Vaccine: X 13 (2023) 100248

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

COVID-19 vaccination and the skin to deltoid MUSCLE distance in adults with diabetes

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ARTICLE INFO

Article history:
Received 10 March 2022
Received in revised form 2 October 2022
Accepted 14 December 2022
Available online 15 December 2022

Keywords:
COVID-19
Deltoid
Diabetes
Needle length
Vaccination

ABSTRACT

Objectives: To estimate the proportion of adult diabetics with a skin to deltoid muscle distance (SDMD) of > 25 mm, representing a distance greater than the standard needle length used for intramuscular COVID-19 vaccination, and to assess whether anthropometric measurements predict ultrasound SDMD measurements.
Design: Non-interventional cross-sectional study.
Setting: Single site, non-clinical setting, Wellington, New Zealand.
Participants: One hundred participants (50 females) aged at least 18 years diagnosis with diabetes. All participants completed the study.
Main outcome measures: The proportions of participants with a SDMD > 25 mm and a SDMD > 20 mm (indicating that the needle would not have penetrated at least 5 mm into the deltoid, which is considered necessary to ensure deposition of vaccine into muscle); the relationship between anthropometric measurements (body weight, body height, body mass index (BMI), skinfold thickness, arm circumference) and SDMD measured by ultrasound.
Results: The proportion (95 %CI) of participants with a SDMD > 25 mm was 6/100; 6 % (2.2 to 12.6), and the proportion with a SDMD > 20 mm was 11 % (5.6 to 18.8), of which 9/11 had a BMI $\geq$ 30 kg/m^2 and 9/11 were female. The strongest relationships between anthropometric measurements and SDMD were with arm circumference ($r = 0.76$, $P < 0.001$) and BMI ($r = 0.73$, $P < 0.001$). Arm circumference and BMI were the best predictors of SDMD measurements with AUC for ROC curves of 0.99 and 0.94 above the 25 mm cut point, 0.97 and 0.89 above the 20 mm cut point respectively.
Conclusions: The standard needle length of 25 mm is likely to be insufficient to ensure deposition of COVID-19 vaccine within the deltoid muscle in a small but important proportion of obese adults with diabetes. Arm circumference and BMI are simple measurements that could identify those that need a long needle to ensure successful intramuscular vaccine administration.
Funding: Ruth Maud Ring Spencer Estate; Health Research Council of New Zealand (Independent Research Organisation).

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https://doi.org/10.1016/j.jvacx.2022.100248
2590-1362/

Introduction

Diabetes is associated with an increased risk of morbidity and mortality due to COVID-19 [1–4]. Vaccinating people with diabetes against coronavirus is a priority to reduce the burden of disease, risk of hospitalisation and death. The COVID-19 pandemic has seen the development of vaccines that use novel technologies that are administered by intramuscular injection. This route of delivery may be particularly important for mRNA vaccines that use lipid nanoparticle technology, delivered by intramuscular injection, to facilitate the expression of the SARS-CoV-2 spike glycoprotein from muscle cells [5]. It is unclear whether sufficient spike glycoprotein can be produced if the mRNA vaccine is injected into the subcutaneous tissue. This is in contrast to other vaccine technologies, which retain their immunogenicity when delivered via subcutaneous injection [6]. Importantly, approved mRNA COVID-19 vaccines are only licensed for intramuscular injection and the deltoid muscle is the recommended injection site [7,8].

Diabetes, and in particular Type 2 diabetes, is commonly associated with obesity. There is evidence that obesity may reduce the likelihood of successful injection into the deltoid muscle, due to a larger fat pad thickness at the injection site [9–11]. It is unclear how vaccine administration with a needle that does not reach the deltoid muscle affects the immunogenicity of COVID-19 mRNA vaccines. For other vaccinations, deposition into subcutaneous fat may slow mobilisation and processing of antigens, which in turn may lead to vaccine failure [12,13]. Suboptimal vaccine delivery also results in a greater risk of adverse events including local reactions, localised cellulitis, granuloma formation and abscesses [10,12,14].

The standard needle length used for the COVID-19 vaccination in New Zealand is 25 mm. A longer 38 mm needle was originally recommended for 'larger patients' [15], and subsequently also for those with 'a larger arm' [16]. Similarly, in the United Kingdom (UK), 'The Green Book' recommends that in larger adults, a longer length (e.g. 38 mm) may be required, and an individual assessment as to the length of the needle should be made [17]. It is unclear at what point an adult, or their arm, is large enough that the 38 mm needle would be required. Clear, practical, and evidence-based guidance on how to select the optimal needle length for people receiving an intramuscular COVID-19 vaccine is needed. This is an important issue, particularly for obese individuals and those with diabetes, who are at risk of worse health outcomes should they develop COVID-19 [18,19].

The objective of this study was to estimate the proportion of adults with diabetes with a skin to deltoid muscle distance (SDMD) ultrasound measurement > 25 mm, at the recommended COVID-19 vaccination site in the non-dominant arm. We also assessed whether anthropometric measurements might predict ultrasound measurements of SDMD, and thereby guide selection of the optimal needle length for vaccine delivery into the deltoid muscle.

Methods

Study design

This was a single site non-interventional cross-sectional study conducted at the Medical Research Institute of New Zealand (MRINZ) in Wellington, New Zealand. The original intent was to undertake the study at the MRINZ-affiliated Papakura Marae Health Centre in Auckland, however this was not possible due to a prolonged government-mandated lockdown of the Auckland region due to COVID-19. All investigations were completed in a single visit of approximately 30 min after providing signed informed consent. This study was approved by the Auckland Health Research Ethics Committee (Ref. AH23130) on 29 September 2021.

Participants

Participants were eligible, regardless of COVID-19 vaccination status, if aged 18 years or older, diagnosed with diabetes of any type and able and willing to provide informed consent prior to participation. Recruitment took place by direct invitation of potential participants on the MRINZ database, through local and national patient organisations, by advertisement on social media, and the MRINZ website. Recruitment continued until 100 participants were enrolled. No stopping criteria applied, provided participants did not withdraw consent before completion of the study.

Methods of measurement

In addition to date of birth, as part of the eligibility review, participants provided confirmation of diagnosis of diabetes: for which a prescription of diabetes medication or a clinical record was accepted. If requested by the participant, a study investigator contacted their clinical health care provider to obtain confirmation of diagnosis after consent was given. Once enrolled in the study, the following demographic and clinical data were obtained: sex, ethnicity, COVID-19 vaccination status (unvaccinated, partially vaccinated, fully vaccinated), side of non-dominant arm, diabetes treatment regimen and comorbidities.

Anthropometric measurements

Body height was measured by using a calibrated stadiometer. Body weight and body fat were measured by using the B-587 Body composition Monitor (Tanita, Japan). For accuracy, 'athletic mode' was chosen for athletic participants as per the user manual. Derived BMI was calculated.

Arm measurements

Participants were instructed to expose their non-dominant arm and hang it relaxed by their side. The protocol stated the site for measurements was the deltoid intramuscular vaccination site at the intersection of a line connecting the acromion process and deltoid tuberosity, at the level of the axilla, as recommended in New Zealand guidelines [20]. However, when operationalised, the exact midpoint between the acromion process and deltoid tuberosity was used, as recommended in Australian immunisation guidelines [21]. This latter site was marked with an indelible pen, checked by a second study investigator and corrected if needed. Two consecutive measurements of arm circumference were performed and three measurements of skinfold thickness were taken with a skinfold calliper at the marked recommended injection site. For each participant, three ultrasound images displaying the skin, subcutaneous tissue and fascia and the deltoid muscle were captured and saved using a high-frequency (13–6 MHz) linear transducer (Sonosite X-Porte, Fujifilm, Japan), after using sufficient water-soluble ultrasound transmission gel as an acoustic standoff. The middle of the ultrasound probe was placed at the marked injection site, with minimal pressure, at a 90-degree angle with the skin, in the sagittal plane and a penetration depth of 3.4 cm. Penetration depth setting was increased as required to ensure a sufficient volume of the deltoid muscle was displayed. Ultrasound images were obtained by trained clinical staff (LK, RS, SK). Measurements of the distance (in mm, to the nearest whole mm) between the skin and the fascia of the deltoid muscle were performed by a radiology registrar (JB).

Table 1
Demographic data and anthropometric measurements (n = 100).

Variable	Mean (SD)	Median (IQR)	Min to Max
Age (years), n = 100	61 (14.6)	63 (51 to 73)	25 to 85
Height (m), n = 100	1.7 (0.1)	1.69 (1.64 to 1.77)	1.47 to 1.93
Weight (kg), n = 100	89.4 (22.5)	84.75 (73.65 to 101.1)	48.6 to 171.7
BMI (kg/m^2), n = 100	30.9 (7.3)	29.9 (25.1 to 35.9)	18.6 to 61.5
Body fat (%), n = 99	34.7 (12.4)	36 (25.9 to 43.9)	5.8 to 66.2
Arm circumference (cm), n = 100	37.1 (5.8)	35.95 (32.85 to 40.35)	27.2 to 57.6
Skinfold thickness (mm), n = 100	30.9 (10.6)	30 (23 to 38)	10 to 55
Skin to deltoid muscle distance (mm), n = 100	14.3 (5.9)	13.5 (10 to 16)	5 to 36

Sample size

The sample size of 100 was chosen to give a 95 % CI for a proportion of plus or minus 10 %.

Statistical analysis

For arm circumference, skinfold thickness and ultrasound measurements, the mean of the repeated measurements was used. Data descriptions used mean and standard deviation (SD); median, 25th and 75th percentiles (interquartile range); and minimum to maximum, for continuous variables; and counts and proportions expressed as percentages for categorical variables. Frequency histograms were used to show the distribution of the continuous variables. 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 25 mm and 20 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 various cut-points. These illustrative cut-points were chosen initially for 25 mm distance in relation to the 100 % sensitivity cut-point and two readings with a greater value (apart from height using lesser values); and by the same criteria for the 20 mm distance but with the addition of the same values chosen for the 25 mm illustrative cut-points. For skinfold thickness the same illustrative cut-points were used. The estimate of the intra-class correlation coefficient in relation to SDMD for the three investigators was by a mixed linear model estimating the variance components.

In a post hoc analysis, simple data descriptions were shown for the participant characteristics and anthropometric variables by sex, and mean values compared by t-tests.

SAS (version 9.4, Cary, NC) was used for all statistical analyses.

Results

There were 50 female and 50 male (n = 100) participants with a mean (SD) age of 61 (14.6) years. There was no missing data apart from one participant who was wheel chair dependent in whom body fat percentage could not be recorded. In all participants the diagnosis of diabetes was confirmed by MB or MD as part of eligibility check before being enrolled into the study. Demographic and anthropometric data are shown in Table 1. Mean (SD) BMI was 30.9 (7.3) kg/m^2, mean (SD) body fat was 34.7 (12.4) %, and the mean (SD) SDMD was 14.3 (5.9) mm. Of all participants, 82 % were European, 9 % were Māori, 8 % were Asian, and 1 % was of Middle Eastern/Latin American/African ethnicity. 54 % of participants were prescribed insulin, 52 % metformin, and 39 % another oral diabetes medicine. Cardiovascular comorbidity was common, being present in 62 %, followed by respiratory disease in 33 %. 97 % of the study population were fully vaccinated (n = 93) or partially vaccinated (n = 4) and 3 % were unvaccinated against COVID-19.

Skin to deltoid muscle distance

The proportion (95 % CI) of the study population with a SDMD > 25 mm was 6/100: 6 % (2.2 to 12.6). The proportion of the study population with a SDMD > 20 mm, >32 mm and > 38 mm was 11 % (5.6 to 18.8), 2 % (0.2 to 7.0) and 0 % respectively (Fig. 1).

All six participants with a SDMD of > 25 mm had a BMI $\geq$ 35 kg/m^2, and five of the six participants were female (Fig. 2). Nine of the 11 participants with a SDMD of > 20 mm were female, and 9/11 had a BMI $\geq$ 35 kg/m^2.

Relationship between anthropometric measurements and skin to deltoid muscle distance

There was a linear relationship between all anthropometric measures and SDMD (Fig. 3). The strongest relationships to SDMD were with arm circumference, BMI and body fat percentage, with correlation coefficients greater than 0.7. (Table 2).

Discrimination of anthropometric measurements for skin to deltoid muscle distance cut point

Arm circumference and BMI were the best predictors of SDMD measurements above the 25 mm and 20 mm cut points with AUC ROC curves of 0.99 and 0.94, and 0.97 and 0.89 respectively

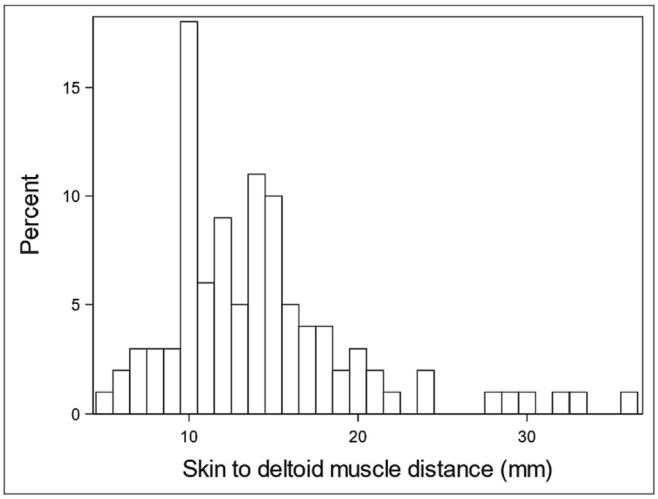

Fig. 1. Distribution of the skin to deltoid muscle distance measurements.

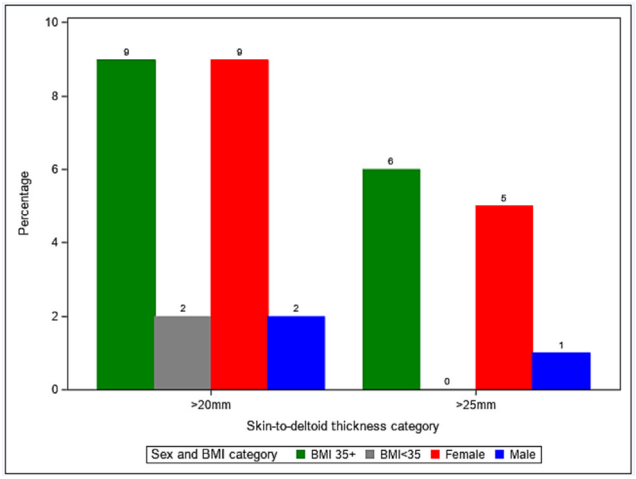

Fig. 2. The percentage of participants with SDMD > 20 mm and > 25 mm by sex and BMI category.

(Table 3, Supplement Figure S1). An arm circumference of ≥ 45.9 cm had a sensitivity of 100 % and specificity of 95.7 % for a SDMD measurement ≥ 25 mm; the corresponding values for a SDMD measurement ≥ 20 mm were 72.7 % and 97.8 % respectively (Supplement Table S1). A BMI of ≥ 36.6 kg/m^2 had a sensitivity of 100 % and specificity of 85.1 % for a SDMD measurement ≥ 25 mm; the corresponding values for a SDMD measurement ≥ 20 mm were 72.7 % and 86.5 % respectively.

Variance components in relation to investigator

There was little evidence of investigator variability in relation to SDMD measurement, with variance components of 0.079 for investigator and 34.38 for residual with an estimated intraclass correlation coefficient of > 0.99.

Sex differences in anthropometric measurements

Women were shorter and had a lower weight than men, but had an increased skinfold thickness, body fat percentage and SDMD (Table 4). There was no evidence of a difference in arm circumference, BMI or age between women and men.

Discussion

This study has shown that the standard needle length of 25 mm may be insufficient to ensure deposition of COVID-19 vaccine in the deltoid muscle in a small but important proportion of obese adults with diabetes. In total, six percent of participants overall and 12 % of participants with a BMI ≥ 30 kg/m^2 had an ultrasound measure of SDMD greater than 25 mm at the recommended COVID-19 vaccination site, indicating that in such individuals the vaccine administered with a standard needle may not have reached the deltoid muscle. In 11 % of participants overall, and in 20 % of participants with a BMI ≥ 30 kg/m^2, the ultrasound-measured SDMD was greater than 20 mm, indicating that the use of a 25 mm needle may not penetrate at least 5 mm into the muscle, as recommended to ensure deposition of the vaccine within the muscle [10]. Measures of BMI and arm circumference at the site of injection were strong predictors of ultrasound measures of SDMD, potentially providing simple, practical and low-cost alternatives to ultrasound for assessment of required needle length at the point of vaccination.

These findings extend the current knowledge of the SDMD in adults for which there is insufficient evidence to enable specific recommendations to be made for the appropriate needle length for deltoid intramuscular injection based on demography and anthropometry [10,22–28]. The previous observation that female sex is associated with greater SDMD was confirmed in our study [10,22,25,26]. In women, the SDMD was 5.2 mm greater than men, together with a higher body fat percentage, despite no evidence of a difference in BMI or arm circumference. This is consistent with the known physiological association of female sex with

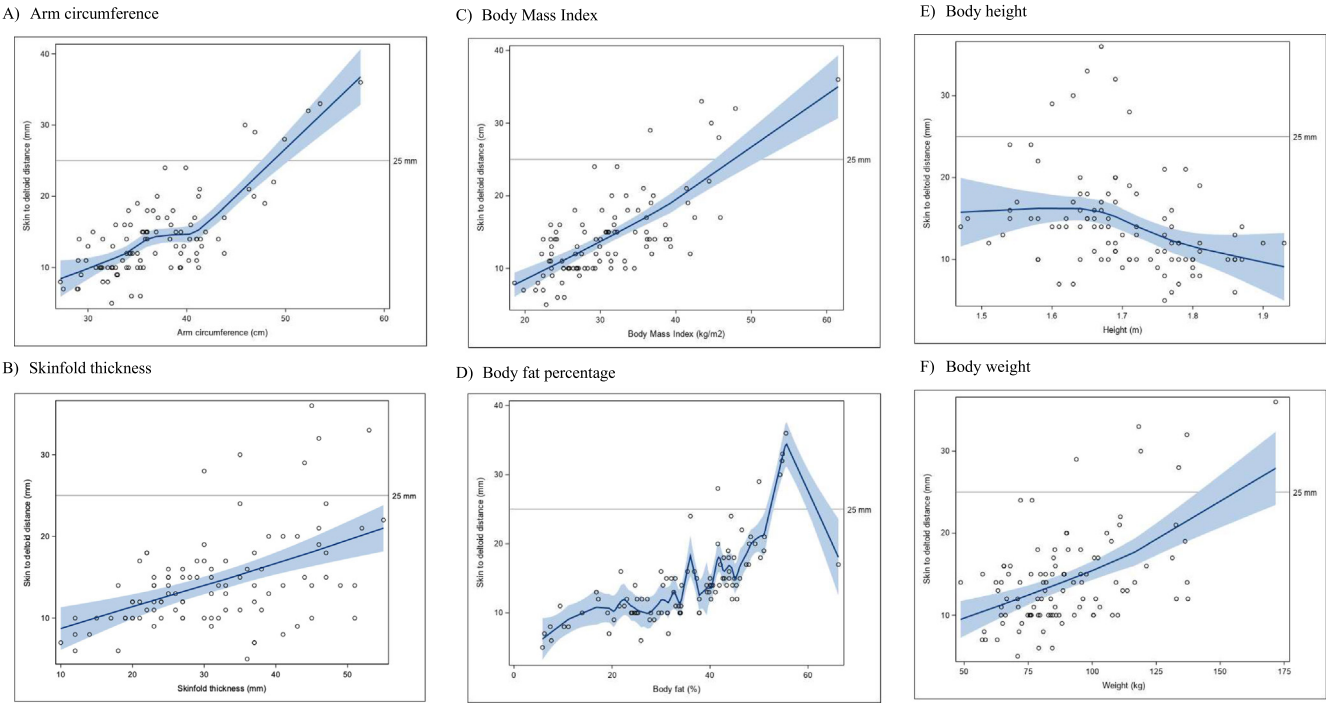

Fig. 3. LOESS plots of the relationship between ultrasound skin to deltoid muscle distance (SDMD) and anthropometric measurements.

Table 2
Association between skin to deltoid muscle measurements and anthropometric measurements by linear regression.

Predictor	Skin to deltoid muscle distance per unit increase predictor (95 % CI)	R-squared	Correlation coefficient	P
Arm circumference (cm)	0.77 (0.64 to 0.90)	57.8	0.76	<0.001
Skinfold thickness (mm)	0.28 (0.18 to 0.37)	25.5	0.50	<0.001
BMI (kg/m^2)	0.59 (0.48 to 0.70)	53.5	0.73	<0.001
Body fat (%)	0.34 (0.27 to 0.40)	50.7	0.71	<0.001
Height (m)	−20.0 (−31.5 to −8.5)	10.9	−0.33	<0.001
Weight (kg)	0.14 (0.09 to 0.18)	28.4	0.53	<0.001

Table 3
Area under the receiver operating characteristic curve for skin to deltoid muscle distance.

	Cut-point AUC ROC	
Predictor	20 mm	25 mm
Arm circumference (cm)	0.94	0.99
Skinfold thickness (mm)	0.88	0.81
BMI (kg/m^2)	0.89	0.97
Body fat (%)	0.90	0.94
Height (m)	0.66	0.66
Weight (kg)	0.81	0.92

Table 4
Comparisons of anthropometric measurement variables in relation to sex.

Variable	Female minus Male Estimate (95 % CI)	P
Age (years)	−0.02 (−5.86 to 5.82)	0.99
Arm circumference (cm)	0.71 (−1.60 to 3.02)	0.54
Skinfold thickness (mm)	4.68 (0.54 to 8.82)	0.027
BMI (kg/m2)	1.46 (−1.45 to 4.36)	0.32
Body fat (%)	13.6 (9.5 to 17.8)	<0.001
Height (m)	−0.14 (−0.17 to −0.12)	<0.001
Skin to deltoid muscle distance (mm)	5.24 (3.15 to 7.33)	<0.001
Weight (kg)	−10.34 (−19.06 to −1.62)	0.02

increased body fat to lean body mass ratio compared with men [29]. These results suggest that different anthropometric cut points for predicting SDMD are required for female and male adults.

The relationship between anthropometric measures and SDMD measured by ultrasound was investigated as a basis for determining if cut points for such measures could be used at vaccination sites, recognising that ultrasound would not be a feasible method to use in mass vaccination programmes. We extended the previous reports that BMI was strongly associated with SDMD measured by ultrasound [10,22,25,26]. Arm circumference, BMI and body fat percentage all had strong linear relationships with SDMD, with correlation coefficients greater than 0.7. In this dataset, arm circumference was the best predictor of SDMD measurements. An arm circumference of 45.9 cm or greater had a sensitivity of 100 % and a specificity of 96 % for a SDMD of > 25 mm. BMI also had good predictive ability; for example, a BMI of 36.6 kg/m^2 or greater had a sensitivity and specificity for a SDMD of > 25 mm of 100 % and 85 % respectively.

Strengths and weaknesses

We studied a population that was predominantly European New Zealanders and so the findings may not be generalisable to other ethnic groups in which differences in body fat distribution may occur [30]. Further study in ethnic groups with high rates of comorbidities such as obesity, and which have greater risk of severe disease with COVID-19 is required. The relatively small dataset including 100 participants limited the precision of our estimates.

Compression from the ultrasound probe could distort subcutaneous tissue and result in underestimation of the SDMD [10,22]. To minimise this risk, minimal pressure was used in obtaining the recordings. In future research the option of utilizing other modalities such as CT or MRI scanning exists, although practical, cost and other issues such as radiation dose with CT scanning may limit their utility.

The recommended site of deltoid intramuscular injection varies between national vaccination guidelines [17,20,21,31]. This is potentially an important consideration, given evidence that the precise location used influences the SDMD [23,24]. The site measured in this study (recommended in Australian 2020 immunisation guidelines), may result in a greater SDMD than a measurement taken at the site recommended in American guidelines [31], and a smaller SDMD than at the site recommended in New Zealand guidelines [20]. In the UK, 'The Green Book' recommends injections within a broad triangular area over the deltoid muscle, within which the SDMD will vary depending on the site chosen [17]. The injection site in local vaccination guidelines should be considered when interpreting the results of this study.

In addition to reporting the proportion in whom the SDMD was greater than the standard 25 mm needle length, the proportions greater than 20 mm, 32 mm and 38 mm were also reported. The 20 mm distance was chosen due to the expert opinion that the vaccine must be delivered at least 5 mm within the muscle to ensure adequate intramuscular delivery [10], whereas the 32 mm and 38 mm distances were chosen to represent the alternative needle lengths available internationally [17,20,21,31]. Using these criteria, in 11 % of participants the 25 mm needle length may not have ensured intramuscular delivery, and in 2 % and 0 % the 32 mm and 38 mm needles respectively, may not have reached the deltoid muscle at the studied injection site.

Public health implications

The findings can be viewed from a number of public health perspectives. Firstly, and most importantly, regulatory approval has only been granted for the intramuscular administration of mRNA and viral vector COVID-19 vaccines, indicating that if the vaccine is delivered into the subcutaneous tissue, it is not being administered in accordance with its approved registered use.

Secondly, and more generally, it is known that underpenetration of the needle risks reduced immunogenic response to other intramuscular vaccines [10,32]. The magnitude by which lack of intramuscular delivery of COVID-19 vaccines may reduce the intended immune response to COVID-19 vaccines has not been investigated, although relevant to this study, it has been reported that the antibody response to SARS-CoV-2 BNT162b2 vaccine is higher in low and normal-weight individuals than overweight and obese [33,34]. However, the length of the needles used was not reported, and there may be confounding by the systemic inflammatory response in obesity, which may also impair immune functioning [35]. Reduced levels of anti-SARS-CoV-2 IgG and neutralising antibodies after COVID-19 mRNA vaccination have been reported in people with Type 2 diabetes compared with healthy

people with no effect due to obesity [36]. Recently, Watanabe et al reported that central obesity (as assessed by waist circumference) was associated with lower antibody responses to the same vaccine, but not BMI [37]. As obesity is a major risk factor for increased morbidity and mortality in COVID-19 infection, and is a predictor of required needle length to ensure deposition of the COVID-19 vaccine into muscle, determining the interactions between obesity, COVID-19 vaccine deposition and the COVID-19 vaccine response will be important to resolve.

Thirdly, subcutaneous injection may result in an increased risk of adverse effects, such as local tissue reaction, abscesses, and granulomas, compared with intramuscular injection [10,12,14]. It is possible that such risk could adversely influence vaccine take up, an important issue with COVID-19 vaccine hesitancy.

Fourthly, it is apparent that a 25 mm needle should not be a universal needle length for COVID-19 vaccine administration and particularly not for obese adults with diabetes. While recognising that body fat distribution may differ in diabetes [26,38], it may be reasonable to infer that this interpretation also applies to obese adults generally, regardless of the diagnosis of diabetes; however, this will need to be the subject of further study.

Fifthly, 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.

Finally, the potential for reduced efficacy due to the COVID-19 vaccine not being delivered into the muscle could apply to a substantial proportion of the population. In New Zealand, the prevalence of diabetes is about 5.5 % of the adult population [39], and around one in three adults are obese [40]. The proportion of adolescents and adults in whom a needle longer than 25 mm was used in the New Zealand COVID-19 vaccination programme is currently 2.04 % [37]. Our findings suggest a larger proportion of the New Zealand population may benefit from vaccination with a larger needle.

In conclusion, the standard needle length of 25 mm is likely to be insufficient to ensure deposition of COVID-19 vaccine in the deltoid muscle of a small but important proportion of obese adults with diabetes. The risk of extra-intramuscular deposition of COVID-19 vaccine is greater in females and progressively increases with increasing BMI. Further research is urgently required to inform the relationship between anthropometric characteristics and SDMD in both children and adults in different populations to guide the needle length used in COVID-19 vaccination programmes globally.

Data availability

Data will be made available on request.

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.

Acknowledgements

We thank the volunteers who generously took part in this study. We thank the Ruth Maud Ring Spencer Estate, proudly managed by Perpetual Guardian, for funding the study.

Funding:

The study was funded by the Ruth Maud Ring Spencer Estate. The MRINZ receives Independent Research Organisation funding from the Health Research Council of New Zealand.

Contributions:

Concept and design of the study: AM, AS, CK, IB, MH, MW (Mark Weatherall), RB, TH. Acquisition of data: LK, MB, MD, MW (Michaela Walton), RS, SK. Recruitment material and online advertising: CK. Analysis and interpretation of data: AE, CK, JB, MD, MW (Mark Weatherall), RB, TH. Drafting the article: MD, RB, TH. All authors revised the manuscript and have given approval for submission of the final article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100248.

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