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# Inadequate deltoid muscle penetration and concerns of improper COVID mRNA vaccine administration can be avoided by injection technique modification

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ABSTRACT

*Background:* Recent phase-3 clinical trials have demonstrated very encouraging results for mRNA based vaccines against COVID-19. Current FDA and manufacturer guidelines mandate intramuscular administration of these vaccines, as other administration routes may not provide the same levels of effectiveness and safety. Observing the vast amount of published media images of persons receiving their vaccines, the authors noted in many cases the injection technique involved skin bunching, raising concerns of inadequate deltoid muscle penetration and consequent lowered vaccine efficacy. Our study hypothesis was that skin bunching will increase the skin-to-muscle distance over 20 mm, the maximal distance allowing the required 5 mm muscle penetration with a 25 mm needle.

*Materials and methods:* 60 adult volunteers from our hospital staff were recruited, and using ultrasound, the skin-to-muscle distance measured in three positions: flat, skin bunching and muscle bunching. The skin-to-muscle distance difference and correlation with gender and BMI were calculated.

*Results:* Skin bunching significantly increased the skin-to-muscle distance in all subjects. In 6 (10%) subjects, this increase exceeded the 20 mm limit. Having a skin-to-deltoid distance of 20 mm or more strongly correlated with a BMI of 30 or more.

*Conclusions:* Skin bunching will prevent adequate intramuscular injection of vaccines in a small percentage of persons, but as hundreds of millions are expected to receive mRNA vaccines in the coming months, the multiplied result can have significant personal and societal consequences for millions of people globally, especially in obese populations, and therefore this practice should be strictly discouraged.



## 1. Background

Two phase-3 clinical trials of mRNA vaccines against Corona virus disease 2019 (COVID-19) have been recently published [1,2] demonstrating the safety and efficacy of this new technology, giving great hope in the fight against the current pandemic. In both trials, the vaccination protocol mandated intramuscular (IM) administration of the lipid nanoparticle (LNP) encapsulated mRNA vaccine, in line with previous evidence demonstrating a higher immune response when compared with other delivery or administration methods [3]. Both pharmaceutical companies manufacturing the two vaccines have provided administration instructions, specifying intra-deltoid muscle injection as the only option in adults [4,5].

Vaccines based on mRNA technology can be injected intradermally, subcutaneously, intramuscularly or intravenously [6], with possible significant differences in response [7]. While subcutaneous injection of a LNP coated vaccine in an animal model has shown a different lymph node distribution pattern but similar immune response [8], there is no evidence to support the same in humans or in the currently used mRNA COVID-19 vaccines specifically. Substantial evidence to the contrary is available regarding other vaccine types such as Hepatitis B, influenza and Rabies, demonstrating lower immune response when injected subcutaneously (SC) [9,10].

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IM injection at the deltoid muscle is common practice. It is performed blindly according to anatomical landmarks without imaging verification of needle tip position; therefore, it is unclear what percentage of injections are indeed IM. Current Centers for Disease Control (CDC) practice guidelines for IM vaccine injections [11] are based on a single deltoid fat pad thickness study in adults [12] and a single study in adolescents [13]. Both studies found that in non-obese patients, a 16–25 mm needle length will provide at least 5 mm of muscle penetration, if directed at a $90^0$ angle to the skin. If the subcutaneous fat layer is thicker, or the trajectory different than $90^0$, a longer needle might be needed.

Several agencies and regulatory bodies instruct health care professionals to either flatten the overlying skin before injection or squeeze the deltoid muscle in persons with a suspected smaller muscle mass [14]. Observing the large numbers of recently published media images of persons receiving their vaccine, the authors noted that in many cases the injection technique involved "bunching" of the skin over the injection site i.e. folding the skin overlaying the deltoid muscle between two fingers and inserting the hypodermic needle into the fold (Fig. 1), thus theoretically increasing the distance between the skin and the deltoid muscle and casting significant doubt whether the injection was indeed within the required 5 mm IM penetration.

Other concerns of deleterious effects of inadvertent subcutaneous injection secondary to short needles or skin bunching include increased risk of vaccine failure [15,16], and local adverse events following immunization (AEFI), namely pain, subcutaneous fat necrosis and scarring [16,17]. Shoulder injury related to vaccine administration (SIRVA) is another concern, although it is theorized to be the result of intracapsular penetration of the shoulder joint rather than subcutaneous injection [18,19].

As hundreds of millions of people around the world are expected to receive an mRNA COVID-19 vaccine in the upcoming months [20], it is essential that injections be done effectively. If only 10 percent are mis-injected, many millions might incorrectly be assumed to be immune, with possibly significant personal and societal consequences.

Searching the PubMed and google scholar databases, we have not found a study examining the effect of skin bunching on the skin-to-deltoid distance. Our study hypothesis was that skin bunching can increase the skin-to-muscle distance to 20 mm or more and that the higher the body mass index or arm circumference, the greater the probability of this occurring.

**Fig. 1.** Bunching of the skin during intramuscular vaccine administration, raising the question of appropriate depth of muscle penetration. Pictured: An Arizona National Guard soldier administers COVID-19 vaccine in Payson in Jan. 4th 2021 (Photo by Tech. Sgt. Michael Matkin, Arizona National Guard, Creative Commons copyright).

Materials and methods

Using intrahospital messaging groups (Whatsapp inc., Mountainview, CA, USA), 60 healthy adult volunteers from our hospital personnel, 29 female and 31 male, with no prior injury or medical comorbidity affecting their arms, were recruited and consented to have the distance between the skin and the deltoid muscle measured by ultrasound (US). Following a directive from our institutional ethics committee, volunteers from the corresponding author's department were not recruited.

With the arm resting at the side of the body, a standardized reference point (SRP), 6 cm distal to the acromion and midway in the sagittal plane was marked with non-soluble ink on the skin of the dominant arm and the circumference of the arm at the axillary fold was measured (Fig. 2). Weight, height and age of each volunteer were recorded and body mass index (BMI) calculated.

Ultrasound examinations were performed and interpreted by two radiologists. To reduce inter-observer differences, all examinations in women were done by one radiologist and in men by the other.

Image storage and visualization were done on our hospitals picture archiving storage system (Centricity Universal Viewer, GE healthcare, USA).

Using real-time ultrasonography (EPIQ5G scanner, Philips, USA) and a high-frequency 5–12 MHz linear-array transducer with standard general musculoskeletal (MSK-general) pre-set, three images and measurements of the subcutaneous adipose tissue (skin to deltoid muscle distance) were obtained for each subject:

1. Flat: The measurement taken as-is; without any skin pressure, flattening or bunching, using copious amounts of gel and a non-compression technique (Fig. 3).
2. Skin bunching (SB): measurement taken while bunching the skin (Figs. 4 and 5).


**Fig. 2.** Skin markings for standard reference point (SRP).

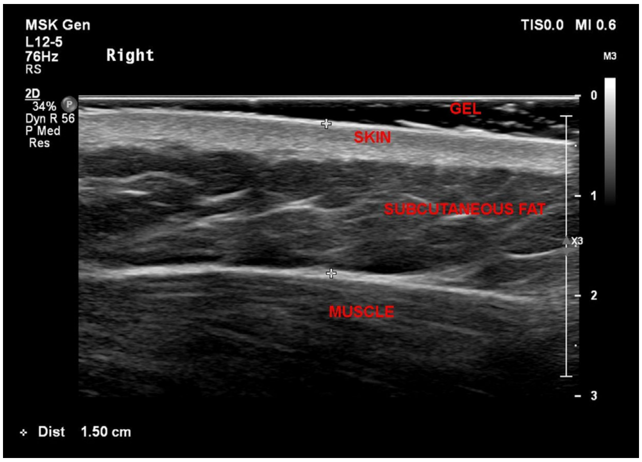


**Fig. 3.** Skin to muscle distance in subject A when the skin or muscle were not bunched. The overlaying copious amount of gel is clearly visualized demonstrating this measurement was done without the transducer exerting pressure on the skin.

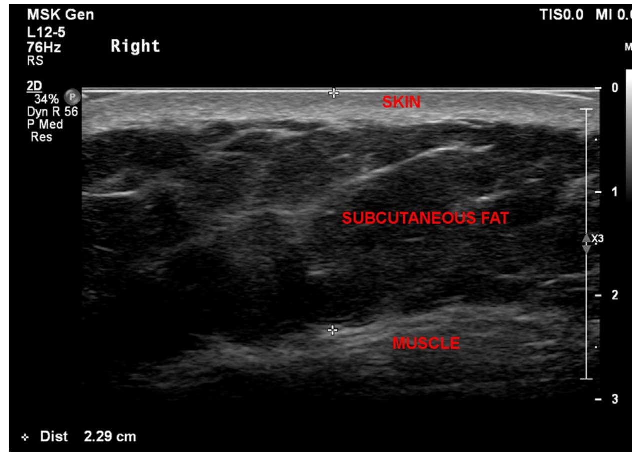


**Fig. 5.** Skin to muscle distance in subject A when the skin is bunched. Although still within the acceptable range for proper IM needle penetration, skin bunching increased the distance by approximately 50%.

**Fig. 4.** Examination while skin bunching.

3. Muscle bunching (MB): measurement taken while bunching the deltoid muscle (MB). This is done by squeezing the muscle between two fingers in the anterior-posterior direction in order to increase the muscle depth in the lateral-to-medial direction.

Statistical analysis and sample size calculation

Based on data available from previous studies [12,21], the average depth of the skin and underlying fat pad over the deltoid muscle is 8.3 mm in men and 11.7 in women. Current practice guidelines recommend using a needle 25 mm in length, to ensure a 5 mm penetration of the tip into the deltoid muscle, so a difference of more than 8 mm in women and 12 mm in men, or a total of 20 mm or larger difference between the flat injection technique and the SB technique could be considered significant.

Sample size was calculated using IBM SPSS SamplePower software, version 3.0.

For 30 women, based on a one-sample *t*-test with 1% significance and a two-tailed test, the calculated power was 94%.

For 30 men, based on a one-sample *t*-test with 1% significance and a two tailed test, the calculated power was 100%.

Results are expressed as mean and SD for normally distributed data and median and interquartile range for non-normally distributed data. Differences between the means of different groups were analyzed using Student *t*-test for normally distributed and Wilcoxon signed ranks test for non-normally distributed data. Differences in frequency distribution were estimated using the $\chi 2$ test.

## 2. Results

Sixty adult volunteers were recruited, 29 female and 31 male. The mean age was 44.77 (24–68, sdv 12.3), mean BMI was 26.09 (19.03–33.21, sdv 3.32) and mean arm circumference 340.5 mm (250–440, sdv 40.86). 24 (40%) of the subjects had a BMI of 18.5–24.9, 26 (43.33%) had a BMI of 25–29.9, and 10 (16.66%) subjects were obese, having a BMI greater than 30 (table 1). None of the subjects had a BMI of<18.5.

The mean skin-to-muscle (STM) distance was 9.97 mm (sdv 2.65) in females and 8.06 mm (sdv 2.62) in males when measured flat, 15.24 mm (sdv 3.19) in females and 12.29 mm (sdv 3.79) in males with skin bunching and 8.5 mm (sdv 2.78) in females and 7.16 mm (sdv 2.49) in males with muscle bunching (table 2).

In both females and males, we found a significant difference between flat to SB ($P < 0.001$), flat to MB ($P < 0.001$) and SB to MB ($P < 0.001$) (Table 3).

Regarding our study hypothesis, in 6 (10%) of all subjects, SB increased the skin-to-muscle distance to the threshold of 20 mm or more. This was more common in the female group (4/29 or 13.8%) but the difference between genders could not be analyzed statistically because the numbers were too small. In five of these subjects, (four females) the BMI was over 30. Arm circumference correlated with the BMI (Pearson correlation coefficient 0.732, 2-sided T-test $P = 0.01$)

## 3. Discussion

We have found that in 6/60 (10%) of our study population, skin bunching can create a skin-to-muscle distance of 20 mm or greater,

**Table 1**
Age, weight, height, BMI and arm circumference of all subjects combined and divided into female and male.

| TOTAL | Range | Mean | Median | SDV |
|---|---|---|---|---|
| Age (years) | 24–68 | 44.77 | 42.00 | 12.3 |
| Weight (KG) | 47–110 | 77.62 | 75.00 | 14.0 |
| Height (CM) | 1.52–1.92 | 1.72 | 1.71 | 0.10 |
| BMI | 19.03–33.21 | 26.09 | 25.325 | 3.32 |
| Arm circumference (CM) | 250–440 | 340.50 | 340.00 | 40.86 |
| **MALES** | Range | Mean | Median | SDV |
| Age (years) | 24–68 | 44.77 | 38.00 | 12.315 |
| Weight (KG) | 55–110 | 86.47 | 88.00 | 12.33 |
| Height (CM) | 1.70–1.92 | 1.795 | 1.78 | 0.067 |
| BMI | 19.03–33.21 | 26.80 | 27.15 | 3.39 |
| Arm circumference (CM) | 270–440 | 365 | 360.0 | 33.57 |
| **FEMALES** | Range | Mean | Median | SDV |
| Age (years) | 25–64 | 47.97 | 52.01 | 11.7 |
| Weight (KG) | 47–85 | 68.16 | 70.00 | 8.51 |
| Height (CM) | 1.52–1.75 | 1.64 | 1.63 | 0.06 |
| BMI | 20.34–30.85 | 25.34 | 24.95 | 3.12 |
| Arm circumference (CM) | 250–380 | 314.31 | 310.0 | 30.58 |

**Table 2**
skin-to-muscle measurements in the three positions.

| FEMALES | Range | Mean | Median | SDV |
|---|---|---|---|---|
| flat | 6–17 | 9.97 | 10.0 | 2.625 |
| Skin bunching | 10–22 | 15.24 | 15.0 | 3.19 |
| Muscle bunching | 5–17 | 8.50 | 8.00 | 2.78 |
| MALES | Range | Mean | Median | SDV |
| flat | 4–16 | 8.06 | 8.00 | 2.62 |
| Skin bunching | 7–23 | 12.29 | 12.00 | 3.76 |
| Muscle bunching | 4–14 | 7.16 | 7.00 | 2.49 |
| All numbers are in millimeters | | | | |

**Table 3**
The differences in skin-to-muscle distance between the three measurement positions were significant in both females and males.

| FEMALES | Range | Mean | Median | SDV | | test |
|---|---|---|---|---|---|---|
| SB-FLAT | 2–8 | 5.28 | 5 | 1.62 | P < 0.001 | Paired samples test |
| MB-FLAT | (-3)-2 | −1.38 | −2.00 | 1.35 | P < 0.001 | Wilcoxon signed ranks test |
| SB-MB | 0–10 | 6.65 | 7.00 | 2.27 | P < 0.001 | Paired samples test |
| MALES | Range | Mean | Median | SDV | | test |
| FLAT-SB | 2–9 | 4.22 | 4.00 | 1.94 | P<0.001 | Wilcoxon signed ranks test |
| FLAT-MB | (-3)-1 | −0.90 | 1.00 | 0.94 | P<0.001 | Paired Samples Test |
| SB-MB | 2–11 | 5.13 | 4.00 | 2.16 | P<0.001 | Paired Samples Test |

leading to insufficient muscle penetration concerns. 5/6 (83.33%) of these subjects had a BMI greater than 30. Searching the PubMed and Google scholar databases, we have not found another study describing the differences in skin-to-muscle distance when bunching the skin over the injection site or if the needle is directed at a different angle than $90^0$. Using real-time sonography we were able to visualize this substantial difference and quantify it.

Ten out of the sixty subjects (10–60, 16.6%) were obese, having a BMI of 30 or more. As having a skin-to-deltoid distance of 20 mm or more strongly correlated with obesity, and the obesity rate in the Israeli general population is 23.2% for men and 29% for women [22], our study under-represented this group, hence it is reasonable to assume that more than 10% of the general population will have an injection depth of 20 mm or more if their skin is bunched while receiving their vaccination. In countries where obesity is more prevalent – these differences may be even higher.

We have found that muscle bunching, advocated by some vaccination guidelines for persons with suspected lower muscle mass, leads to a minimal reduction in the skin-to-muscle distance in normal, overweight and obese subjects, but, if done incorrectly, will bunch the skin and increase this distance. Our cohort did not include underweight subjects so we cannot state whether muscle bunching will produce significant changes in skin-to muscle distance in this subset, although it stands to reason that the deltoid fat pad will be thinner in this group than in the other three BMI groups, and therefore not change significantly.

Muscle bunching is indeed recommended only in patients with suspected lower muscle mass, but in common practice this recommendation is difficult to implement for two reasons: BMI is not always calculated, especially in mass-immunization efforts such as the current pandemic, and because muscle bunching requires anatomical understanding and some practice to do correctly. The two radiologists performing the measurements in our study found that even when done under US control, some practice and repeated attempts were needed to actually bunch the deltoid muscle. We feel that the vaccine provider in the field, sometimes a person with only basic training, will find this task beyond their skill set.

The result of these difficulties is that in some cases, inadvertent skin bunching is done instead of muscle bunching, along the entire range of BMI, producing the injection-depth issue we point to in this study.

In addition, the radiologists in our group who did the muscle bunching under US guidance, felt this maneuver is often not easy to achieve, and in some cases took several attempts. As the only reason muscle bunching is performed is to reduce concerns of needle penetration to the bone, we feel this practice should be abandoned altogether to prevent inadvertent skin bunching and SC injection instead.

Another possible concern is the injection angle. Our measurements assume an accurate $90^0$ trajectory. If the injection needle is not inserted at an angle of $90^0$ to the skin, the skin-to-muscle distance will increase by [$90^0$ skin-to-muscle distance] + 20/sin(90-injection angle), increasing the percentage of improper muscle penetration.

Our study's main significance is in the multipliers. Although the immune effects of inadequate IM penetration while receiving an mRNA vaccine have not been clinically studied, and the concern is valid in a relatively small number of patients, multiplying this small effect by the large numbers expected to receive mRNA vaccines raises concerns that many millions of people will be under-vaccinated globally, especially in countries where obesity is prevalent. In countries opting for a one-dose regimen, the effect might be more profound as there is no "second chance" if the first was indeed mis-administered.

Our study has several limitations. Our cohort included healthy hospital personnel, none with a BMI reflecting underweight or aging, groups where muscle bunching is advocated by immunization guidelines. As subjects were examined by the two radiologists according to gender, this might produce a different inter-observer bias.

As intentional or inadvertent skin bunching in normal, overweight and obese persons can increase the skin-to-muscle distance beyond the 20 mm threshold required by immunization guidelines for adequate muscle penetration, and in light of the current pandemic and the importance of the global immunization effort, we join other opinions voiced [17,23,24] and recommend that health care providers injecting mRNA vaccines be instructed to insert the hypodermic needle at the deltoid injection site "as is" without attempted skin or muscle bunching, verifying a $90^0$ insertion angle.

**Ethical declaration**: This study was approved by the Galilee medical center's ethics committee (0005-21-NHR). Informed consent was obtained from all volunteers.

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## 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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