandemic preparedness. Lancet Glob Health 2022;10:e570–3. https://doi:10.1016/S2214-109X(22)00075-4.

[22] Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health 2021;194:245–51. https://doi:10.1016/j.puhe.2021.02.025.

[23] Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021;397:1023–34. https://doi:10.1016/S0140-6736(21)00306-8.

[24] Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrachi M, Zigron A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol 2020;35:775–9. https://doi:10.1007/s10654-020-00671-y.

[25] Kreps S, Prasad S, Brownstein JS, Hswen Y, Garibaldi BT, Zhang B, et al. Factors associated with US adults' likelihood of accepting COVID-19 vaccination. JAMA Netw Open 2020;3:e2025594. https://doi:10.1001/jamanetworkopen.2020.25594.

[26] Euser S, Kroese FM, Derks M, de Bruin M. Understanding COVID-19 vaccination willingness among youth: a survey study in The Netherlands. Vaccine 2022;40:833–6. https://doi:10.1016/j.vaccine.2021.12.062.

[27] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022;386:1046–57. https://doi:10.1056/NEJMoa2116414.