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Preclinical evaluation of performance, safety and usability of VAX-ID®, a novel intradermal injection device

Koen C.L. Beyers [a,*,1], Momen N.M. Rbeihat [a,1], Daniele S. Vasconcelos [a], Danielle Pasmans [a], Stijn Verwulgen [a,c], Vanessa V.J. Vankerckhoven [a,b]

[a] Idevax BV, Wijnegem, Belgium
[b] Center for evaluation of vaccination, University of Antwerp, Belgium
[c] Faculty of Design Sciences, Department of Product Development, University of Antwerp, Belgium

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ABSTRACT

The recent SARS-Cov2 pandemic and mpox health emergency have led to renewed interest in intradermal vaccination due to its dose sparing potential. Indeed, intradermal vaccination is particularly of interest for use in mass vaccination campaigns, pandemic preparedness programs, and/or for vaccines that are expensive or in short supply. Moreover, the rich immune network in the skin makes it an attractive target not only for prophylactic vaccination, but also for therapeutic vaccination, like immunotherapy and (dendritic) cell-based therapies.

The aim of the current paper was to provide an overview of preclinical data generated with VAX-ID®, a novel intradermal drug delivery device, to allow assessing it performance, safety and usability. The device can overcome challenges seen with the Mantoux technique whereby the needle needs to be inserted under a shallow angle. Various parameters of VAX-ID® were evaluated, including dead-space volume, dose accuracy, penetration depth & liquid deposit in piglets, as well as usability by healthcare professionals.

The device has shown to have a low dead volume and a high dose accuracy. Importantly, the device performed successful injections at a predefined depth into the dermis with a high safety profile as confirmed by visual and histological evaluation in piglets. Moreover, the device was rated as easy to use by healthcare professionals.

The combined preclinical performance and usability findings indicate that VAX-ID® can provide reliable, standardized and accurate drug delivery in the dermal layer of the skin with a high ease of use. The device offers a solution for injection of various prophylactic as well as therapeutic vaccines.

1. Introduction

The recent Sars-CoV-2 pandemic and the mpox health emergency have led to a renewed interest in intradermal (ID) vaccination, i.e., injection in the skin, due to its dose-sparing potential. Studies have shown that ID vaccination, using 1/5th or even 1/10th of the dose, elicited a non-inferior immune response compared to a full dose administered intramuscularly (IM) or subcutaneously (SC) [1–4].

Indeed, the dermis is highly vascularized and is rich in different types of immune cells, including dermal Dendritic Cells, macrophages, mast cells, Gammadelta T cells (γδ T cells), and Innate Lymphoid Cells. It is therefore considered an attractive target for both prophylactic and therapeutic vaccine applications [5]. Indeed, clinical applicability has been shown for a variety of vaccines, including Influenza [6,7], Polio [8], Hepatitis B [9–11], Hepatitis A [12], Rabies [13], Yellow Fever [14], COVID-19 [15], and mpox [16]. Although there might not be a sufficiently strong commercial incentive for manufacturers to undertake the necessary steps to change the delivery route for existing vaccines, novel vaccines can be considered likely candidates as the ID route can be evaluated early in the development process. In case of emerging pandemics and health emergencies, ID formulations may help to save doses, achieve herd immunity quickly and aid in rapid scaling of production capacity.

Abbreviations: GLP, Good Laboratory Practice; ID, Intradermal; IFU, Instruction for Use; IM, Intramuscular; SC, Subcutaneous; SD, Standard Deviation; WHO, World Health Organization.

* Corresponding author at: Idevax BV, Bijkhoevelaan 32c, 2110 Wijnegem, Belgium.
E-mail address: koen.beyers@idevax.com (K.C.L. Beyers).

[1] Koen CL Beyers and Momen Rbeihat have equal contribution to authorship.

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Additionally, intradermal vaccination activates Langerhans cells and dermal dendritic cells in the skin dermis. These cells capture and present the antigen(s) to T and B lymphocytes, triggering both a systemic and mucosal immunity. The triggering of the mucosal immunity is evident as this administration route induces the production of secretory Immunoglobulin A (SIgA) [17]. Importantly, the approval of two COVID-19 mRNA vaccines has accelerated mRNA vaccine technology and introduced a new era in vaccinology [18]. Recent data suggest that mRNA vaccines have the potential to solve many of the challenges in vaccine development for both infectious diseases and cancer (prophylactic and therapeutic vaccines). Technological advances have overcome the initial issues of instability and inefficient in vivo delivery [19]. Dendritic cell-based delivery could become a major delivery route for mRNA vaccines that can be achieved by intradermal injection [20].

The current standard of care for ID injections is the Mantoux technique, which uses a syringe and a needle that need to be inserted nearly parallel to the skin, at an angle of 5–15 degrees, bevel up. Following an ID injection, a bleb or wheel will form, which is considered a visual indication of a successful injection [21]. The Mantoux technique is challenging, requiring extensive training for healthcare workers, and is perceived as painful by the recipients. Importantly, it has been shown that over 70 % of the injections are incorrectly performed based on data analysed from 140 skin samples [22].

Over the past decades, various innovative technologies have been developed to overcome the challenges associated with the Mantoux technique, such as liquid jet injectors, microneedles, and microinjection devices [2]. Hollow single microneedles and microneedle arrays can be used to deliver currently available liquid formulations and dendritic cells. Solid coated single microneedles and microneedle arrays offer advantages in terms of vaccine stability during storage, but this requires significant reformulations [23]. Needle-free ID delivery can be achieved via jet injection or particle injection, but they have been commonly associated with local injection-site reactions when compared to traditional IM injections and the cost per unit may prohibit its use as a vaccination device [24]. Today, a variety of intradermal delivery devices with different capabilities has proven to be successful in human clinical trials [25]. There however remains an urgent need for easy-to-use drug delivery devices allowing painless, accurate and standardized intradermal vaccination.

Skin thickness measurements in adults [26] have been key in defining the optimal needle length for targeting drug delivery in the dermal layer of the skin of a novel drug delivery device, VAX-ID®. The first generation of the device was evaluated for its performance and safety in a non-inferiority and immunogenicity trial using a commercially available Hepatitis B vaccine [9]. The insights gained on performance and usability from this trial, next to preclinical evaluations in piglets (Unpublished data) and usability studies (Unpublished data), led to the development of a next generation of VAX-ID®.

The aim of this paper is to provide a comprehensive review of data generated on (i) performance, safety from a technical device study as well as a study in piglets and (ii) usability from a study in 15 HCPs of the newest generation of VAX-ID®, an intradermal drug delivery device by Idevax BV.

2. Materials and methods

2.1. Intradermal drug delivery device VAX-ID®

VAX-ID® (Idevax BV, Belgium; Fig. 1) is a patented drug delivery device developed to allow for reliable ID injections with a high ease of use. Injections are performed perpendicular to the skin at a predefined depth. The device can be pre-configured with a 32G, 30G, or 27G needle with a penetration depth of 0.85, 1.15 and 1.55 mm, respectively.

The main driver to select a specific needle gauge/diameter is driven by (i) viscosity and (ii) composition of the liquid to be injected. Plenty of vaccines have a low 'water-like' viscosity of approximately 1 centiPoise (cP). These can be ejected f.i. with a 32G needle. Substances with a higher viscosity (e.g. 10cP) or with non-Newtonian properties can cause high counterpressure, making it difficult or impossible the eject through thinner needles. In this case, 30G or 27G can be better suited.

Linked to that, needle length is a product of needle gauge, bevel and lancet cut of the needle tip. Therefore, a 32G needle could have a penetration depth of a mere 0.85 mm, when a 27G needle would go as deep as 1.55 mm, depending on cut and grinding angles of the tip. VAX-ID® requires minimal training from a healthcare professional and is straightforward to use. As seen in Fig. 2, a low dead space syringe is loaded with a medicinal product from the vial. Next, the syringe is mounted on VAX-ID® Luer slip opening at the rear end of the device. - VAX-ID is activated by removing the safety pin, after which VAX-ID® is placed on the skin at the dorsal side of the forearm, keeping the adaptor in a perpendicular position. The penetration at the predefined depth into the skin is performed by pushing the housing part of the device down to meet the foot part. By retaining a slight pressure with one hand on the hous-

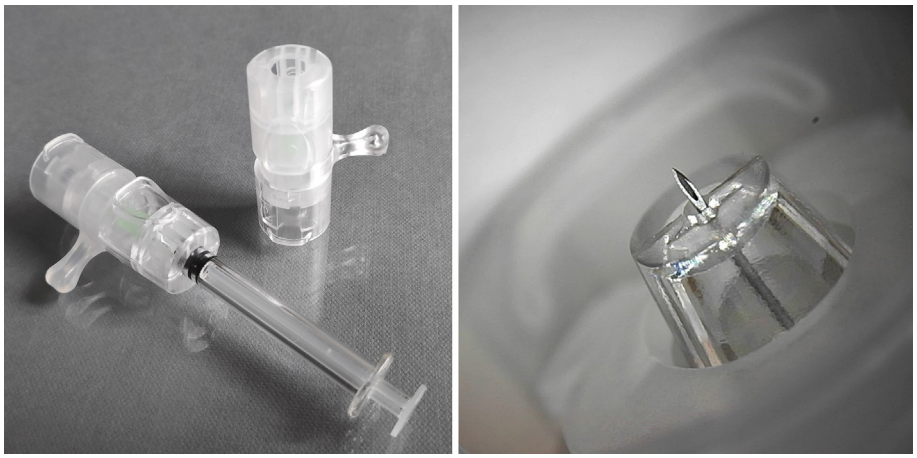

Fig. 1. VAX-ID, intradermal drug delivery device by Idevax.

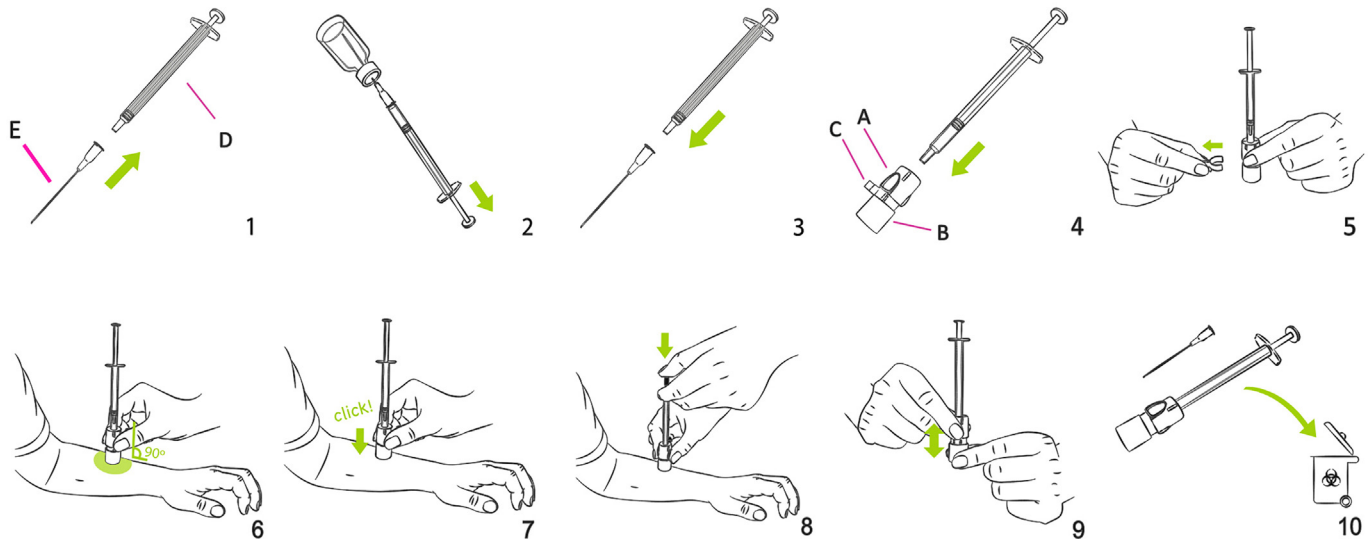

Fig. 2. VAX-ID, instructions for use.

ing part and using the other hand to push the plunger, the fluid is injected.

2.2. Performance using VAX-ID®

2.2.1. Ejection volume, dead-space volume and dose accuracy

A combined sample size of 180 ethylene oxide (EO unvalidated cycle, Steris, the Netherlands) sterilized VAX-ID® (32G devices, n = 115 and 27G devices, n = 65) according to Table 3 of ISO11608 [27], that had previously gone through stress and testing loads of hot and cold atmospheres (n = 60), life cycle tests (n = 20, re-used), free fall (n = 20, re-used), heat storage (n = 60), damp heat (n = 20), cyclical tests (n = 20), and vibration (n = 20) were used to assess ejection volume, dead (residual) volume and dose accuracy.

Dead-space or residual volume is defined as the amount/volume of drug that is wasted after each injection. Dead-space was assessed weighing a non-filled VAX-ID® vs weighing a filled VAX-ID® device. For the filled device, a low dead space syringe (B-Braun, BE) was filled with 0.1 mL of water. The dead-space was calculated by subtracting the measurements of the empty delivery systems from devices loaded with 0 mL of water. Water was used to fill the syringes, to represent water-like substances in density and viscosity. Based on the dead-space of the individual samples, the mean and Standard Deviation (SD) were calculated. The calculated SD of the dead-space volume is a measure of how reliable that dead-space prediction is.

Dose accuracy is defined as the ability to consistently and accurately deliver an intended dose to a vaccinee or a patient. When f.i. consistently drawing 100 µL from a vial and considering 23 µL of dead-space, one can state that from that 100 µL, that 77 µL will be delivered with a standard deviation taken into account on top of that. Definition of dose accuracy is important for any delivery method, be that ID delivery with Mantoux, with VAX-ID, or IM delivery with needle and syringe. Additionally, dose accuracy insights can be a guide to consider overfill for dead volumes and possible deviations.

For this study liquid was drawn by one operator with the aim to fill a 1 mL syringe with at least and as close as possible to 100 µL volume by visual check of the scale printed on that syringe. Of 115 fillings, the average volume was 115 µL, with a standard deviation of 9 µL. Subsequently, the syringe was mounted in the VAX-ID device and the liquid was ejected. Weight measurements were taken of (i) each individual device + empty syringe, (ii) each individual device + filled syringe respectively and (iii) the residual weight of device + emptied syringe. The sum of this gave an ejected average volume of 92 µL with a standard deviation of 9 µL, and a resulting dead-space of 23 µL with a deviation of 6 µL. Consequently, dose delivery accuracy on any drawn volume minus dead-space can be concluded to be 9 µL.

The following data were obtained (in weight) for the VAX-ID® devices (1) Empty, (2) Pre-loaded, (3) Dead (residual) volume. Descriptive statistics were applied on the following parameters: (1) Average dead-space volume in the system, (2) Average liquid withdrawn volume, (3) Average ejected volume.

2.2.2. Evaluation of bleb formation, liquid dispersion, and safety in piglets

Two female piglets of 12 kg were purchased from Topigs (Belgium) and housed at the facilities of Medanex Clinic (Diest, Belgium). The trial was conducted under ethical approval (EC MxCl 2016–066) and according to GLP.

The piglets were anaesthetized for a maximum of one hour with Tiletamine-Zolazepam (2.75 mg Tiletamine + 2.75 mg Zolazepam)/kg IM and Xylazine (Xyl-M®) 2.4 mg/kg IM. A total of 0.10 cc was injected using VAX-ID® configured with a 32G having a protrusion length of 0.85 mm during anaesthesia. Injections were given in triplicate at the following injection sites (regions): neck, back, abdomen. The injection fluid was a mixture of NaCl 0,9 % and Chinese ink in a 1:0.15 ratio. Visual inspection was performed immediately after injection to evaluate bleb formation (i.e., dome-shaped marking), leakage to the outside, and local adverse effects.

The piglets were euthanized immediately after the injections using VAX-ID® by intravenous injection (T61®; 1 mL/10 kg). Biopsy sampling was performed by collecting skin samples reaching a small portion of the muscle underlining (average dimension 10 cm × 10 cm) where the injections were administered. Tissue samples were fixed in 4 % buffered formalin for further histological examination by AML/MedVet (Antwerp, Belgium). Each sample was dehydrated in alcohol solutions of increasing concentrations, cleared in xylene, and embedded in paraffin. The samples were then cross sectioned at 4.0 µm and stained with standard hematoxylin and eosin (H&E). Digital images of the slides were taken with a digital camera (Motic, Hong Kong, China). For the evaluation of the liquid dispersion, injected ink was measured by means of an image analysis software program (Moticimage plus 2.0).

For the sample size calculation, the resource equation method (Mead 1988) was used: E = N – B – T, For this study we apply the non-blocked design, thus the adapted formula: E = N – T. Wherein, the experimental units N is the number of injections (n-1): 18 –1 = 17; treatment T is the VAX-ID® 32G performance, so T = 1. E = 17 – 1 = 16. As we aim for three injection sites and triplicate injections at each site in 2 piglets, the total number of injections becomes 18. The differences in the injection sites were not considered for this sample size calculation as preliminary data of an experiment assessing skin samples obtained from piglets of different weights at different anatomical locations has already determined that these three specific injection sites for piglets (10–12 kg) have comparable skin thickness to the proximal forearm of humans.

2.3. Assessment of usability by healthcare workers

VAX-ID® was assessed for usability by 15 healthcare professionals. The level of experience of the participants with the queried routes of administration was assessed by means of self-assessment as part of a questionnaire (see Appendix A). The user testing sessions were coordinated by two living labs, one session was held in the Netherlands (GGD Breda, coordinated by CIC, the Netherlands) with 8 participants and one in Belgium (Wit-Gele Kruis Limburg, coordinated by Happy Aging, Belgium) with 7 participants to capture feedback on the usability aspects of VAX-ID®.

The study was conducted by means of injections using VAX-ID® in a tangerine, a commonly used simulation method for injection training [28], and a questionnaire. The self-assessment questionnaire was a combination of open, yes–no and scoring questions rating from 1 fully disagree to 10 fully agree (see Appendix A). Participants received a syringe, a VAX-ID® device, Instruction for Use (IFU; Fig. 2) for the VAX-ID®, and a tangerine.

A short explanation was provided to clarify that the first three steps of the IFU (withdrawal of the medicinal product) will not be executed, and they can start at step 4. All participants were asked to complete the questionnaire during/after use.

3. Results

3.1. Performance of Vax-Id®

3.1.1. Ejection volume, dead-space volume and dose accuracy

The technical ejection test used n = 180 VAX-ID® devices (115 with the 32G needle and 65 with the 27G needle). The dead volume for each ejection test was determined based on the values obtained.

The average dead volume found was 23 µL for the 115 devices, the standard deviation was 0.0056, and this concluded a dose accuracy of 6 µL of the VAX-ID® device.

3.1.2. Evaluation of bleb formation, liquid dispersion and safety in piglets

A total of 18 injections were performed in two piglets (NR 159206 and NR 159212) of 12 kg. Due to counter pressure issues linked to the homogeneity and non-Newtonian property of the ink, the injections in the neck of piglet NR 159206 were not successful. Of the 15 successful injections (6 in NR 159206 and 9 in NR 159212), visual inspection showed bleb formation in 93 % (14/15) of the samples with an average bleb diameter of 0.56 cm with the smallest being 0.4 cm and the largest 0.8 cm (Fig. 3). As for adverse events, only transient erythema was observed at the injection site. Only one sample showed micro bleeding and none of the samples showed macro bleeding. No serious adverse effects were observed. After injection, typically a small droplet was seen of diameter < 0.1 cm at the point of penetration which was not considered to be leakage as no dye was lost upon injection.

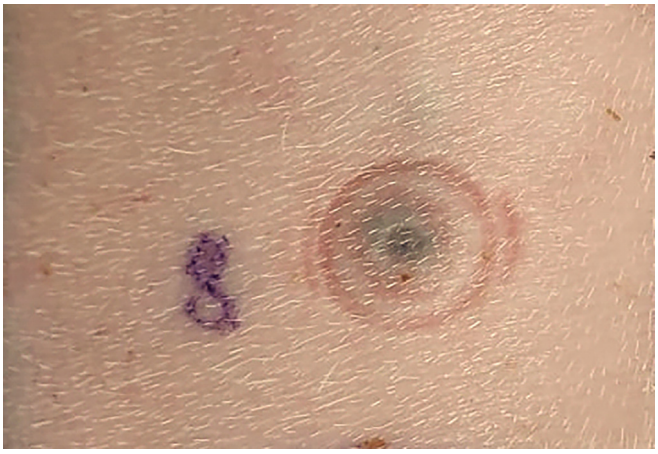

Fig. 3. Bleb formation following injection of 100 µL dye using VAX-ID with 32G needle.

Histological examination was performed on 12 out of 15 samples (Fig. 4). A total of 3 samples (1 sample of each injection site from NR 159212) had to be excluded as images could not be analysed due to bad quality of the HE staining. The deposition of the ink was shown to reach both the papillary and reticular dermis in all (100 %) analysed of the samples.

3.2. Assessment of usability by healthcare workers

Demographics of the participants is shown in Table 1.

The level of experience of the participants with different routes of administration showed an average score of experience with intramuscular injections of 8.73/10, with subcutaneous injections of 9.13/10 and with intradermal injections of 3.73/10.

The overall score of the device for user friendliness was 8.2/10, where the lowest score was 6 and highest was 10. For look and feel an average score of 8.39/10 was given, where the lowest score was 7 and the highest 10. The risk of needle-stick injuries was rated as low (8.47/10), where (high risk) 1–10 (low risk). Of the different handling steps, activation of the device was rated as clearer compared to the deactivation of the device. All participants confirmed an IFU is needed prior to the first-time usage of the device.

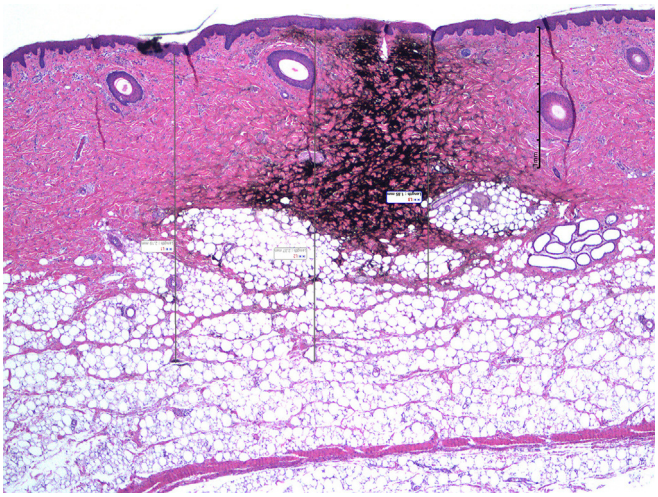

Fig. 4. Histology results showing dye deposition in the skin post injection with VAX-ID with 32G needle. H&E stain 20x.

Table 1
Showing demographics of Healthcare participants in usability assessment of VAX-ID®.

Variables	Results
N	15
Age	
Mean ± STD	43.8 ± 9.8
Min-Max	29–59
Median	40
Gender	
Female	13 (86.67 %)
Male	2 (13.33 %)
Right – or Left - Handed	
Right-Handed	14 (93.33 %)
Left-Handed	1 (6.67 %)

The open question elicited mainly positive feedback on the design of the device, safety (no fear for needle-stick injuries) and user friendliness of intradermal vaccination. Drawbacks included difficult/unclear handling steps and the need to learn a new technique/need practice.

4. Discussion

Studies have shown that only 10 to 20 % of the standard IM or SC dose was needed for an ID vaccination to elicit a non-inferior or even superior immune response over IM/SC vaccination using the full dose [6–14]. Considering the state of the art in vaccination and vaccine delivery, several challenges are still being faced in the field of ID vaccination [2]. Most are linked to the difficulties seen in accurate, standardized and easy administration of the vaccine in the dermal layer as a high level of training is needed to perform the Mantoux technique [1,2,23]. The current study assessed the performance and safety of a novel intradermal delivery device, VAX-ID®. Results have shown that VAX-ID® was able to reliably deposit the substance at the device's predefined needle depth having a low dead volume, high dose accuracy and a high ease of use.

Importantly, VAX-ID's predefined optimal protrusion depth banks on knowledge gained from skin thickness studies performed in adults, adolescents and children [29,30]. Indeed, the skin thickness at the proximal and dorsal forearm as well as the deltoid were shown to be affected by gender and BMI (body mass index) in adults and by age and BMI in children. These insights allowed to design VAX-ID® to guarantee a standardized and accurate injection as well as reliable deposition of the injected substance in the dermis.

The passive mechanics of the device consist of a foot of diameter 16 mm to position the device perpendicular to the skin. This foot is mounted in a friction rail that needs 5 N of manual force to move down the needle. This user-independent force both bulges the skin slightly and makes the needle travel towards the skin at 1 m/s, guaranteeing skin penetration instead of skin tenting. Additionally, the needle in the device can be mounted with an accuracy of +/-0.1 mm, allowing an accurate and standardised injection depth. The technology has been protected by 3 patent families.

To assess the reliability of the injection and deposition of the substance using the newest generation VAX-ID®, piglets of 12 kg were used. Pigs' skin, also known as "porcine skin," is a well-established animal model for skin testing because of its large similarities to human skin [31,32].

Looking at bleb formation, which is considered an important visual check of a successful ID injection by a physician, VAX-ID® caused a unique oval shape imprint on the skin of the piglets. The shape is different from the bleb formed after ID injection using the Mantoux technique which causes more of a circular elevation of the skin [26], while with VAX-ID® it is more oval and less elevated allowing for more dispersion of the injected substance into the dermis. Thus, bleb formation, although it is a visual sign of successful ID injection, might not be the best indicator for the success of injection due to the different variables that affect the bleb formation, shape, and diameter. This is also in line with the findings of Lallow et al. [34] who also demonstrated that the puddle (distribution of the liquid in the skin) is more important than the shape and formation of the bleb.

Considering that scarce and/or expensive vaccines are intended to be optimally delivered to the skin for achieving more efficient results using low(er) doses, it was considered important to evaluate the dose accuracy and dead volume. A dose accuracy of 6 μL was seen for VAX-ID® which aligns with data from Strauss et al. [35] who studied the dose accuracy and vaccine wastage for 7 syringes from leading manufacturers. Their results showed that for the models utilizing regular needles and syringes (as in the Mantoux technique), variable volumes of the withdrawn vaccine is left in the injection device following administration of the vaccine, which indeed goes to waste [35]. In addition to the dose accuracy, dead or residual volume is an important factor in ID drug delivery. The average dead volume for VAX-ID® seen in the current study was 23 μL, which means that VAX-ID® delivers vaccines within a 'safe' range of dead-space [36], as the selection of a suited intradermal device can have a substantial impact on vaccine wasted during administration [33].

Next to performance, safety is an important feature of drug delivery devices of which Needle Stick Injuries (NSIs) is one of these considerations. The majority of NSIs are caused by hypodermic needles, which are the type of needles used in the Mantoux technique for ID injection [37]. Rough estimates indicate that in the US alone, there are nearly 600,000 needlestick injuries of which half are not reported [38]. The most important organisms that can be acquired after a needlestick injury include HIV, Hepatitis C, and Hepatitis B, which have an associated risk of infection transmission of 0.3 %, 3 %, and 30 %, respectively [39]. In an effort to reduce the incidence of NSIs, special safety engineered devices (SEDs) have been developed. However, contrary to an expected drop in NSIs, the needle stick rate increased from 1.9 to 2.2 per 100 healthcare workers after implementation of SEDs in the Netherlands due to difficulties in operating the safety device and continued improper disposal of needles. [40]. To aid in prevention of NSIs and related bloodborne infections, VAX-ID® is configured with a safety pin which needs to be removed prior to use and placed back after use. After injection, VAX-ID® is to be placed in the sharps container.

In contrast to the Mantoux technique which has been shown to be very challenging to learn and master to accurately deliver the injected substance to the skin [41], usability studies using VAX-ID ® confirmed the ease of use by high acceptability and usability scores by healthcare professionals [42].

Importantly, as no changes were made to the (patented) mode of action of VAX-ID®, it is anticipated that its ability to elicit non-inferior immunogenicity following the delivery of fractional dose of vaccines also holds for the newest (second) generation of the device. Indeed, based on a previous study of VAX-ID® using a commercially available Hepatitis B vaccine, VAX-ID® was shown to be non-inferior using fractional dose (1/4th) to the standard of care (IM) using full dose as well as to the Mantoux technique [9]. This offers possibilities for the newest VAX-ID® generation as the device of choice for ID delivery linked to the ongoing need for efficient vaccination strategies to fight against pandemics, health emergencies, vaccine supply shortages, as well as a means to aid people with insufficient immune responses e.g., those at high risk of poorly responding to Hepatitis B vaccines [10,11].

The study has several limitations: (i) Mantoux was not included as comparator to VAX-ID in the piglet study which could provide additional insights on dye deposit and injectability; (ii) usability

was evaluated in a limited amount of subjects whereby gender and handedness could have been more balanced. Also, only a questionnaire was used, while interviews with the subjects could confer more insights. In a next study, these aspects will be addressed in greater detail.

5. Conclusion

ID drug delivery is gaining higher interests with the newly emerging global infectious diseases, as it offers dose-sparing characteristics, which renders its use in mass vaccination campaigns or when supply shortage is being encountered. VAX-ID® has been shown to allow for a safe, standardized and reliable ID injection with a high ease-of-use. The device was well accepted by healthcare professionals. As no changes were made to the (patented) mode of action of VAX-ID®, it is anticipated that the findings of the first generation like the low pain perception by vaccinees, which is also very important for cancer treatment, as well as its ability to elicit non-inferior immunogenicity following the delivery of fractional dose of vaccines also hold for the newest (second) generation of the device. VAX-ID® can thus be considered a promising solution for reliable, safe, and easy delivery of prophylactic and therapeutic (cancer) vaccines compared to regular injection methods.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: V.V. and K.B. are co-founders, shareholders and Board members of Idevax BV, S.V. is co-founder and shareholder of Idevax BV. M.R. and D.S.V. are employees of Idevax BV.

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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.2023.06.028.

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