The Skin: Nature's Immunological Gateway for Vaccination

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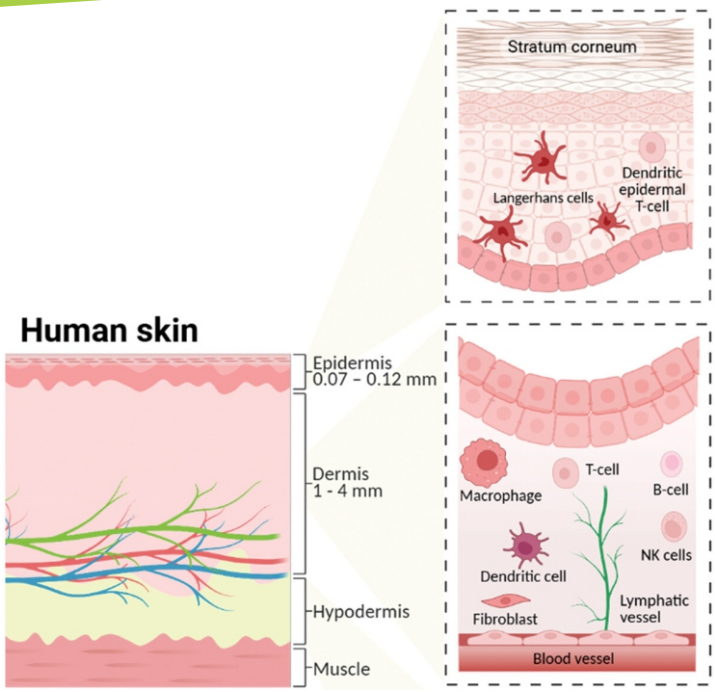
Skin is our largest organ; it is a dynamic, multilayered barrier that not only protects us from the outside world but also plays a key role in immune defense. With a surface area of nearly two square meters and populated by billions of cells, it constantly communicates with the immune and nervous systems to maintain homeostasis and defend against pathogens. Structurally, it consists of three main layers: the epidermis, dermis, and hypodermis [1].
A schematic view of the different cell types populating the skin [2].

The epidermis, our outer barrier, is composed primarily of keratinocytes tightly bound together to form the stratum corneum, a wall-like structure that prevents water loss and protects against microbes and mechanical damage. Langerhans cells reside in the epidermis and contribute to immune surveillance at the skin surface. Beneath this lies the dermis, the true immunological engine of the skin. The dermis is richly vascularized and contains a dense network of immune cells, including dendritic cells (DCs) and T cells, which play essential roles in recognizing pathogens and initiating immune responses [1]. This cellular abundance makes the dermis an exceptionally promising site for vaccine delivery [3].



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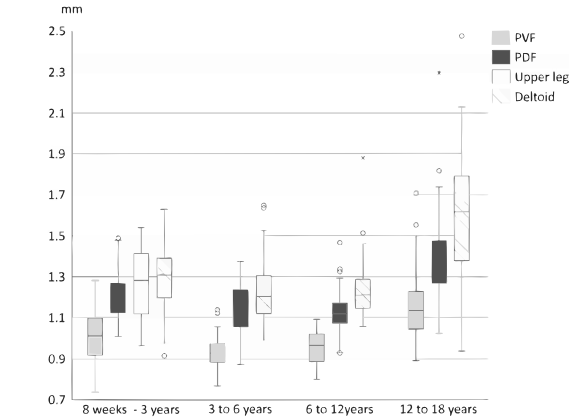
Why is skin an optimal target for vaccination?

Traditional vaccine administration routes, intramuscular (IM) or subcutaneous (SC), were chosen largely for convenience, rather than immunological efficiency. In contrast, the intradermal (ID) route directly targets antigen-presenting cells within the skin, triggering strong and rapid immune activation. Studies have consistently shown that intradermal vaccination can achieve equivalent protection with only 10–20 % of the dose used intramuscularly [4].
Non-inferiority of reduced-dose ID vaccination has been successfully demonstrated compared to SC vaccination for mpox [5-7], and compared to IM vaccination for hepatitis B [8,9], polio [10-13], rabies [14], hepatitis A [15,16], influenza [8,17-19], yellow fever [20,21], and SARS-CoV-2 [22,23]. During vaccine shortages, health authorities such as WHO, EMA, and FDA have recommended intradermal administration of fractional doses, typically one-fifth of the usual volume, without compromising immune protection [11,24].
Beyond dose sparing, the ID route targets the outer layers of the skin, which are rich in DCs that play a key role in initiating immune responses. ID administration typically uses smaller needles to deliver the vaccine superficially, without penetrating deeply enough to reach blood vessels or most pain receptors, which may contribute to improved tolerability while also enhancing immune responses [25,26].

The challenge of intradermal vaccination: precision and reproducibility

Despite its clear advantages, accurate intradermal injections are technically challenging. The target zone, the dermis, is only 1.6 to 1.8 mm thick in adults, depending on location, gender, and body mass index, and approximately 1.2 mm in children. Men tend to have thicker dermal layers, while the skin on the ventral side of the forearm is thinner than on the dorsal side or upper arm [25,27].



Body site Skin thickness in milimeter - Mean (SD)					p-value*
PVF	1.01 (0.12)	0.91 (0.08)	0.93 (0.08)	1.14 (0.15)	< 0.001
PDF	1.23 (0.11)	1.13 (0.12)	1.10 (0.10)	1.36 (0.20)	< 0.001
Upper leg	1.29 (0.15)	NA	NA	NA	NA
Deltoid	1.30 (0.16)	1.20 (0.14)	1.20 (0.13)	1.59 (0.28)	< 0.001

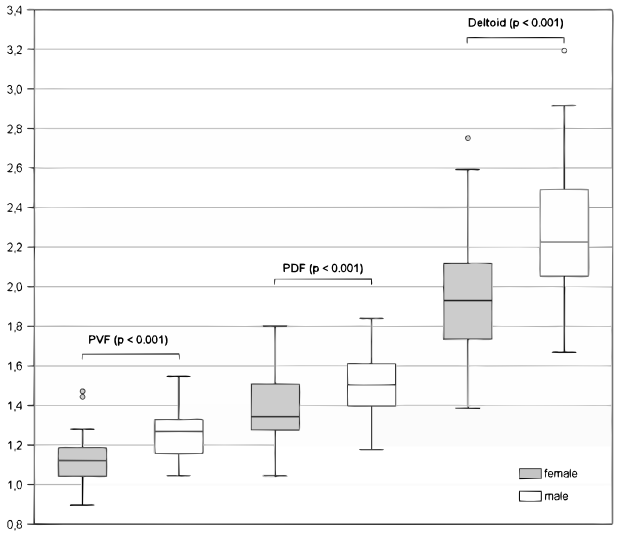
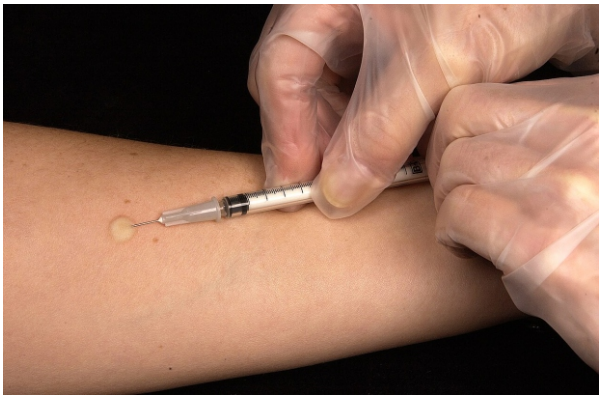
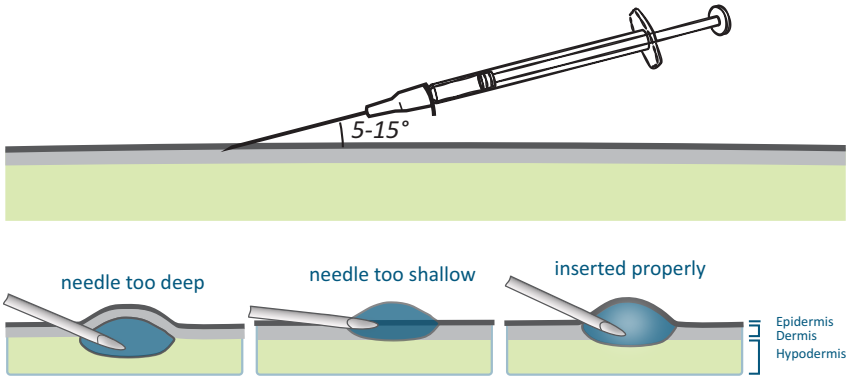


Figure: Skin thickness children 8 weeks to 18 years [8] (left); Skin thickness adults 18+ [10] (right)

Conventional Mantoux injections, performed manually with a hypodermic needle, require a shallow 5–15° angle and precise insertion depth. Even among trained professionals, up to 70 % of ID injections are performed incorrectly, often missing the dermis entirely, leading to variability in immune response [28].





Mantoux technique with possible incorrect administrations of the injection.

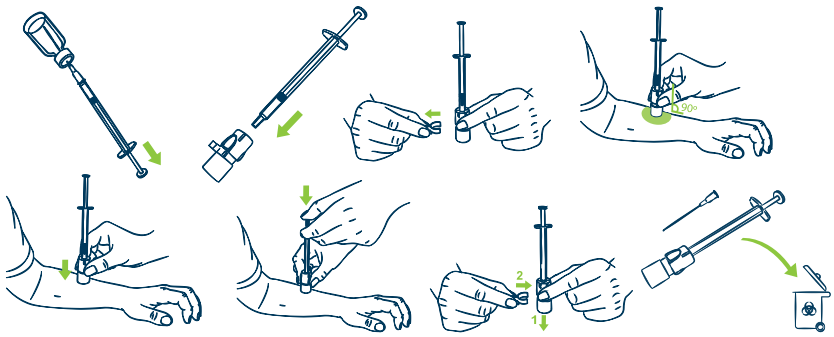
Interethnic Variability in Skin Thickness

Comparative studies investigating skin thickness across different ethnic populations have shown only minor variations in total epidermal and dermal thickness. Although minor differences have been seen in skin thickness when comparing different ethnic skin types, including Caucasian, African, Asian, and Latin American skin, the findings do not appear to be consistent across studies [27,29,30,31,32]. The observed interethnic differences—typically less than 0.1 mm—are far smaller than the natural variation seen between anatomical sites, such as the forearm and deltoid regions. Also, research in African populations has shown that melatonin content impacts skin characteristics and that African skin is not uniformly thicker compared to other skin types. [33, 34]. This anatomical variability outweighs any ethnicity-based differences, supporting the expectation that intradermal delivery devices like VAX-ID® perform consistently across populations, including Caucasian, African, Asian, and Latin American cohorts [35].

Technological innovations: making intradermal delivery reliable and easy

To unlock the full potential of the skin, innovative delivery systems are essential. One such device is VAX-ID®, developed by Idevax. The technology allows controlled, reproducible, and virtually painless intradermal administration, ensuring that vaccines are precisely deposited into the dermal layer, independent of operator skill [36].

VAX-ID® has been validated through ultrasound and histological studies in both humans and preclinical models, demonstrating accurate injection depth and consistent vaccine deposition. In a clinical study using a fractional dose Hepatitis B vaccine, VAX-ID® achieved equivalent immunogenicity to full-dose intramuscular injection, with only mild local redness reported as a side effect [9].



Why intradermal vaccination matters?

Intradermal vaccination taps into the immunological richness of the skin, enabling lower doses, fewer side effects, and scalable protection for more people, all with a smaller environmental and economic footprint. By bridging advanced biomedical engineering with natural immunology, the skin can truly become the gateway for equitable, efficient, and sustainable global immunization.

References

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