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

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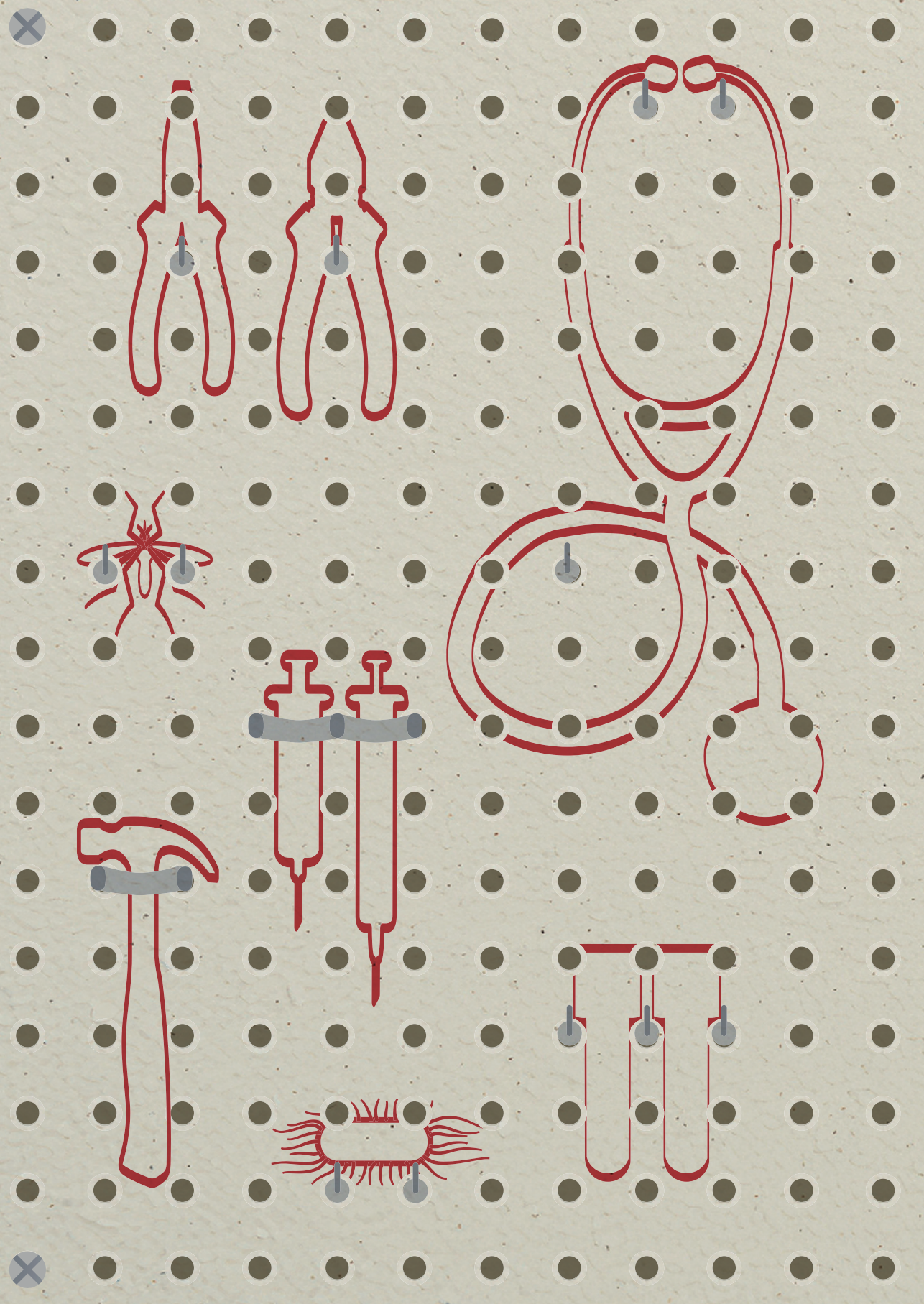

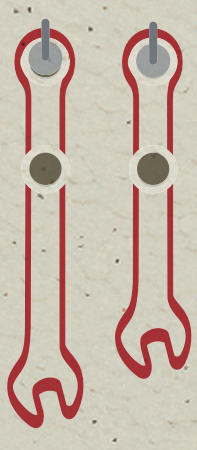

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Intradermal Fractional Dose Vaccination as a Method to Vaccinate Individuals with Suspected Allergy to mRNA COVID-19 Vaccines

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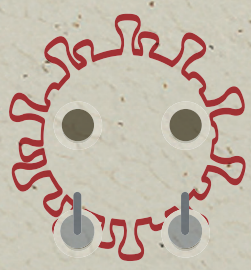

Abstract

Suspected allergic reactions after mRNA COVID-19 vaccination withheld multiple individuals from getting fully vaccinated during the pandemic. We vaccinated adults who had experienced possible allergic symptoms after their first intramuscular dose of a COVID-19 mRNA vaccine with a 1/5th fractional intradermal test dose of the mRNA-COVID-19 vaccine 1273 (Moderna Spikevax®). No anaphylactic reactions were observed after intradermal vaccination (n=56). Serum anti-S1 IgG concentrations were measured using a bead-based multiplex assay four weeks after vaccinations. Antibody concentrations were compared with a previously collected nationwide cohort that had received two intramuscular doses of mRNA-1273. Antibody responses in all subjects tested (n=47) were comparable to standard of care intramuscular dosing. Fractional intradermal dosing of mRNA COVID-19 vaccines may provide a pragmatic solution that is safe, time efficient compared to skin prick testing, dose sparing and immunogenic in individuals with suspected vaccine allergy.

Introduction

Even though severe allergic reactions to mRNA COVID-19 vaccines are rare[1], the global immunization campaigns in the COVID-19 pandemic, with around 1.5 billion mRNA COVID-19 vaccines administered in the European Union and United States alone,[2, 3] inherently led to a large number of people with suspected allergic reactions to the first dose. This stressful experience made these persons anxious to receive any further vaccinations.[4] In some cases, physicians working at these vaccination centers were also hesitant to further vaccinate these individuals.[4]

Anaphylaxis is an acute mast-cell mediated severe hypersensitivity reaction with multi-organ involvement that can present as a life-threatening respiratory impairment or shock.[5] Anaphylaxis is very rare after vaccination with mRNA COVID-19; only occurring about 1.3 to 17 times per million doses.[1] Even in persons with an immediate allergic reaction of any severity to a first mRNA COVID-19 vaccine, the absolute risk of a second-dose severe reaction to the same mRNA COVID-19 vaccine is as low as 0.16% (95% confidence intervals: 0.01%-2.94%).[1]

The European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology recommended a skin prick test for persons with a generalized immediate reaction to any mRNA vaccine,[6] even though the sensitivity of this method (using the vaccine as the skin test reagent) is very low (0.2, 0.01–0.52).[7] For this group graded dosing has been proposed, i.e. splitting the vaccine dose in multiple (equal or increasing) fractional doses that are administered at intervals (usually around 30 to 60 minutes),[6, 8] but there is no data supporting whether this intervention will lead to fewer allergic reactions.

Since the added value of the skin prick test and graded dosing were unclear and since these methods were practically unfeasible in times of a pandemic due to their time consuming nature, we chose a more pragmatic approach of fractional dosing followed by an observation period. During the first rounds of COVID-19 vaccinations in the Netherlands, we have administered a fractional dose (20 µg, equal to 1/5th of the standard 100 µg dose) of the mRNA-1273 COVID-19 vaccine (Moderna Spikevax®) in individuals with suspected allergic responses after their first COVID-19 vaccination. We hypothesized that the intradermal (ID) route in patients would be an efficacious immunization method with a reduced potential allergen exposure and concomitant risk. Previously, we have shown that a fractional ID dose induced immune responses that are comparable to the responses induced by a full dose administered through the intramuscular (IM) route in healthy, non-allergic persons.[9-11] In terms of vaccine dose used, fractional ID administration holds the middle between a skin prick test and graded dosing. It can thus be used both as a method to assess hypersensitivity responses in people with alleged allergies and at the same time to encourage hesitant persons to get vaccinated. In the Netherlands, this method is standard practice for yellow fever vaccination of patients traveling to a highly endemic region, who are at risk of hypersensitivity to the vaccine due to a suspected chicken egg allergy.[12, 13]

To assess if the 1/5th fractional ID dose was also sufficient as a means of immunization in this population, we measured antibody responses four weeks after ID vaccination. Here, we report on observed symptoms and immunogenicity associated with an allergic reaction after fractional ID administration.

Methods

This was a retrospective chart review study that was approved by the Institutional Review Board of the Leiden University Medical Center (LUMC) in the Netherlands for observational COVID-19 studies. The information reported here is the result of a retrospective assessment of an off-label vaccination method that was applied ad-hoc to provide patients with a suspected allergy to COVID-19 vaccines with a possibility to get vaccinated rapidly during the pandemic.

From January 2021 to February 2022, adult patients in the region of Leiden, The Hague and Delft in the Netherlands who had a suspected allergic reaction to their first COVID-19 vaccination were referred to the outpatient vaccination clinic of the LUMC. Some patients were referred without previous vaccination because they were hesitant to undergo COVID-19 vaccination due to (suspected) allergic reactions to multiple allergens including PEG in the past. Referrals were made by general practitioners, allergists, and Municipal Health Services. The outpatient vaccination clinic serves as a specialized travel and vaccination clinic and is situated within the tertiary university hospital LUMC.

Referred patients were first contacted by phone by an Infectious Diseases consultant who registered co-morbidities, allergies, medication use, and self-reported symptoms that occurred after the first COVID-19 vaccination in the electronic patient file of the LUMC. If the risk of anaphylaxis was considered high (i.e. if their self-reported symptoms met the SPEAC case definition of anaphylaxis[14]), patients were planned to receive an ID vaccination at the LUMC day unit under close medical supervision with an intravenous drip installed before vaccination to treat anaphylaxis if needed. All other patients were scheduled at the outpatient vaccination clinic. Patients gave consent to use their data for future research. Patients who had typical type 1 allergic symptoms, e.g. urticarial rash or angio-oedema after the first vaccination were advised to take oral antihistamines before their second vaccination at the LUMC.

A 20 µg (0.1 ml) dose of the mRNA-1273 vaccine was administered ID in the deltoid region using a Becton Dickinson U-100 Micro-Fine insulin syringes with integrated 29 G needle as described previously.[9,10] Patients received 0.1 ml 0.9% saline solution in the deltoid region of the contralateral arm as a control. After vaccination, all patients were observed for at least 30 minutes by a nurse with a doctor on site. If, after the observation period, the cutaneous wheal of the ID vaccination was at least twice the size of the ID saline injection, the patient was considered to have a positive skin test.[13] Patients with a negative skin test were offered to receive the remainder of the vaccine dose IM to provide the opportunity to receive the

standard of care regimen. Patients were asked to return to the vaccination clinic four weeks after vaccination for the collection of a blood sample for immunogenicity analysis. SARS-CoV-2-spike-S1 (Wuhan-Hu-1) and nucleocapsid (N)-binding antibodies in serum were measured by a bead-based multiplex immunoassay (MIA) based on Luminex technology as described previously[10] and reported in geometric mean concentrations (GMC) of Binding Antibody Units per mL (BAU/mL). Anti-N IgG concentrations above 14.3 BAU/mL were considered indicative of a convalescent COVID-19 infection.[15] Patients were registered in the national vaccination database as fully vaccinated if they had received two vaccinations and their serum anti-S1 IgG concentration was 300 BAU/ml or higher, corresponding with a vaccine efficacy of about 90% in the mRNA-1273 phase III clinical trial.[16]

The retrospective chart review took place in February 2022, when the electronic patient files from the LUMC outpatient vaccination clinic were reviewed. Firstly, the goal of this study was to evaluate the occurrence and severity of allergic symptoms and/or anaphylaxis[14] after the ID administration of the second mRNA COVID-19 vaccine dose in patients with a suspected allergy based on symptoms they had experienced after receiving their first mRNA COVID-19 vaccination (hypersensitivity analysis). Secondly, this study aimed to determine whether a second fractional ID vaccination with mRNA-1273 induced sufficient humoral immune responses. Therefore, only patients who had received a first vaccination with an mRNA COVID-19 vaccine through the IM route and a fractional ID dose as a second vaccination were included; patients who had received a non-mRNA COVID-19 as their first vaccination, or patients who received their first vaccination through the ID route were excluded. All eligible patients who had their symptoms recorded after the ID vaccination were included in the hypersensitivity assessment. Symptoms experienced by patients after receiving the remainder of the dose IM were not included in the hypersensitivity assessment. All eligible patients from whom a serology sample was taken and who did not receive the remainder of their second dose IM, were included in the immunogenicity assessment. The information collected in the review comprised demographics, co-morbidities, self-reported symptoms after the first full-dose vaccination, symptoms and signs observed by a healthcare worker in the first half hour after the second fractional ID dose and antibody responses one month later.

For comparison of immunogenicity, antibody concentrations were compared with a previously collected cohort of the PIENTER-Corona study. PIENTER-Corona is a nationwide study conducted by the National Institute for Public Health and the Environment including all age groups of the Dutch general population, with serum samples collected at regular time intervals irrespective of the moment of infection or vaccination.[17] For the reference group of this study, all sera from PIENTER-Corona were selected that had been collected from adults vaccinated with two full IM doses of mRNA-1273 between two weeks to ten weeks after their second vaccination.

The PIENTER-Corona study was approved by the medical ethical committee MED-U, Nieuwegein, the Netherlands and registered in the Netherlands Trial Register under number NL8473 (https://onderzoekmetmensen.nl/nl/trial/21435).

Results

Eighty-five records were screened (Fig. 1). Of those, 56 were included in the hypersensitivity assessment and 47 in the immunogenicity assessment.

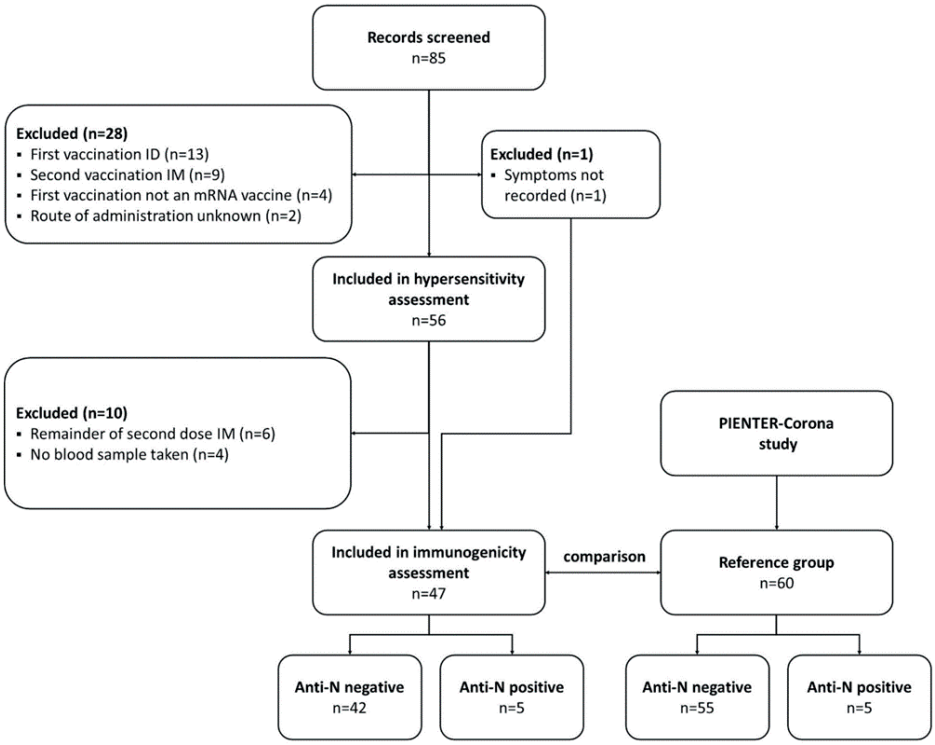

Figure 1. Flowchart of records screened and reasons for in- and exclusion in hypersensitivity assessment and immunogenicity assessment

Patients who received their first vaccination as a full IM dose with a mRNA COVID-19 vaccine and their second dose as fractional ID dose were included. All patients of whom symptoms were recorded after vaccinations were included in hypersensitivity assessment. All patients who had their blood sample taken and had not received the remainder of the second dose IM were included in the immunogenicity assessment. As a comparison, sixty sera were selected from adults in the PIENTER -Corona study that had been collected two to ten weeks after their second vaccination with full dose mRNA-1273 IM. The PIENTER study was a nationwide observational study including all age groups of the Dutch general population. Immunogenicity of patients who had a history of COVID-19 (based on anti-N IgG serology) is reported separately.
Anti-N = anti-nucleocapsid; ID = intradermal; IM = intramuscular.

Two out of 56 (3.6%) patients received their ID vaccination at the LUMC day unit because their self-reported symptoms after their first vaccination satisfied the criteria of an anaphylactic reaction according to the SPEAC case definition.[14] Although a wide variety of symptoms were self-reported after the first vaccination, only a fraction of these were observed after the second vaccination at the LUMC (Table 1). Angioedema, which was the most self-reported symptom after the first vaccination, was not observed after the second vaccination in this cohort. Thirty-four patients (60.7%) had used an oral antihistamine before ID administration of the vaccine. Dizziness or light headedness, localized itch and erythema were the most observed symptoms and signs after the ID vaccination. None of the patients, including the two high-risk patients vaccinated on the day unit, developed severe hypersensitivity reactions or anaphylaxis (according to the SPEAC case definition[14]). Although frequencies were not formally recorded, we noticed that many patients were very anxious before and during the observation period. This was also reflected by the fact that only six patients with a negative skin test accepted the offer of receiving the remaining dose IM. Most patients with a negative skin test rejected this offer because they still feared hypersensitivity reactions if they were to receive the full dose.

The characteristics of the patients included in the immunogenicity assessment were as a group very similar to the selected reference group (in terms of age, sex and time between the second vaccination and sampling) (Table 2). The main difference was that the majority of patients referred to the vaccination clinic had received the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech Comirnaty®) as their first vaccination, together with the fact that the interval between the two vaccinations in the primary series was longer than for the reference group. Co-morbidities related to an atopic constitution such as asthma, hay fever, and drug and food allergies were higher in the patients with suspected vaccine allergies, compared to the reference group.

Anti-spike-S1 IgG concentrations are reported in Fig. 2. All patients vaccinated with a fractional ID dose at had detectable anti-spike-S1 IgG antibodies. On average, patients with a suspected allergy had higher antibody concentrations than the reference group from the general population, but confidence intervals were overlapping. This was also true for patients with a history of COVID-19. There were no significant differences in antibody responses between patients using antihistamines compared to patients not using antihistamines or for patients with positive skin tests compared to patients without positive skin tests (results not shown), but groups were too small to make sound comparisons.

Table 1. Hypersensitivity assessment: symptoms after first and second mRNA COVID-19 vaccination

N=56	First vaccination (standard dose IM) Self-reported	Second vaccination (fractional dose ID) Observed
First vaccination, n (%)		
mRNA-1273	7 (12.5)	56 (100)
BNT162b2	49 (87.5)	0 (0.0)
Symptoms, n (%)		
Loss of consciousness	2 (3.6)	0 (0.0)
Tingling of lips or mouth	2 (3.6)	0 (0.0)
Palpitations	2 (3.6)	1 (1.8)
Vomiting or nausea	3 (5.4)	0 (0.0)
Diarrhea	3 (5.4)	0 (0.0)
Shivering	4 (7.1)	0 (0.0)
Hypotension	4 (7.1)	0 (0.0)
Fever	4 (7.1)	0 (0.0)
Stridor	5 (8.9)	0 (0.0)
Headache	10 (17.9)	4 (7.1)
Dizziness or light headedness	11 (19.6)	9 (16.1)
Urticaria	14 (25.0)	2 (3.6)
Bronchospasm	19 (33.9)	3 (5.4)
Itch (other than vaccination site)	20 (35.7)	10 (17.9)
Erythema (other than vaccination site)	20 (35.7)	14 (25.0)
Angioedema	33 (58.9)	0 (0.0)
Positive skin test, n (%)		
Yes	N/A	31 (55.4)
No	N/A	18 (32.1)
Missing	N/A	7 (12.5)

Symptoms after first vaccination (full dose IM vaccination with mRNA-1273 or BNT162b2 at general practitioner or municipal public health service) are self-reported. Symptoms after second vaccination ($1/5^{th}$ fractional ID dose of mRNA-1273) are from observation by a health care worker. Patients received 0.1 ml 0.9% saline solution in the deltoid region of the contralateral arm as a control. The skin test was positive if the cutaneous wheal of the ID vaccination was at least twice the size of the ID saline injection after 30 minutes.
ID = intradermal; IM = intramuscular.

Table 2. Characteristics of patients in immunogenicity assessment

	LUMC 20 µg ID (n=47)	PIENTER-Corona 100 µg IM (n=60)
Mean age, years (SD)	46 (16)	46 (12)
Sex, n (%)		
Male	2 (4.3)	8 (13.3)
Female	45 (95.7)	52 (86.7)
First vaccination, n (%)		
mRNA-1273	7 (14.9)	60 (100)
BNT162b2	40 (85.1)	0 (0.0)
Vaccination interval between 1st and 2nd dose, days (SD)	143 (68)	33 (12)
Time since 2nd dose, days (SD)	28 (7)	38 (14)
Co-morbidities, n (%)		
Diabetes	1 (2.1)	1 (1.7)
Hypertension	5 (10.6)	8 (13.3)
Hay fever	13 (27.7)	5 (8.3)
Asthma	15 (31.9)	3 (5.0)
Food allergy	23 (48.9)	0 (0.0)
Drug allergy	31 (66.0)	2 (3.3)

Patients received a full IM dose of mRNA-1273 or BNT162b2 as a first vaccination and a second vaccination with a 20 µg ID dose with mRNA-1273 (LUMC cohort). The reference group received the standard regimen with two IM vaccinations with 100 µg mRNA-1273 (PIENTER-Corona cohort). Co-morbidities, including allergies, are self-reported.
ID = intradermal; IM = intramuscular; SD = standard deviation.

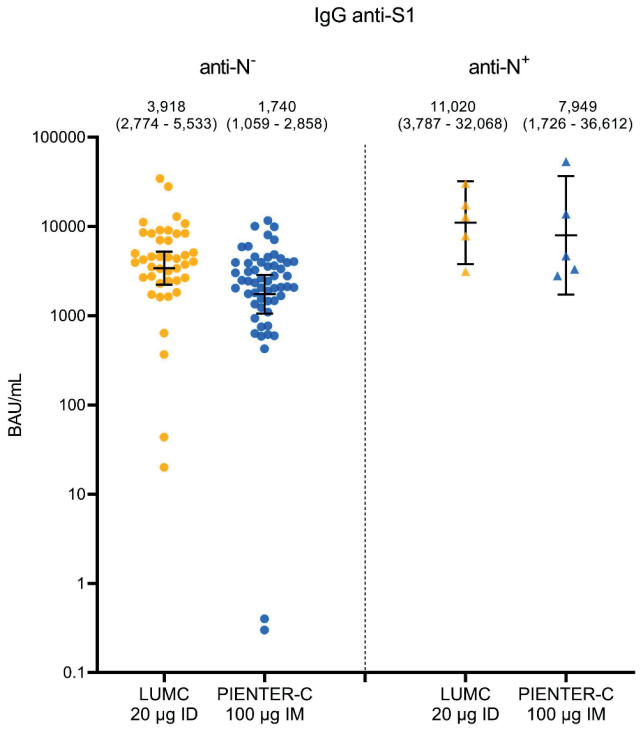

Figure 2. Immunogenicity assessment: anti-spike-S1 IgG concentrations

SARS-CoV-2-spike-S1 binding antibodies in serum were measured by a bead-based multiplex immunoassay (MIA) based on Luminex technology and are reported in geometric mean concentrations of binding antibody units per milliliter (BAU/mL). Every data point represents a separate patient. Patients with a history of COVID-19 (anti-N positive) are reported as separate groups. Error bars represent GMC with 95% confidence intervals.
Anti-S1 = anti-spike-1; anti-N = anti-nucleocapsid; BAU = binding antibody units; ID = intradermal; IM = intramuscular; GMC = geometric mean concentrations.

Discussion

This study provides evidence that a fractional dose of the mRNA-1273 vaccine administered through the ID route is an effective way to vaccinate individuals with a suspected allergic reaction after their first vaccination with an mRNA COVID-19 vaccine. This is in line with our previous study, which shows that an immunization regimen with fractional ID vaccine dose induces adequate immune responses.[10] A trend towards a higher antibody response in the ID vaccinated group was observed, but this was most probably caused by the longer interval between the two vaccinations in this group. Previously, it has been shown for mRNA COVID-19 vaccine BNT162b2 that an immunization regimen with a longer interval is more immunogenic.[18]

We observed no anaphylaxis in our patients, which is not surprising given the low incidence of anaphylaxis after mRNA COVID-19 vaccines, even in those with allergic reactions to previous administrations.[1] The markedly lower number of symptoms observed after the second vaccination compared to the self-reported symptoms after the first vaccination is noteworthy and can have multiple explanations. The reduction in dose may have caused fewer symptoms than the full IM dose. The fact that the majority of patients had taken oral antihistamines before the second vaccination may have also lowered the incidence of symptoms. Additionally, the fact that the ID vaccination was performed with the mRNA-1273 vaccine and the majority of patients had received a first dose with the BNT162b2 vaccine, that is composed of slightly different components may also have led to less symptoms. Finally, symptoms self-reported after the first vaccination may have been stress-related rather than hypersensitivity signals. Receiving the vaccine in a small outpatient clinic (contrary to a large municipal vaccination center) while being observed by an experienced medical professional, may be reassuring for patients and may have thus contributed to fewer experienced symptoms after the second vaccination.

A limitation of this study is the fact that the serology before the second vaccination is lacking, and therefore we could not calculate a fold increase of anti-SARS-CoV-2 antibody concentration. In addition, the majority of patients were COVID-naïve, whereas most people currently have had at least one episode of COVID-19. However, the results in the anti-N IgG positive groups do suggest that our results also apply to individuals with a history of COVID-19. Although the results reported here are from the primary vaccination series, we believe ID administration can also be used to give booster vaccinations to patients with suspected allergies, as we have previously shown that fractional ID dosing induces immune responses comparable to full IM booster dose administrations.[11]

Some have proposed, that due to the extremely low risk of anaphylaxis, and the lack of evidence for skin prick testing or graded dosing, individuals with a suspected allergy to mRNA COVID-19 vaccines can receive the regular full IM dose according to the standard of care as long as it is in a setting where there is experience with handling anaphylactic reactions.[1] This does not take into consideration that general practitioners and health care workers at mass vaccination clinics might be hesitant to administer further vaccinations to these individuals. Even if the risk of anaphylaxis is low from an evidence-based point of view, it also fails to consider that it can be quite stressful for patients to receive another full dose when they previously have experienced symptoms that they might have associated with an anaphylactic reaction. In these situations, fractional ID dosing may provide a pragmatic solution that is time efficient and sufficiently immunogenic.

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