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The effect of needle length and skin to deltoid muscle distance in adults receiving an mRNA COVID-19 vaccine

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ABSTRACT

Background: The mRNA COVID vaccines are only licensed for intramuscular injection but it is unclear whether successful intramuscular administration is required for immunogenicity.
Methods: In this observational study, eligible adults receiving their first Comirnaty™/BNT162b2 dose had their skin to deltoid muscle distance (SDMD) measured by ultrasound. The relationship between SDMD and height, weight, body mass index, and arm circumference was assessed. Three needle length groups were identified: 'clearly sufficient' (needle exceeding SDMD by >5 mm), 'probably sufficient' (needle exceeding SDMD by $\leq$ 5 mm), and 'insufficient' (needle length $\leq$ SDMD). Baseline and follow-up finger prick blood samples were collected and the primary outcome variable was mean spike antibody levels in the three needle length groups.
Results: Participants (n = 402) had a mean age of 34.7 years, BMI 29.1 kg/m^2, arm circumference 37.5 cm, and SDMD 13.3 mm. The SDMD was >25 mm in 23/402 (5.7%) and >20 mm in 61/402 (15.2%) participants. Both arm circumference ($\geq$40 cm) and BMI ($\geq$33 kg/m^2) were able to identify those with a SDMD of >25 mm, the length of a standard injection needle, with a sensitivity of 100% and specificities of 71.2 and 79.9%, respectively. Of 249/402 (62%) participants with paired blood samples, there was no significant difference in spike antibody titres between needle length groups. The mean (SD) spike BAU/mL was 464.5 (677.1) in 'clearly sufficient needle length' (n = 217) compared with 506.4 (265.1) in 'probably sufficient' (n = 21, p = 0.09), and 489.4 (452.3) in 'insufficient needle length' (n = 11, p = 0.65).
Conclusions: A 25 mm needle length is likely to be inadequate to ensure vaccine deposition within the deltoid muscle in a small proportion of adults. Vaccine-induced spike antibody titres were comparable in those vaccinated with a needle of sufficient versus insufficient length suggesting deltoid muscle deposition may not be required for an adequate antibody response to mRNA vaccines.
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1. Introduction

Vaccination is a key intervention to reduce the morbidity, mortality, and wider societal harms caused by SARS-CoV-2. The pandemic has seen the rapid development of vaccines that use novel technologies, such as mRNA, to achieve expression of the target SARS–CoV-2 spike glycoprotein. These vaccines employ lipid

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nanoparticle technology as a delivery vehicle that protects the nucleic acid from degradation and facilitates cellular uptake of mRNA, allowing translation machinery in myocytes and other host cells to produce the target spike glycoprotein [1]. The approved mRNA COVID-19 vaccines are only licensed for intramuscular injection and the deltoid muscle is the recommended injection site [2,3].

People with obesity are at risk of poor clinical outcomes from COVID-19 and it is imperative that COVID-19 vaccines are delivered optimally to help protect this population [4]. It has long been recognised that obesity may reduce the likelihood of successful injection into the deltoid muscle due to increased fat pad thickness at the injection site [5–7]. Pre-pandemic evidence suggests that an insufficiently long needle and/or deposition into the subcutaneous fat could slow mobilisation and processing of antigens which may affect immunogenicity and vaccine effectiveness, at least for certain vaccines such as the hepatitis B vaccine [8–10]. In contrast, other vaccine technologies (such as conjugate vaccines) retain their immunogenicity, and have lower reactogenicity, when delivered via subcutaneous injection [11]. Successful intramuscular administration, with uptake of the vaccine particles by myocytes, may be particularly important for SARS–CoV-2 mRNA vaccines given the postulated mechanism of action requires the mRNA that encodes the spike glycoprotein to be translated within the host cells after vaccine administration.

The standard needle length used for COVID-19 vaccination in New Zealand is 25 mm. A longer 38 mm needle was originally recommended for 'larger patients' [12] and subsequently also for those with 'a larger arm'. Similarly, in the United Kingdom, 'The Green Book' (information for public health professionals on immunisation) recommends that, in larger adults, a longer length (e.g. 38 mm) may be required [13]. It is unclear at what point a vaccinee, or their arm, is large enough to require the 38 mm needle. Clear, practical, and evidence-based guidance on how to select the appropriate needle length for people receiving intramuscular mRNA vaccines is needed.

The objectives of this study were to describe the vaccination site skin-to-deltoid muscle distance (SDMD) in adults receiving an mRNA vaccine, to identify measurements that identify those for whom a needle longer than the standard 25 mm needle is needed, and to assess whether SDMD, in relation to needle length, is associated with vaccine immunogenicity.

2. Methods

2.1. Study design

This was a non-interventional observational study embedded within the public health COVID–19 vaccine programme conducted at the Mount Wellington COVID-19 Vaccination Centre in Auckland, New Zealand. In New Zealand, COVID-19 vaccination is free of charge and the Mount Wellington Vaccination centre provided mRNA vaccination with the Pfizer tozinameran/Comirnaty™/BNT162b2 vaccine, to those with and without pre-booked appointments, throughout the study period. Initial study procedures were completed when participants presented for their first dose of a COVID-19 vaccine and after providing signed informed consent. This included the measurements described below, and a baseline finger prick blood sample. Vaccinators may have been aware that the study was being conducted but vaccine recipients were not approached for recruitment until after they had received their vaccination as part of usual care. A follow-up finger prick blood sample was obtained when participants returned for their second vaccine dose. This study was approved by the Auckland Health Research Ethics Committee (AH22963).

2.2. Participants

Participants aged ≥18 years were eligible if they were presenting for their first COVID-19 vaccination, if they planned to attend the same vaccination centre for their second dose, and if they were able to provide written informed consent. Recruitment took place over a 3-week period (30/9/2021–20/10/2021) when 402 participants had been enrolled, meeting the planned minimum sample size of 400 participants. Some 259/402 participants returned to the vaccination centre for their second dose and provided a follow-up finger prick blood sample, prior to the study closing on 18/11/2021.

2.3. Demographic and clinical data collection

The following self-reported demographic data were obtained from each participant: date of birth, age, sex, and ethnicity. Participants answered questions with respect to comorbidities and whether they took any medications to suppress their immune system. Participants were also asked whether they had prior COVID-19 infection. The self-reported comorbidity questions were adapted from those published by Sangha et al. [14].

2.4. Anthropometric and ultrasound measurements

Body height was measured by using a calibrated Seca 206 stadiometer. Body weight was measured by using calibrated Seca 762 flat scales and derived BMI was calculated. Following vaccination, participants were asked to expose their vaccinated arm and hang it relaxed by their side while one measurement of arm circumference at the level of the vaccine injection site was performed using disposable paper tape measures. Ultrasonography of the injection site was performed by a radiologist (RW) or other appropriately trained staff (AM, SB). An Envision scanning pad was placed over the injection site and activated with sterile saline. Images of the skin, subcutaneous tissue and the deltoid muscle were obtained using an ACUSON Sequoia system (Siemens Healthineers) and a 18L6 linear array transducer. The ultrasound probe was centred over the vaccine injection site, with minimal pressure, perpendicular to the skin surface. Measurements (in mm, to the nearest whole mm) were obtained mid transducer with cursors at the skin surface and deltoid muscle fascia. It was originally intended that the site of injection would be recorded as 'confirmed intramuscular' or 'confirmed extramuscular' if the administered vaccine could be visualised by ultrasound. However, during the feasibility phase of the project it was determined that the site of administration could not reliably be determined in two ultrasound planes and so this datapoint was not captured, the protocol was prospectively updated, and participant recruitment continued.

2.5. Needle length measurements

Data on the needle length used for each participants vaccine administration was accessed from the COVID-19 Immunisation Register. When taken together with individual participant SDMD data, a needle was considered 'clearly sufficient' length if it exceeded the SDMD by at least 5 mm, 'probably sufficient' length if exceeded the SDMD by between 0 and 5 mm, and of 'insufficient' length if it was less than or equal to the SDMD. These categories were based on the recommendation that needles used for intramuscular injection are sufficiently long to deposit vaccine at least 5 mm into the muscle [6].

2.6. Spike antibody assay

Mitra devices (20 μL devices; Neoteryx, Torrance, California, USA) were utilised to collect finger prick blood samples. The devices were left to dry at room temperature and stored for a maximum of 3 weeks or frozen at − 20 °C until use. Dried blood spots were eluted as previously described [15]. Briefly, the Mitra device tip was placed in elution buffer (phosphate buffered saline supplemented with 1% bovine serum albumin + 0.05% Tween-20) at a dilution of 1:20 and incubated overnight at 4 °C, with shaking (300 rpm). As serum comprises 50% of the whole blood volume, it was assumed that each eluent was equivalent to a 1:40 dilution of serum. The Quantivac SARS-CoV–2 IgG ELISA (EUROIMMUN Medizinische Labordiagnostika, Germany) was utilised to determine spike antibody titres in the eluents following validation of the assay for this sample collection method. This involved comparison of eluents diluted to their calculated 'serum equivalent' with matched serum samples previously obtained [15]. There was a very strong correlation ($r^2 > 0.99$) between titres determined from Mitra eluents and matched sera (Supplementary Fig. 1). The ELISA was performed following the manufacturer's instructions and titres reported as WHO International Standard units (Binding Antibody Units, BAU/mL).

2.7. Sample size

From published studies the distribution of spike antibody responses, reported as BAU/mL measured against the SARS-CoV-2 spike glycoprotein with a EUROIMMUN ELISA, after a single dose of the Comirnaty COVID-19 vaccine was log-normal with an estimated standard deviation of the logarithm transformed antibody levels of 1.06 [16,17]. While the published data did not match our proposed study population, in terms of co-morbidities, they used the same assay, at the same 21–28 day time point after the first dose of Comirnaty. Based on these data, a total sample size of 400; 200 obese patients (where it is possible the vaccine may be administered into subcutaneous fat) and 200 non-obese patients (where it is likely the vaccine will be administered into muscle), was calculated to have over 80% power to detect a difference in logarithm antibody levels of 0.298; equivalent to a geometric mean ratio of 0.75 i.e. powered to detect an antibody level 25% less in one group compared to another. This sample size has sufficient degrees of freedom to incorporate a multivariate analysis of possible predictors; based on 20 participants per of freedom in a multivariate analysis.

2.8. Statistical analysis

Data descriptions used mean and standard deviation (SD); median, 25th and 75th percentiles (inter-quartile range); and minimum to maximum for continuous variables. Counts are described as proportions expressed as percentages for categorical variables. Frequency histograms were used to show the distribution of the continuous variables. For the boxplots the symbol is the mean, the horizontal lines are the 25th, 50th (median), and 75th percentiles, and the whiskers extend from the minimum to maximum values. LOESS plots showed the relationship between ultrasound measured SDMD and possible predictor variables and the relationships were summarised by linear regression together with R-squared values and correlation coefficients. Estimates of proportions used an exact binomial method. Discrimination for continuous variables for the 25 mm ultrasound SDMD used logistic regression, summarised by the Area under the Curve (AUC) for the Receiver Operating Characteristic (ROC) Curve, and illustrative sensitivity, specificity, and likelihood ratio positive, at the 25 mm cut-point. Antibody levels are natural logarithm transformed for analysis and differences in logarithms or change in logarithms per unit change in predictor can be interpreted as ratio of geometric mean antibody levels. ANOVA was used to estimate differences in continuous response variables in relation to categorical predictors. ANCOVA was used where there is a continuous predictor variable in addition to categorical predictor variables. Logistic regression was used to estimate the area under the receiver operating curve for the discrimination of the continuous predictors: arm circumference, BMI, height, and weight; for cut points of skin to deltoid distance of 25 mm. SAS (version 9.4, Cary, NC) was used for all statistical analyses.

3. Results

3.1. Demographics and self-reported comorbidities

Demographic and comorbidity data summaries are shown in Table 1. In all 136/402 (33.8%) participants were female. The mean age of participants was 34.7 years. For ethnicity 138/402 (34.7%) were European, 97/402 (24.4%) were Pasifika, 82/402 (20.6%) were Māori, and 81 (21.4%) were of other ethnicities. Only 3/402 (0.8%) participants reported past COVID-19. Medical comorbidities were uncommon with hypertension in 25/402 (6.2%), immune suppres-

Table 1
Demographic, comorbidity, anthropometric, and ultrasound data.

Continuous Variables	Male, N = 266	Female, N = 136	Total, N = 402
Age (years) Median (IQR)	30 (24 to 42)	31 (25 to 44)	30.5 (24 to 42)
Min to Max	18 to 93	18 to 86	18 to 93
Measurements	*Mean (SD)* *Min to Max*		
Arm Circumference (cm)	38.3 (6.1) 25.0 to 57.0	35.7 (7.7) 24.0 to 76.8	37.5 (6.8) 24.0 to 76.8
Skin to Deltoid Distance (mm)	12.1 (5.5) 3.9 to 39.5	15.6 (6.5) 4.8 to 36.5	13.3 (6.07) 3.9 to 39.5
Weight (kg)	92.1 (23.8) 51 to 167	76.6 (24.4) 44.2 to 189.0	86.9 (25.1) 44.2 to 189
Height (m)	1.77 (0.07) 1.57 to 2.02	1.63 (0.07) 1.39 to 1.78	1.72 (0.1) 1.39 to 2.02
BMI (kg/m^2)	29.2 (7.1) 16.2 to 57.9	28.8 (8.5) 17.3 to 69.4	29.1 (7.6) 16.2 to 69.4
Categorical Variables	**N/266 (%)**	**N/136 (%)**	**N/402 (%)**
Comorbidities present	41 (15.4)	21 (15.4)	62 (15.4)
Hypertension	13 (4.9)	12 (8.8)	25 (6.2)
Autoimmune Disease	10 (3.8)	5 (3.7)	15 (3.7)
Diabetes	9 (3.4)	2 (1.5)	11 (2.7)
Immune Suppressive Medications	7 (2.6)	3 (2.2)	10 (2.4)
Liver Disease	3 (1.1)	3 (2.2)	6 (1.5)
Heart Disease	3 (1.1)	2 (1.5)	5 (1.2)
Lung Disease	4 (1.5)	1 (0.7)	5 (1.2)
Cancer	1 (0.4)	3 (2.2)	4 (1)
Immune Deficiency	1 (0.4)	3 (2.2)	4 (1)
Kidney Disease	2 (0.8)	0 (0)	2 (0.5)
Organ Transplant	0 (0)	0 (0)	0 (0)
Previous COVID-19 Infection	2 (0.8)	1 (0.7)	3 (0.8)
BMI Categories			
≤24.9	81 (30.5)	56 (41.2)	137 (34.1)
25 to 29.9	79 (29.7)	36 (26.5)	115 (28.6)
30 to 34.9	57 (21.4)	16 (11.8)	73 (18.2)
35 to 39.9	25 (9.4)	14 (10.3)	39 (9.7)
≥40	24 (9.0)	14 (10.3)	38 (9.5)
Ethnicity			
European	99 (37.2)	39 (28.7)	138 (34.7)
Pasifika	64 (24.1)	33 (24.3)	97 (24.4)
Māori	56 (21.1)	26 (19.1)	82 (20.6)
Other Ethnicities*	47 (17.7)	38 (27.9)	81 (21.4)

* Asian, Middle Eastern, Latin American, African & Unknown.

sive medication use in 10/402 (2.4%), liver disease in 6/402 (1.5%), lung disease in 5/402 (1.2%), heart disease in 5/402 (1.2%), immune deficiency in 4/402 (1.0%), kidney disease in 2/402 (0.5%). No participants had a history of organ transplantation.

3.2. Anthropometric data

The mean (standard deviation, SD) height of participants was 1.72 (0.1) m and the mean weight of participants was 86.9 (25.1) kg. The mean BMI was 29.1 (7.6) kg/m^2. The BMI was ≤ 24.9 in 137/402 (34.1%) participants, 25 to 29.9 in 115/402 (28.6%), 30 to 34.9 in 73/402 (18.2%), 35 to 39.9 in 39/402 (9.7%), and ≥40 in 38/402 (9.5%). The mean arm circumference was 37.5 (6.8) cm (Table 1 and Supplementary Fig. 2).

3.3. Ultrasound measurement of the SDMD and needle length

Overall, 392/402 (97.5%) of participants were recorded as being vaccinated with a 25 mm needle, 9/402 (2.2%) participants with a 38 mm length needle, and needle length was not recorded in one participant.

The SDMD was measured by ultrasound at the vaccine administration site for all participants, shown in Table 1 and Supplementary Fig. 3. The mean (SD) SDMD was 13.3 (6.1) mm with a median of 11.8 mm (IQR 9.2–16.0 mm). The maximum SDMD measured was 39.5 mm. 23/402 (5.7%) participants had a SDMD > 25 mm of whom 2/23 (8.7%) had a 38 mm needle used. 61/402 (15.2%) participants had a SDMD > 20 mm of whom 7/61 (11.5%) had a 38 mm needle used.

We classified needle length as 'clearly sufficient' if it exceeded the SDMD by at least 5 mm, 'probably sufficient' if exceeded SDMD by less than or equal to 5 mm, and 'insufficient' if it was less than or equal to the SDMD. The needle was clearly of sufficient length in 346/402 (86.1%) participants, probably of sufficient length in 34/402 (8.5%), and of insufficient length in 22/402 (5.5%) of participants.

3.4. Relationship between anthropometric measurements and SDMD

The SDMD was strongly associated with arm circumference, BMI, weight, and to a lesser extent with height, shown in Table 2 and Fig. 1. Arm circumference gave an area under the Receiver Operator Characteristic (ROC) curve of 0.91 for a SDMD cut point of 25 mm, shown in Fig. 1A and B. An arm circumference of ≥40 cm had 100% sensitivity and 71.2% specificity, with likelihood ratio positive 3.5 for a SDMD cut point of 25 mm. BMI gave an area under the ROC curve of 0.94 for a SDMD cut point of 25 mm, shown in Fig. 1C and D. A BMI of ≥32.9 kg/m2 had sensitivity of 100% and specificity of 79.9% with a likelihood ratio positive of 5 for a SDMD cut point of 25 mm. Weight and height gave an area under the ROC curve of 0.89 and 0.63, respectively, shown in Fig. 1E, F, G, and H.

3.5. Immunogenicity analyses

Paired finger prick blood samples were available for 259/402 (64.4%) participants with a median interval of 22 days after the first vaccine dose (IQR 21 to 27). 10/259 (3.9%) did not have immunogenicity analyses due to: inadequate dried blood in the finger-prick sample (n = 2), follow-up sample > 42 days post-vaccination (n = 1), and detectable antibodies in baseline samples (n = 7). Of the remaining 249 participants, the needle was clearly of sufficient length in 217/249 (87.2%), probably sufficient in 21/249 (8.4%), and insufficient in 11/249 (4.4%) participants. The immunogenicity cohort (n = 249) is proportionally representative of the entire study cohort (Supplementary Table 1).

There was no evidence that the needle length, relative to SDMD, was associated with spike antibody titres. The mean (SD) antibody levels were 464.5 (677.1) BAU/mL, n = 217, in those where the needle was 'clearly sufficient' length; compared to 506.4 (265.1), n = 21, in those with a needle of 'probably sufficient' length; and 489.4 (452.3), n = 11, in those with needle of 'insufficient length'. Because of the highly skewed nature of the data this was analysed on the logarithm transformed scale with mean (SD) logarithm antibody levels of 5.63 (1.06); 6.04 (0.74); and 5.77 (1.06) respectively. There was no overall evidence in ANOVA of an association between the three needle length categories and logarithm antibody levels, P = 0.22. The estimates for a difference (95% CI) in logarithm antibody levels for a needle clearly of sufficient length versus probably of sufficient length was −0.41 (-0.88 to 0.06), equivalent to a geometric mean ratio of 0.66 (0.42 to 1.06); and for a needle clearly of sufficient length versus insufficient length the difference in logarithm antibody levels was −0.14 (−0.78 to 0.49), equivalent to a geometric mean ratio of 0.87 (0.46 to 1.63), illustrated in Fig. 2A. There was no evidence ethnicity influenced this lack of association, interaction P-value 0.12. Similarly, there was no clear association between antibody level and the needle length (relative to SDMD) when assessed as a continuous variable, shown in Fig. 2B. When participants were categorised by BMI and spike antibody titres compared, there was no evidence that BMI influenced antibody levels with no significant difference between groups. Similarly, there was no clear association between antibody level and BMI when assessed as a continuous variable, shown in Fig. 2C and D.

4. Discussion

This observational study suggests that the early antibody response to the Comirnaty/BNT162b2 is not significantly influenced by whether the mRNA vaccine was deposited into muscle or subcutaneous tissue. This is an important consideration, as in at least one in 20 adults attending a COVID vaccination clinic, the needle used was unlikely to be of sufficient length to ensure deposition of vaccine into the deltoid muscle. If the vaccine was delivered into the subcutaneous tissue, it would not have been administered in accordance with its approved registered use, as regulatory approval has only been granted for the intramuscular administration of mRNA and viral vector COVID-19 vaccines.

The lack of a difference in antibody levels is noteworthy as subcutaneous administration of other vaccines can reduce immunogenicity [6,10] and mRNA vaccines were developed to achieve protein expression from myocytes [18,19]. Our results suggest that intramuscular injection is less important for mRNA COVID-19 vaccines than hypothesised. It is possible that vaccine mRNA is taken

Table 2
Correlation between anthropometric variables and skin to deltoid muscle distance.

Main effect	Skin to deltoid distance per unitincrease predictor (95% CI)	R-squared	Correlation coefficient	P
Arm circumference (cm)	0.52 (0.45 to 0.59)	34.1	0.58	<0.001
BMI (kg/m2)	0.61 (0.55 to 0.66)	57.8	0.76	<0.001
Height (m)	−12.0 (-18.0 to −6.0)	3.7	−0.20	<0.001
Weight (kg)	0.15 (0.13 to 0.17)	36.7	0.61	<0.001

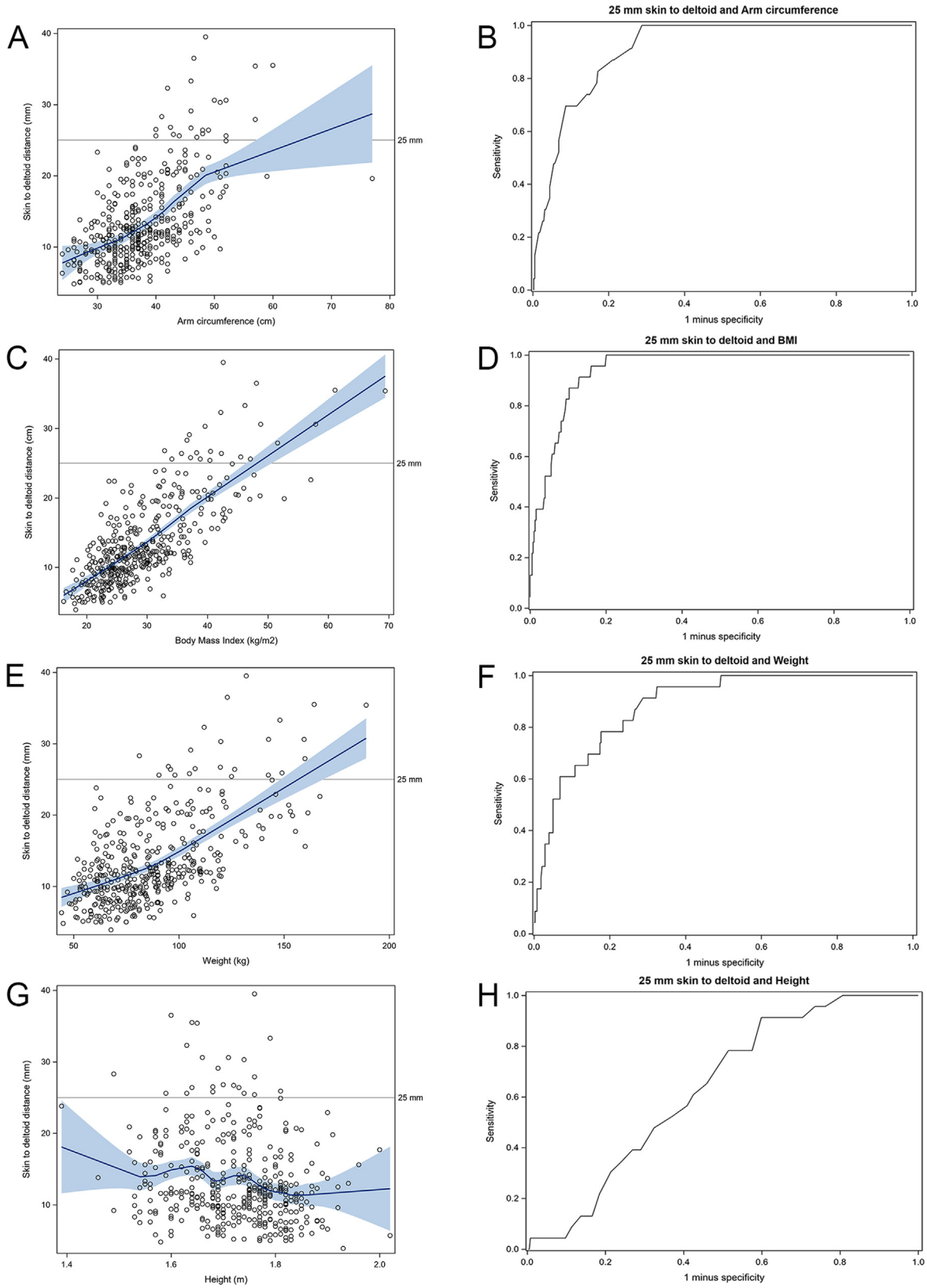

Fig. 1. Correlation between anthropometric variables and skin to deltoid distance (SDMD). The relationship between SDMD and specific anthropometric variables are shown as scatter plots with superimposed LOESS lines and Receiver Operating Characteristic (ROC) curves, respectively, for arm circumference (A) and (B), body mass index (C) and (D), weight (E) and (F), and height (G) and (H); n = 402 participants.

up and translated by cells outside the deltoid muscle, such as fibroblasts, adipocytes, and dendritic cells, and the spike glycoprotein is then available for processing by B cells and other antigen presenting cells. However, our study used needle length and SDMD

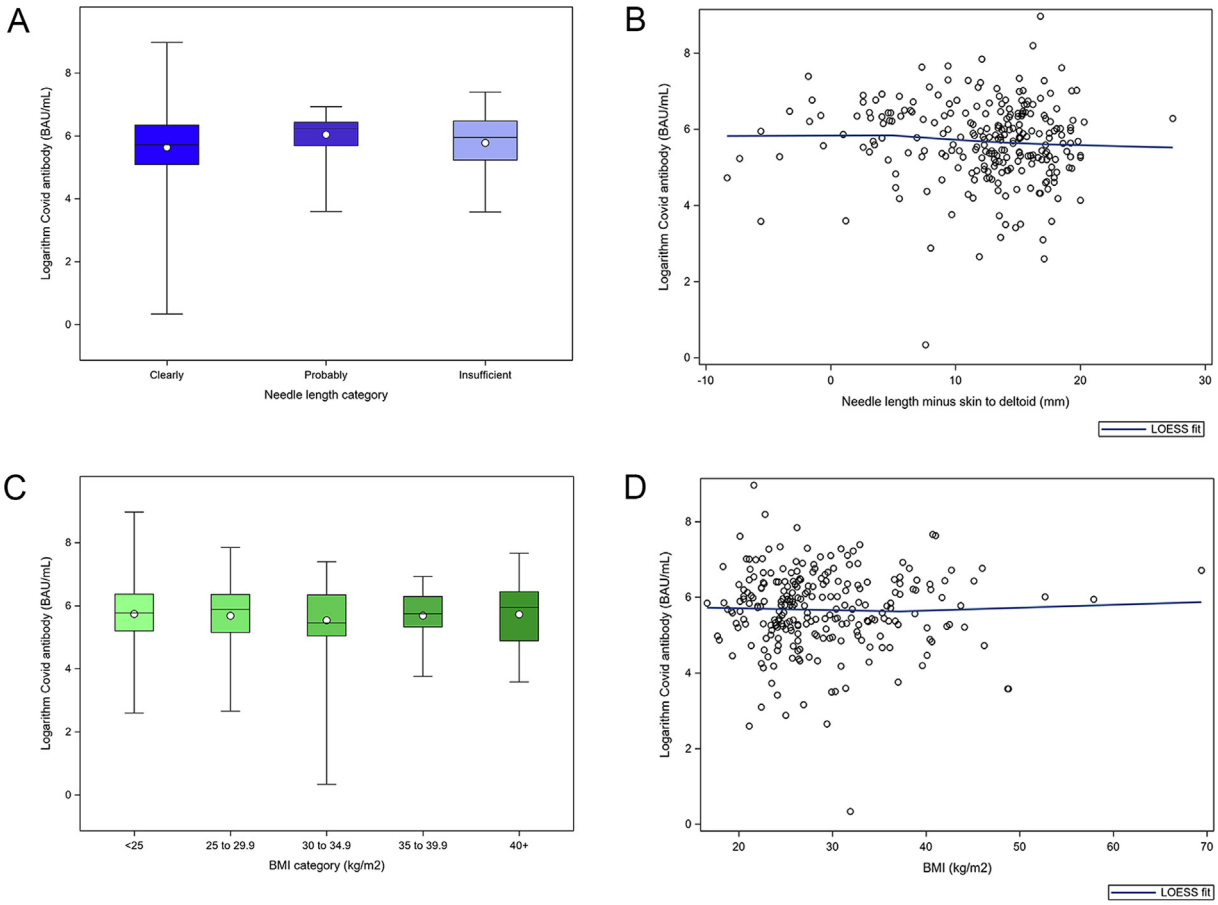

Fig. 2. SARS-CoV-2 spike antibody titres by needle length category and BMI. Logarithm antibody levels are presented as boxplots in different needle length categories (A) and BMI categories (C). Logarithm antibody levels are shown as scatter plots with superimposed LOESS lines for the relationship with needle length (B) and BMI (D) as continuous variables; n = 249 participants.

as a surrogate for successful intramuscular administration and was underpowered to definitively exclude a difference in antibody levels. Our study design sought to have statistical power to detect a reduction in antibody levels of 25% (a geometric mean ratio of 0.75) in one group compared to another. As the confidence intervals for comparisons between different needle length groups contain 0.75, our results do not exclude the possibility that this prespecified difference exists.

Other data on COVID–19 vaccine responses and needle length are lacking, but several studies have investigated the relationship between obesity and vaccine response, generating conflicting findings. Consistent with our finding that BMI did not significantly affect anti-spike antibody levels following vaccination with Comirnaty/BNT162b2, a large study of over 2000 healthcare workers in Japan found no significant correlation between BMI and vaccine antibody response [20]. An Israeli health care worker study (n = 1149) observed a higher vaccine antibody response in those with BMI $\geq$ 30 [21]. In contrast, a study that categorised by abdominal obesity rather than BMI found those with abdominal obesity had both lower spike antibodies and faster antibody waning in the months following vaccination [22]. It is possible that the distribution of body fat, rather than BMI, may be a stronger predicter of vaccine response. Data on whether obese people in clinical trials or observational studies were vaccinated with needles sufficiently long to ensure intra-muscular deposition are lacking.

Our findings provide data to inform recommendations about needle choice for deltoid intramuscular injection, for both COVID-19 and other immunisations. Vaccinators have lacked clear guidance on how to identify participants who might benefit from vaccine administration with a longer needle. Some have argued that point-of-care ultrasound may be useful to "assist clinicians to determine appropriate needle length and penetration level" [23]. However, ultrasound determination of SDMD is unlikely to be practical for people presenting for routine vaccination. We report that SDMD is strongly associated with arm circumference, and BMI. An arm circumference of $\geq$40 cm or a BMI of $\geq$32.9 kg/m2 may be useful simple measurements, able to be performed in routine practice, to identify vaccine recipients who would benefit from vaccination with a needle longer than the standard 25 mm.

The strengths of this study include its recruitment of members of the general population, rather than a specific group such as healthcare workers, receiving their COVID-19 vaccine in a real-word vaccination centre. Recruitment from the post-vaccination waiting area could mitigate the potential for the 'Hawthorne effect' where vaccinator behaviour changes because they are aware a vaccine recipient is participating in a clinical study. In this study, the SDMD was measured at the site of actual vaccine administration. Ultrasound was used and this is an accurate imaging modality to measure the SDMD. The recommended site of deltoid intramuscular injection varies between national vaccination guidelines [13,24,25]. The New Zealand guidance recommends injection at the intersection of a line connecting the acromion process and deltoid tuberosity, at the level of the axilla, and this should be considered when interpreting the results in an international context [24].

Limitations of this study include the relatively young and predominantly male cohort, with few comorbidities, reflecting the

stage of the vaccine rollout in New Zealand where people at higher risk from COVID-19 (those who are older and who have comorbidities) were offered vaccination earlier in the pandemic, prior to this study. It is possible that the SDMD differs significantly in other populations such as those with comorbidities e.g. type two diabetes. Further, the low number of female participants (33.8%) may result in an under-estimate of the actual average SDMD in adults as the subcutaneous fat pad in the deltoid region is thicker in females [6,26]. We did not collect information on how far the needle was advanced through the skin (e.g. partially vs the entire length), whether skin tensioning was used, or whether significant pressure was applied by vaccinators; these practices could influence the SDMD at the time of vaccine injection. Similarly, there was no data collected on local or systemic adverse effects of vaccination, which could differ with subcutaneous vs intramuscular administration. The real-world nature of this study necessitated a focus on antibody responses. No data were collected on T cell responses, which may be influenced by the site of vaccine administration, and are important in protecting against severe COVID-19 disease [27].

The findings of this study have a number of implications for vaccine programmes. Firstly, the standard 25 mm needle cannot be universally anticipated to achieve deltoid intramuscular injection in all adult recipients. Secondly, vaccine recipients with a high BMI and/or larger arms are at risk of being vaccinated with a needle insufficiently long to achieve intramuscular deposition although, reassuringly, we did not demonstrate a difference in antibody levels. Obesity is a major risk factor for COVID-19 morbidity and mortality [4,28] and it is imperative those with obesity are vaccinated in accordance with the licensed route of administration and are adequately protected by COVID-19 vaccination. Thirdly, the measurement of arm circumference or BMI may serve as simple and practical predictors of the requirement for needles longer than 25 mm, recognising that ultrasound measurement is not feasible for mass vaccination programmes.

Future research could define the SDMD at different recommended deltoid injection sites, based on varying guidance for vaccinators, and in different populations – including those with obesity and related comorbidities. Arm circumference and BMI cut-offs, seeking to identify those with a SDMD longer than the standard needle, could be validated in different population groups. Randomised clinical trials of different routes of administration (intramuscular, subcutaneous, and intradermal), with more detailed immunological analyses and serial measurements (before, between, and following each vaccine dose), could help to clarify the importance of intramuscular mRNA vaccine deposition and define the route of administration that achieves optimal immunogenicity.

Given the current focus on successfully immunising the world's adult population against SARS-CoV-2, better evidence is needed to ensure the currently available and highly effective vaccines optimally protect people with a range of different body and arm sizes. Arm circumference and BMI may be simple measurements to identify adults who would benefit from a longer needle to achieve intramuscular vaccination. However, intramuscular vaccine administration may not be necessary to achieve an immune response. Research seeking to understand and optimise COVID-19 vaccine administration could meaningfully improve the intramuscular administration of vaccines and other medicines beyond the pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.06.070.

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