Diagnosis, prevention and treatment of acute respiratory infections

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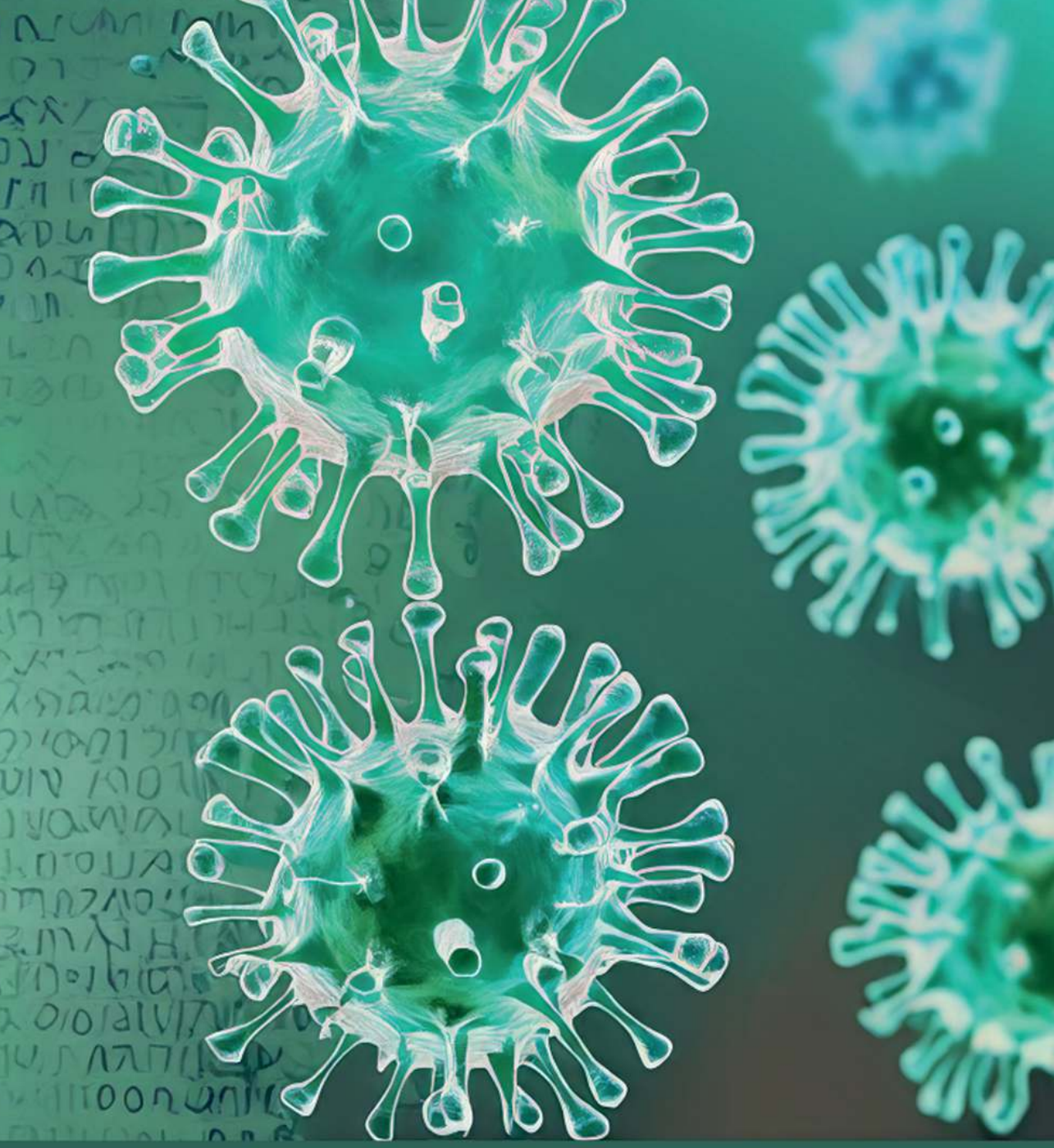

Chapter 4

Safety and Immunogenicity of Intradermal Administration of Fractional Doses of the mRNA-1273 Vaccine: a Proof-of-Concept study

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Ann Intern Med. 2022 Dec; 175 (12): 1771-1774

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) 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 mcg of mRNA-1273 vaccine (0.05 mL [one tenth 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 mcg dose of mRNA-1273 (0.01 mL [one fifth 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, available at Annals.org). 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 (figure).

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

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

Figure. Serum anti- SARS-COV-2 antibody concentration

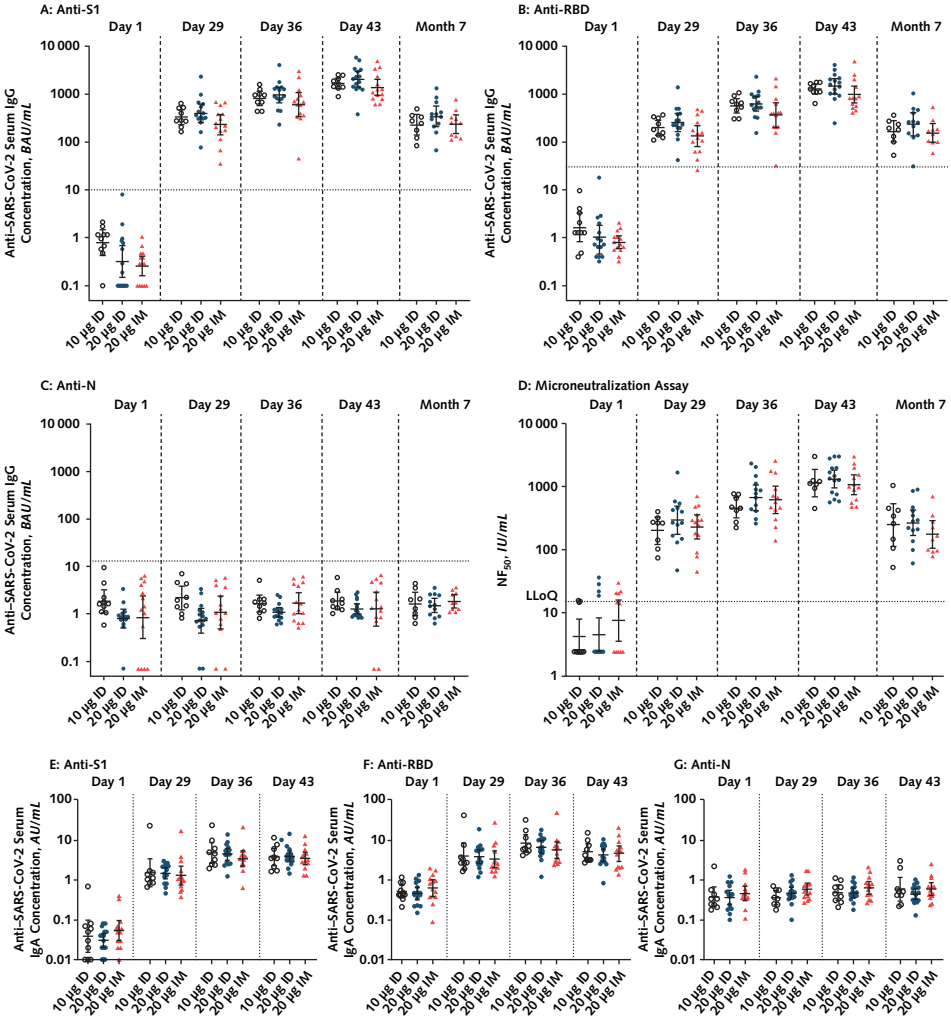

Table. Local and systemic adverse events related to vaccination*

Event	Vaccination 1			Vaccination 2		
	10 mcg ID (n = 10)	20 mcg ID (n = 15)	20 mcg IM (n = 15)	10 mcg ID (n = 9)	20 mcg ID (n = 15)	20 mcg 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)
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)

Table. Local and systemic adverse events related to vaccination*

Event	Vaccination 1			Vaccination 2		
	10 mcg ID (n = 10)	20 mcg ID (n = 15)	20 mcg IM (n = 15)	10 mcg ID (n = 9)	20 mcg ID (n = 15)	20 mcg IM (n = 14)
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)

ID = intradermal; IM = intramuscular.
** 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.*

at the injection site (table; supplement sections E and F, available at Annals.org). One participant in the 20 mcg 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, available at Annals.org).

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 (figure, A to D; supplement sections H and I, available at Annals.org). At day 43, geometric mean concentrations of neutralizing antibody were 1115 IU/mL (95% CI, 669 to 1858 IU/mL) for the 10 mcg group, 1300 IU/mL (CI, 941 to 1796 IU/mL) for the 20 mcg ID group, and 1052 IU/mL (CI, 733 to 1509 IU/mL) for the 20 mcg IM group. The IgA responses were similar between groups, independent of dose or method of administration (figure, E to G; supplement section J, available at Annals.org).

Discussion

Intradermal delivery of a 2-dose regimen of mRNA-1273 vaccine at 10 or 20 mcg was safe, was well tolerated, and induced durable antibody responses.

This study has 2 limitations. First, although the IgG, IgA, and neutralizing antibody concentrations were highest in the 20 mcg 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 3 trial.[3] This is especially true for the 20 mcg 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.

Note
The protocol (available at Annals.org) was approved by the Medical Ethical Committee Leiden, Den Haag, Delft (NL 76702. 058.21).

Acknowledgment
The authors thank all of the trial participants for their contributions and the members of the data safety monitoring board for their invaluable advice. They also thank all of the people who donated to the crowdfunding that supported the trial. The authors acknowledge the support of CEPI and the participation of Viroclinics for performance of the neutralization assay. Finally, the authors thank the Centre for Human Drug Research for its collaboration and its assistance in the recruitment of participants.

Financial Support
The trial was supported by crowdfunding (Wake Up to Corona) set up by the Leiden University Fund. The funder had no influence on the design or conduct of the trial and did not influence the manuscript.

Disclosures
Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-2089.

Data Sharing Statement
The following data and supporting documents will be made available with publication: deidentified participant data and informed consent form (e-mail, a.h.e.roukens@lumc.nl). These will be made available to researchers whose proposed use of the data has been approved, for any purpose, with a signed data access agreement (restrictions: none)

Supplemental Material
All mentioned supplementary figures and tables in this chapter can be found by scanning this QR code.

References

1. 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-e573. [PMID: 35303466] doi:10.1016/S2214-109X (22)00075-4
2. Nicolas JF, Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. Expert Rev Vaccines. 2008;7:1201-14. [PMID: 18844594] doi:10.1586/14760584.7.8.1201
3. Gilbert PB, Montefiori DC, McDermott AB, et al. Immune Assays Team. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science. 2022;375:43-50. [PMID: 34812653] doi:10.1126/ science.abm3425