The sharpest tool in the shed: question-based clinical development of vaccines to address global health priorities

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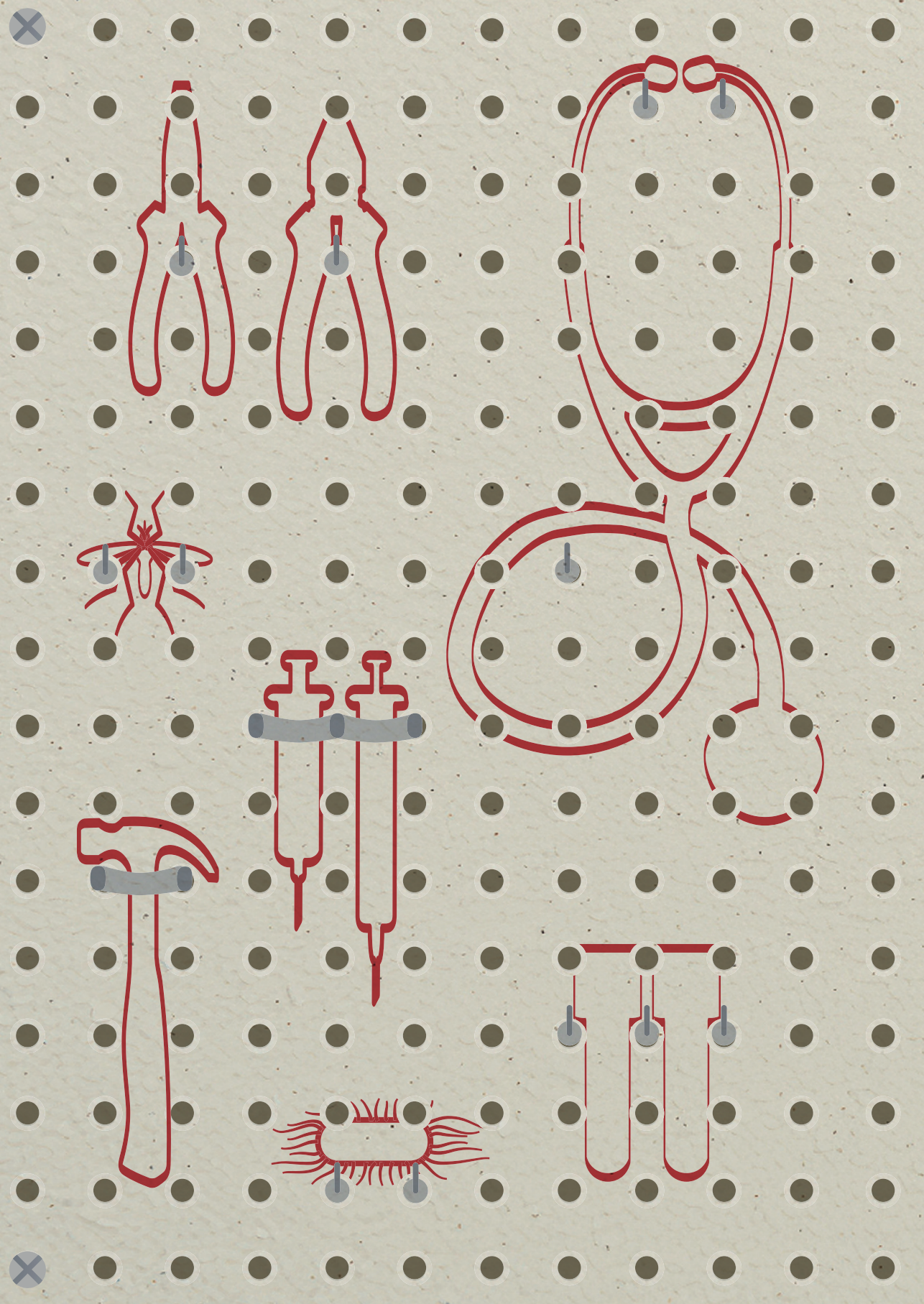

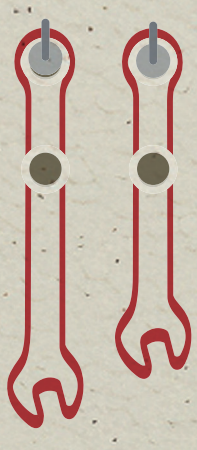

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Safety and Immunogenicity of Intradermal Fractional Dose Administration of the mRNA-1273 Vaccine: A Proof-of-Concept Study

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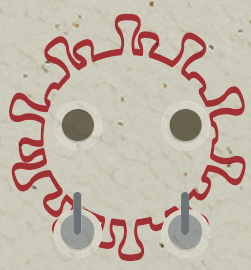

Abstract

Background

There is an urgent need for fair and equitable access to safe and effective COVID-19 vaccines. Intradermal (ID) delivery is a dose-sparing technique that can be used to immunize more people with the same limited vaccine stockpile.[1] The papillary dermis contains a higher density of antigen-presenting cells than muscle tissue; therefore, ID delivery of a fractional vaccine dose into this skin layer can be as effective as intramuscular (IM) administration of the standard dose.[2]

Objective

To assess the safety, tolerability, and immunogenicity of ID fractional dose administration of the mRNA-1273 (Moderna Spikevax®) vaccine as a potential dose-sparing strategy.

Methods and findings

We conducted a proof-of-concept, dose-escalation, open-label, randomized controlled trial in a tertiary medical center in Leiden, the Netherlands. Participants were recruited in April and May 2021 from a database of people who had previously shown interest in participating in upcoming COVID-19 vaccine trials. Eligible participants were healthy adults aged 18 to 30 years with no history of COVID-19. At every visit, participants were screened for past SARS-CoV-2 infection via serologic testing and polymerase chain reaction and were excluded from further participation if results were positive.

In part one, 10 participants received 10 μg of mRNA-1273 vaccine (0.05 mL [1/10th of the standard dose]) intradermally at days 1 and 29. In part two, 30 participants were randomly assigned in a 1:1 ratio to receive a 20-μg dose of mRNA-1273 (0.01 mL [1/5th of the standard dose]) either intradermally or intramuscularly at days 1 and 29. All ID vaccinations were administered using a Becton Dickinson U-100 Micro-Fine insulin syringe with an integrated 29G needle.

Diaries were used to collect self-reported local and systemic adverse events for 14 days after every vaccination (Supplement Sections A and B). Concentrations of IgG- and IgA-binding antibodies against SARS-CoV-2 spike S1 and receptor-binding domain (RBD) and virus neutralization titers were measured at day 36, day 43, and month 7 (Fig. 1).

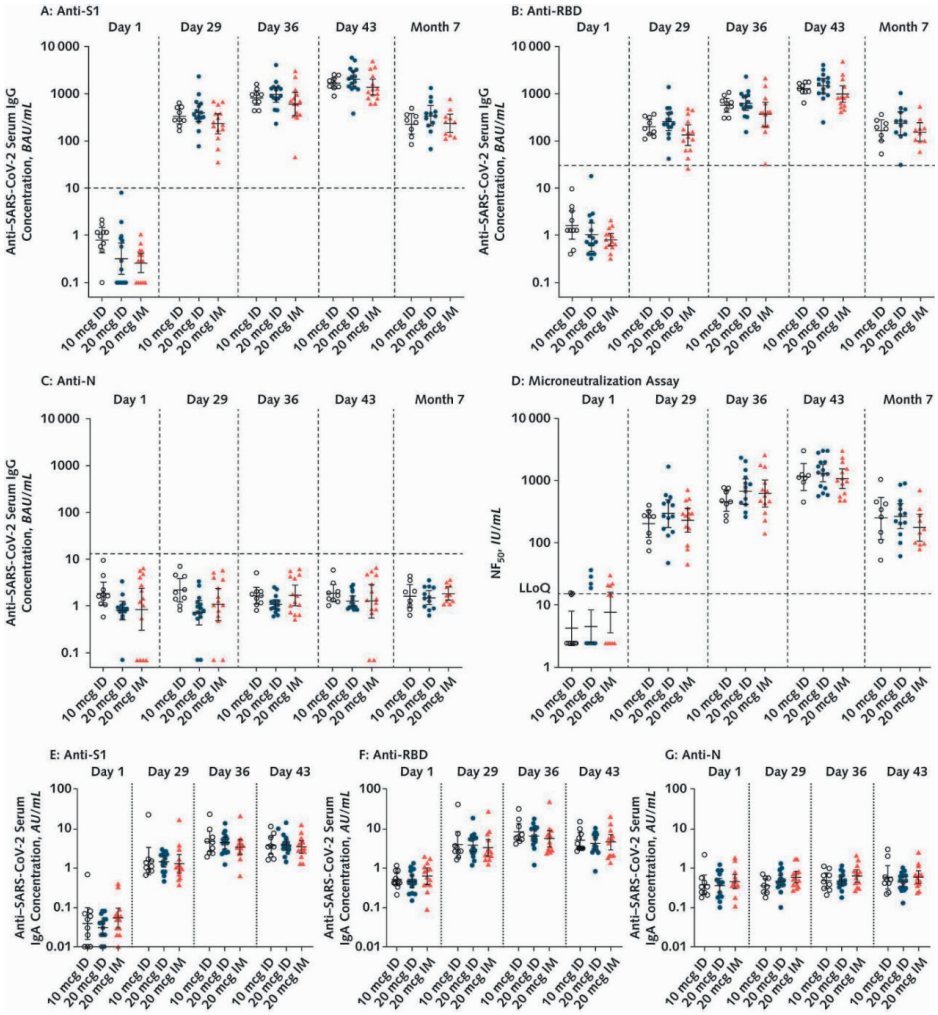

Figure 1. Serum anti–SARS-CoV-2 antibody concentrations

A, B, and C. Anti–SARS-CoV-2 serum IgG concentrations for anti-S1 (A), anti-RBD (B), and anti-N (C), assessed by bead-based immunoassay and reported in BAUs per milliliter. Data at day 1 (before receipt of the first vaccination), day 29 (before receipt of the second vaccination), day 36 (1 week after receipt of the second vaccination), day 43 (2 weeks after receipt of the second vaccination), and month 7 (half a year after receipt of the second vaccination) are reported for the 10- µg ID dose, the 20- µg ID dose, and the 20-µg IM dose. Horizontal dashed lines represent the cutoff for seropositivity (10 BAU/mL for anti-S1, 30 BAU/mL for anti-RBD, and 14 BAU/mL for anti-N). **D.** Wild-type SARS-CoV-2 (Wuhan strain) microneutralization assay. NF_{50} is reported in international units per milliliter. The conversion rate from titer to international units was 1 / 4.064. The horizontal dashed line represents the LLoQ at 15 IU/mL (titer of 62). Values with an NF_{50} below the LLoQ were set to 2 IU/mL (titer of 10). Values above the upper limit of quantitation (n=2 in the 20-µg ID group and 1 in the 20-µg IM group at day 43) were set to 2953 IU/mL (titer of 12 000). **E, F, and G.** Anti–SARS-CoV-2 serum IgA concentrations for anti-S1 (E), anti-RBD (F), and anti-N (G), assessed by bead-based immunoassay and reported in AUs per milliliter. Data at days 1, 29,

36, and 43 are reported for the 10-µg ID dose, the 20-µg ID dose, and the 20-µg IM dose.
Each symbol represents a sample from an individual participant at a certain time point. Error bars represent geometric mean concentrations with 95% confidence intervals.
Anti-N = anti-nucleocapsid; anti-RBD = anti–receptor-binding domain; anti-S1 = anti–spike S1; AU = arbitrary unit; BAU = binding antibody unit; ID = intradermal; IM = intramuscular; LLoQ = lower limit of quantitation; NF_{50} = neutralizing factor at 50% normalized against an international reference serum.

Thirty-eight of 40 participants remained in the study through day 43, and 31 remained through month 7 (Supplement Section C). The main reasons for premature study termination were COVID-19 or receipt of an additional vaccination elsewhere (Supplement Section C).

The average wheal sizes after the first and second 10-µg ID vaccinations were 8 mm (SD: 1) and 7 mm (SD: 1), respectively. For the 20-µg dose, the average wheal sizes were 8 mm (SD: 1) and 10 mm (SD: 1), respectively, for the first and second vaccinations.

No serious adverse events occurred. The most commonly reported adverse events were short-lasting and consisted of mild pain, itching, erythema, and swelling at the injection site (Table 1, Supplement Sections E and F). One participant in the 20-µg ID group reported severe erythema of more than 10 cm in diameter and moderate swelling. This lasted 6 days and was self-limiting and well tolerated (Supplement Section G).

Table 1. Local and systemic adverse events related to vaccination

Event	Vaccination 1			Vaccination 2		
	10 µg ID (n=10)	20 µg ID (n=15)	20 µg IM (n=15)	10 µg ID (n=9)	20 µg ID (n=15)	20 µg IM (n=14)
Local adverse events						
Mild hyperpigmentation	1 (10.0)	2 (13.3)	0 (0.0)	2 (22.2)	1 (6.7)	0 (0.0)
Mild local muscle stiffness	4 (40.0)	4 (26.7)	12 (80.0)	0 (0.0)	6 (40.0)	9 (64.3)
Moderate local muscle stiffness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Mild itching at injection site	2 (20.0)	8 (80.0)	0 (0.0)	3 (33.3)	10 (66.7)	0 (0.0)
Mild pain at injection site	7 (70.0)	11 (73.3)	12 (80.0)	6 (66.7)	11 (73.3)	9 (64.3)
Moderate pain at injection site	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)
Mild swelling	1 (10.0)	5 (33.3)	1 (6.7)	1 (11.1)	2 (13.3)	2 (14.3)
Moderate swelling	0 (0.0)	3 (20.0)	0 (0.0)	0 (0.0)	3 (20.0)	0 (0.0)
Mild erythema	3 (30.0)	10 (60.0)	0 (0.0)	5 (55.6)	3 (20.0)	2 (14.3)
Moderate erythema	0 (0.0)	2 (13.3)	1 (6.7)	0 (0.0)	10 (66.7)	0 (0.0)
Severe erythema	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1. Local and systemic adverse events related to vaccination (continued)

Event	Vaccination 1			Vaccination 2		
	10 µg ID (n=10)	20 µg ID (n=15)	20 µg IM (n=15)	10 µg ID (n=9)	20 µg ID (n=15)	20 µg IM (n=14)
Mild axillar lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)
Systemic adverse events						
Mild nausea and vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Mild myalgia	0 (0.0)	2 (13.3)	2 (13.3)	0 (0.0)	3 (20.0)	2 (14.3)
Moderate myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (14.3)
Mild headache	0 (0.0)	3 (20.0)	5 (33.3)	0 (0.0)	3 (20.0)	3 (21.4)
Moderate headache	1 (10.0)	1 (6.7)	0 (0.0)	0 (0.0)	2 (13.3)	2 (13.4)
Mild diarrhea	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mild chills	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	1 (6.7)	1 (7.1)
Moderate chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Mild fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild fatigue and malaise	0 (0.0)	5 (20.0)	5 (20.0)	0 (0.0)	5 (20.0)	1 (7.1)
Moderate fatigue and malaise	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	5 (20.0)	3 (21.4)
Mild arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)

Data are numbers (percentages) of participants who experienced the adverse event. All adverse events possibly, probably, or definitely related to the vaccine in the 28 days after administration are reported. Grade 4 (potentially life-threatening) adverse events did not occur.
ID = intradermal; IM = intramuscular.

All participants showed robust antibody responses at day 43 that were still detectable at month 7. The binding antibody responses for anti-S1 IgG, anti-RBD IgG, and neutralizing antibodies showed similar patterns (Fig. 1 A-D, Supplement Sections H and I). At day 43, geometric mean concentrations of neutralizing antibody were 1115 IU/mL (95% CI: 669 to 1858 IU/mL) for the 10-µg group, 1300 IU/mL (CI: 941 to 1796 IU/mL) for the 20-µg ID group, and 1052 IU/mL (CI: 733 to 1509 IU/mL) for the 20-µg IM group. The IgA responses were similar between groups, independent of dose or method of administration (Fig. 1E-G, Supplement Section J).

Discussion

Intradermal delivery of a two-dose regimen of mRNA-1273 vaccine at 10 or 20 µg was safe, was well tolerated, and induced durable antibody responses.

This study has two limitations. First, although the IgG, IgA, and neutralizing antibody concentrations were highest in the 20-µg ID group, the sample size did not allow demonstration of statistically significant superiority of ID over IM injection. Second, only healthy volunteers aged 18 to 30 years were included, so the findings on safety and immunogenicity may not apply to the general population.

Although true vaccine efficacy depends on several factors, antibody concentrations measured after fractional dose vaccination in our trial are within the ranges that correlated with high levels of protection in the mRNA-1273 Phase III trial.[3] This is especially true for the 20-µg ID group.

In conclusion, the safety and immunogenicity results from this trial strongly support advancement of the investigation of ID vaccination with the mRNA-1273 vaccine.

Acknowledgment

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Supplemental material

Supplemental material is available online: https://www.acpjournals.org/doi/10.7326/M22-2089

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