Assessment of acceptability and usability of new delivery prototype device for intradermal vaccination in healthy subjects

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Assessment of acceptability and usability of new delivery prototype device for intradermal vaccination in healthy subjects

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The objectives of this study were to assess the acceptability and usability of a newly developed intradermal prototype device, VAX-ID[TM], in healthy subjects. In April 2012 an investigational study was conducted in healthy subjects aged 18 to 65 y. To compare injection site and route of administration, subjects were allocated to 4 subgroups, either receiving subsequently 2 intradermal (ID) injections (one in the forearm and one in the deltoid) or an ID (forearm) and an intramuscular (IM) (deltoid) injection. All injections contained saline solution. Acceptability was assessed with a subjects' questionnaire and a daily electronic diary for 5 d. Usability was assessed with a vaccinators' questionnaire and an expert panel. A 10-point Visual Analog Scale was used to score several statements on usability and acceptability. A total of 102 healthy subjects were enrolled in the study (age: 19–63). No statistically significant differences were seen in demographic characteristics between the ID and IM groups. Anxiety before injection, pain during injection and duration of injection were rated significantly lower for ID compared to IM. One day after the injections, redness was reported more often after ID injection in the forearm versus ID in the deltoid; pain at injection site was reported significantly more often after IM vs. ID injection. The new VAX-ID prototype device was found easy to handle, easy to use and safe. The new VAX-ID prototype device was shown to have a high degree of acceptability as well as usability. Further studies with VAX-ID will be conducted using vaccine antigen allowing assessment of immunogenicity and safety. Additionally, these studies will help to further improve VAX-ID in terms of accuracy of delivered dose and feedback to the vaccinator. (NCT01963338).

Introduction

To date, most vaccines are administered intramuscularly (IM) and a few subcutaneously (SC) using a needle and syringe. For intradermal (ID) vaccination the Mantoux technique is considered the gold standard and is currently used for administration of Bacille Calmette-Guérin and rabies vaccines.[1,2] The technique requires insertion of the needle, bevel upwards, almost parallel to the skin surface after which the vaccine is injected slowly into the dermal layer of the skin.[3,4] The method is however difficult to standardize, requires training and is perceived as painful by vaccinees.[1-3,5,6] For intradermal influenza vaccination, the ID microneedle system Soluvia[TM] (Becton-Dickinson; registered as Intanza/Fluzone by Sanofi Pasteur) is currently commercially available and used.

The skin is one of the largest organs of the body providing the first line of defense against invading pathogens and one of the most obvious sites for achieving immune responses due to the presence of high number of T cells and specialized cells such as dendritic cells and macrophages in the epidermis and dermis.[2-9]

Studies have shown that for some vaccines ID administration can induce a higher or equal immunogenicity compared to IM, especially in people with lower immunogenicity, such as elderly.[2,6,9,10]

Some studies have shown that 1/5 of the amount of antigen required for IM vaccination elicited similar immunogenic responses with ID administration; such dose-saving potential could be an important economic argument when facing expensive antigens or limited antigen production capacity[2-4,6,9-12]. When production of vaccine antigen is under time-pressure or in case of production capacity problems the dose-saving potential could also lead to improved mass vaccination in high-risk populations or in pandemic situations.[2,6;9,13-15]

Difficulties encountered using the Mantoux technique could be overcome by the use of alternative ID delivery systems that confer more uniform and standardized procedures. People with
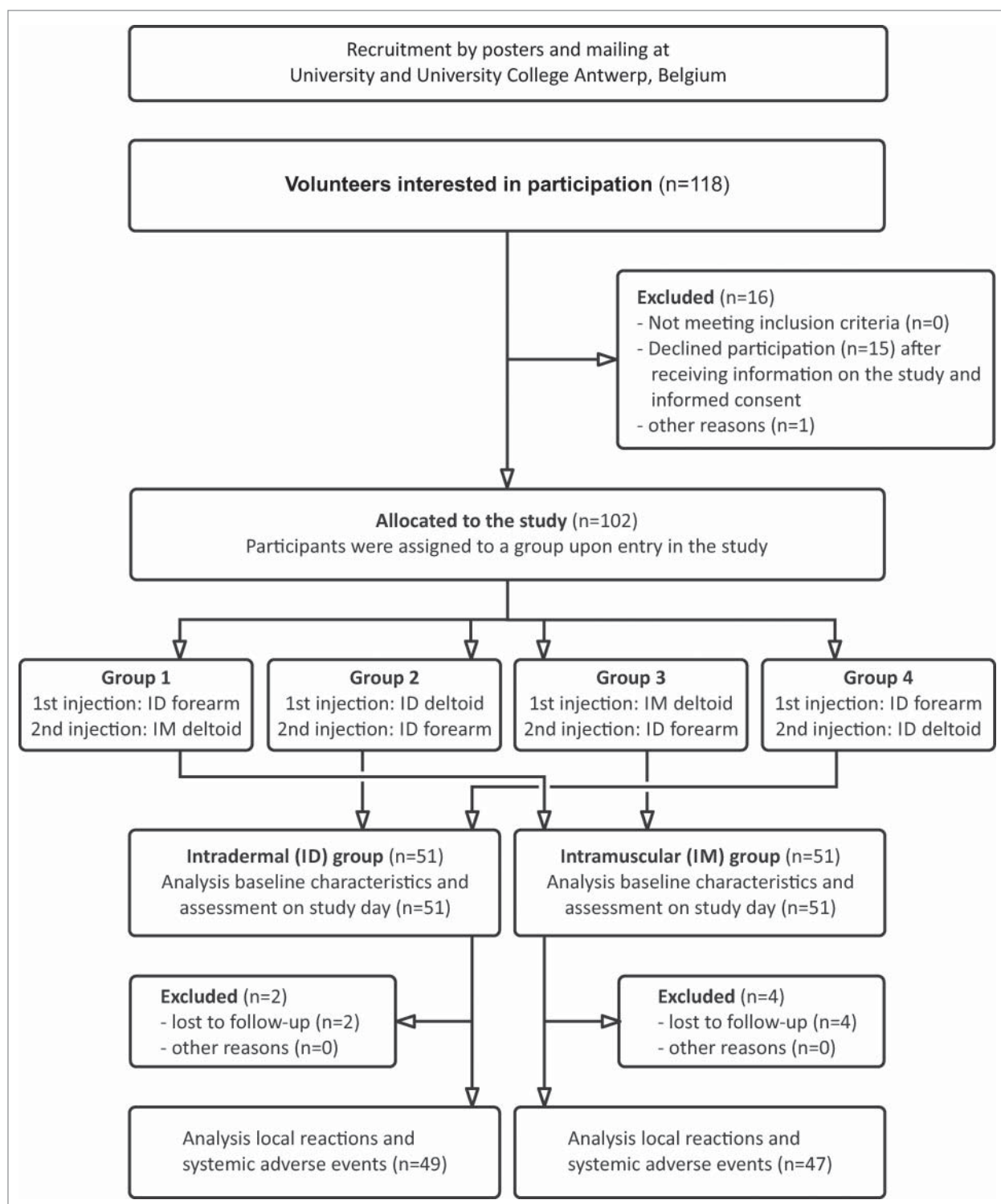
Figure 1. Flow chart: Enrollment of study subjects.

needle phobia, estimated at 3.5–10% of the population,[16] as well as children could also profit from the availability of such ID-devices because of increased vaccine acceptance.[2,3,5-7,10,14,17,18] However, currently few devices allowing vaccination via the ID route are commercially available (e.g. Soluvia[TM], MicronJet[TM] or

needle-free injection systems), while some prototypes are in development (e.g., vaccine patch, coated, dissolving or solid microneedles).[3-6,19,20] Needle-based ID injection systems targeting the deltoid region for vaccination, include the MicronJet[TM] microneedle device (Nanopass) and the Soluvia[TM] intradermal

microinjection system (Becton-Dickinson). These ID devices have frequently been investigated in clinical trials.[2,5]

The current study is the result of an interdisciplinary project of the University of Antwerp and the Artesis University College. The goal was to develop a prototype device suited for intradermal vaccination, to explore applicable business models and to examine the acceptability and usability

Figure 2. Exploded view of VAX-ID prototype device (3D render).

in a clinical study. Data of the business opportunities are not mentioned in this paper, nor are they part of the aim of the current study.

The objectives of the current exploratory study were to assess the acceptability of the injection (anxiety, pain, redness, swelling, myalgia...) with a newly developed prototype device, VAX-ID, in healthy adults and usability of the device (safety, ease of use,...) by vaccinators. VAX-ID was developed to allow for vaccination in the dermal layer of the skin.[21] Throughout this paper the term VAX-ID will be used to describe the newly developed prototype device.

Results

Subjects

A total of 118 healthy subjects expressed their interest in the study of which 102 were enrolled after signing the informed consent form. A total of 16 subjects withdrew from participation after having received detailed information with regard to study design and expectations. All 102 subjects completed the questionnaires, of which 96 completed the first day of the 5-day diary and 75 completed the diary during the 5 consecutive days.

No statistically significant differences were seen in demographic characteristics between the 2 groups (**Table 1**). Approximately 54% of the subjects were men. Subjects were on average 32 y old. During the last 5 years, subjects had received on average 2 vaccinations and had 3 blood samples taken.

Four of the 9 vaccinators were male. The vaccinators were on average 38 y old and had an average working experience as a nurse of 14 y. During the last 5 months the nurses had received on average one vaccination (mean: 0.7; range: 0–3). They administer vaccines on average 2 times per month; in the last 5 y no one had experience with the Mantoux technique; 6 vaccinators draw blood or insert intravenous catheters on a daily basis.

Assessment of acceptability of VAX-ID by healthy subjects

When comparing IM to ID administration (**Fig. 3**), anxiety before injection was rated significantly lower for ID in the forearm compared to IM (mean(SD): 2.4(1.9) and 3.7(2.4); $P < 0.001$). Also, the anxiety level was significantly lower for ID injections in the deltoid compared to the forearm (mean(SD): 1.7(0.9) and 1.9(1.1); $p = 0.009$). The subjects from the IM-group scored pain during injection significantly lower when receiving an ID injection compared to an IM injection (mean (SD): 1.1(0.4) and 4.1(2.3); $P < 0.001$). Using VAX-ID nearly no pain was reported during the injection in the forearm nor in the deltoid (mean(SD):1.2(0.5) and 1.3(0.6), $p = 0.444$). The duration of injection time with VAX-ID was perceived as being shorter compared to the injection with needle and syringe (IM) by the subjects (mean(SD): 1.3(0.8) and 2.9(2.2); $P < 0.001$).

Local reactions reported one day after the injections are shown in **Table 2**. Almost no local reactions were reported after injection. Redness was reported more often after ID injection in the forearm compared to ID injection in the deltoid (mean(SD): 1.27(0.61) and 1.10(0.37), $p = 0.031$), however the diameter

Table 1. Demographics healthy volunteers (n = 102)

Characteristics		Total group N: 102	ID group n: 51	IM group n: 51	p
Gender %	man	53.9	58.8	49	.427
	woman	46.1	41.2	51	
Age in years: mean (range)		31.9 (19–63)	30.8 (19–58)	33.0 (19–63)	.326
Proportion health care related job or education		16.7	12.0	22.0	.183
Number of vaccinations last 5 years mean (range)		2.3 (0–7)	2.3 (0 – 7)	2.3 (0–7)	.929
Number of blood collections last 5 years mean (range)		3.3 (0–40)	3.0 (0– 0)	3.4 (0–40)	.653

Chi-Square: comparison of education; Fisher's Exact Test: comparison of gender.
Independent Samples T-Test: comparison of age, vaccination and blood collections
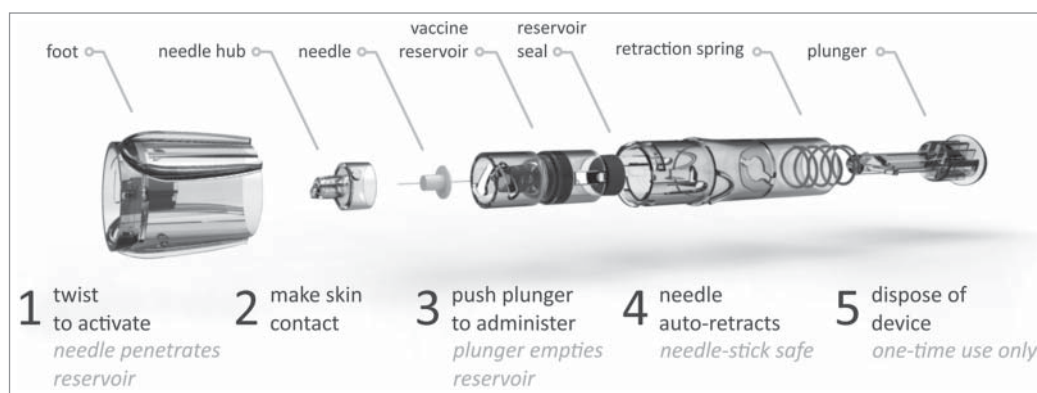
	Mean (SD)	p†	p††
Anxious before injection			
ID (deltoid)	1.7 (0.9)	.009	
ID (forearm)	1.9 (1.1)		
ID (forearm)	2.4 (1.9)		< .001
IM (deltoid)	3.7 (2.4)		
Pain experience			
ID (deltoid)	1.3 (0.6)	.444	
ID (forearm)	1.2 (0.5)		
ID (forearm)	1.1 (0.4)		< .001
IM (deltoid)	4.1 (2.3)		
Duration injection			
ID (deltoid)	1.2 (0.4)	.569	
ID (forearm)	1.2 (0.5)		
ID (forearm)	1.3 (0.8)		< .001
IM (deltoid)	2.9 (2.2)		

† Paired Samples T-Test between ID injection deltoid and ID injection forearm (ID group; n:51).
†† Paired Samples T-Test between ID injection forearm and IM injection deltoid (IM group; n:51).
o refers to outliers with an interquartile range between 1.5 to 3
* refers to extreme outliers with an interquartile range >3
All injections contained sterile, pyrogen free 0.9% NaCl solution (Mini-Plasco, B. Braun). The solution was injected at room temperature. For IM injections 0.5cc was injected, while 0.1cc was injected via the ID route using VAX-ID.
The presence of local reactions was scored by a Visual Analogue Scale (VAS): 1 = no presence and 10 = strong presence.
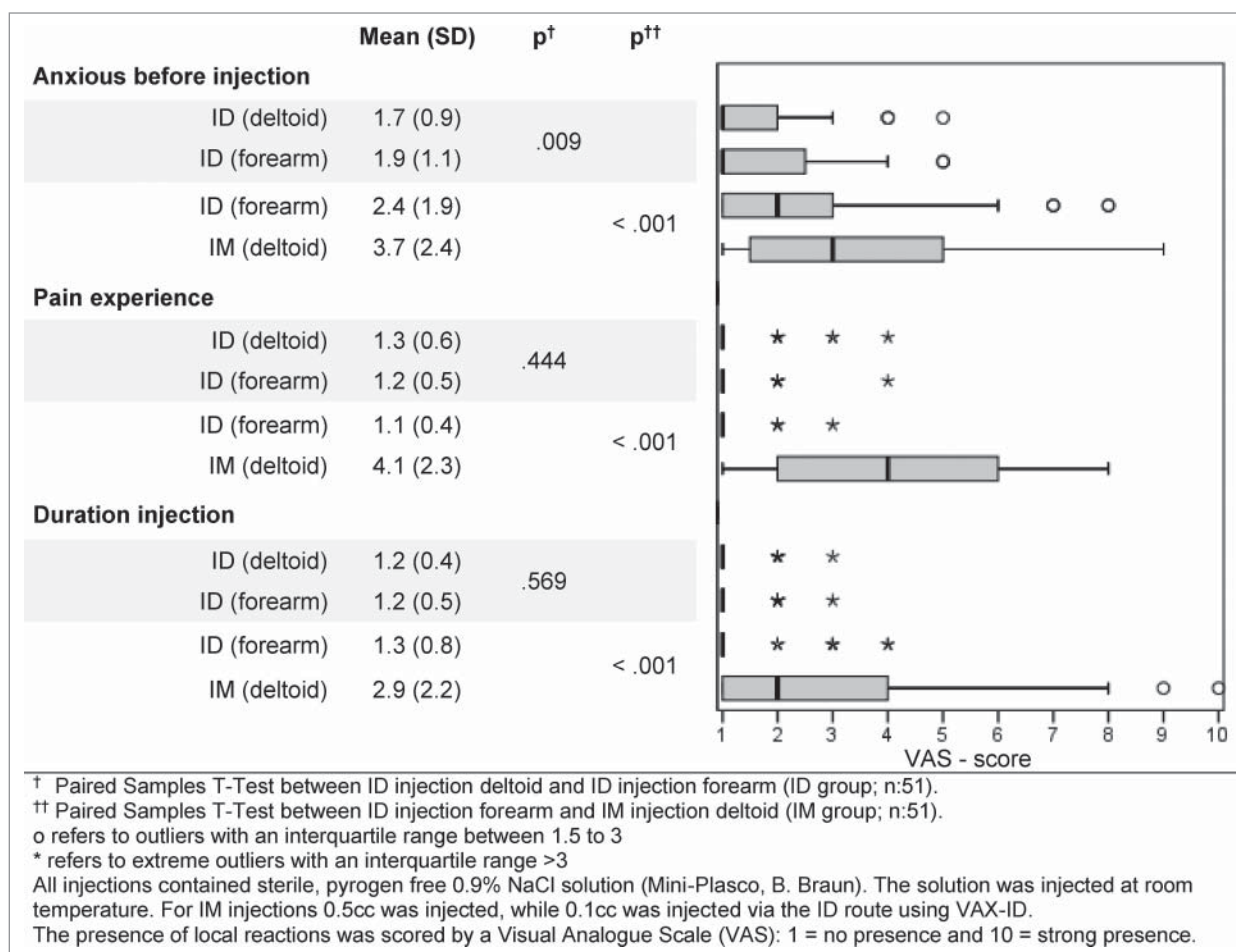
Figure 3. Outcome 10-point Visual Analog Scale per injection (n: 102).

(in mm) of the reported redness was not significantly different (mean(SD): 0.20(0.58) and 0.14(0.50), p = 0.261). Pain at injection site was reported significantly more often after an IM injection compared to an ID injection in the forearm (mean (SD): 1.64(1.07) and 1.04(0.20), $P < 0.001$).

Only minor systemic effects were reported. No significant differences were found for these systemic adverse events between the injection groups (data provided as supplementary material).

Assessment of usability by the vaccinators

According to the vaccinators VAX-ID was attractive (6/9 or 66.7%), easy to handle (8/9 or 88.9%), safe (9/9 or 100%) and easy to use (8/9 or 88.9%). The injection time using VAX-ID was recorded as being faster compared to needle and syringe (8/9 or 88.9%). The vaccinators did not perceive the forearm as an unnatural site for injections (7/9 or 77.8%).

Based on the feedback given by the vaccinators during the expert panel interview, the vaccinators confirmed next to the high degree of usability, that VAX-ID could be also used by non-medical personnel (having been provided with a few instructions), and by any subject through self-administration (8/9 or 88.9%). The vaccinators also emphasized the need for an

improved visual indication of both the activation mode of the device and the correctness of the injection.

Discussion

The current study assessed the acceptability and usability of VAX-ID by subjects and vaccinators.

Higher anxiety rates were shown for needle and syringe compared to VAX-ID. In addition, subjects indicated a higher anxiety level for an injection with VAX-ID in the forearm than in the deltoid. This could be caused by the fact that subjects perceived the forearm skin as a more sensitive area than the skin overlying their deltoid.

Laurent et al.[22] showed that the needle insertion did not cause pain with the tested microinjection system and also no pain was reported using the Mantoux technique; mild pain was however reported upon injection of fluid. Although we didn't split these 2 observations in the current study, pain at injection was rated low by the subjects after ID injection with saline solution. It should however be noted that in our study saline solution was used, which might not be fully comparable to injection with the vaccine antigen; the composition of a vaccine and/or induction of

Table 2. Local reactions reported on day 1 after injection (n = 96)

	ID group (n:49)			IM Group (n:47)		
	ID injection upper arm Mean (SD)	ID injection forearm Mean (SD)	p*	ID injection forearm Mean (SD)	IM injection upper arm Mean (SD)	p†
Pain[§]	1.12 (0.44)	1.10 (0.37)	.785	1.04 (0.20)	1.64 (1.01)	< .001
Redness[§]	1.10 (0.37)	1.27 (0.61)	.031	1.11 (0.32)	1.26 (0.64)	.109
Redness in mm	0.14 (0.50)	0.20 (0.58)	.261	0.33 (1.37)	0.93 (3.06)	.211
Swelling[§]	1.00 (0.00)	1.00 (0.00)	—	1.02 (0.15)	1.06 (0.25)	.569
Swelling in mm	0	0	—	0	0.19 (0.83)	.197
Ecchymosis[§]	1.00 (0.00)	1.00 (0.00)	—	1.04 (0.21)	1.13 (0.54)	.710
Ecchymosis in mm	0	0	—	0	0.30 (1.16)	.162
Hardening/induration[§]	1.02 (0.14)	1.00 (0.00)	.322	1.07 (0.33)	1.19 (0.54)	.323
Hardening in mm	0.08 (0.57)	0	.322	0.02 (0.15)	0.19 (0.54)	.083

* Paired Samples T-Test between ID injection upper arm and ID injection forearm.
† Paired Samples T-Test between ID injection forearm and IM injection upper arm.
§ The presence of local reactions was scored by a Visual Analogue Scale (VAS): 1 = no presence and 10 = strong presence

an immune response might also cause an additional pain sensation. Our results are in contrast to some reports of pain sensation after injection via the Mantoux technique as this method is generally perceived as painful by vaccinees.[1,2,4-6] This could be due to the angle under which the injection needs to be placed for administration in the dermis, the lack of expertise with the injection method and the use of saline versus antigen-containing liquid. Also, the Mantoux technique uses a 26G needle, which could inflict more damage to the skin more than with a 31G needle (used in VAX-ID). Our results are also in contrast with previous vaccine studies using microinjection systems in which no differences in pain sensation between IM and ID injection were seen at the moment of injection.[2,6,11,12,20,23,24] Arnou et al.[10] compared an ID micro-injection system with an IM injection, whereby the subjects reported even more local pain with the ID injection.

To further explore the acceptability of VAX-ID, subjects were requested to rate the duration of injection time. The injection with VAX-ID was not experienced as long-lasting in contrast to the perception of duration of an IM injection, which could benefit acceptability. VAX-ID could offer an overall time-reduction for vaccination by healthcare workers when using the forearm as injection site. For example, in winter times, which are pre-eminently times to conduct influenza vaccination campaigns in the Northern hemisphere, there would be no longer need for patients to undress themselves before vaccination.

Both IM and ID injections were well-tolerated by the subjects and no differences were found in erythema, swelling, induration or pruritus between the two injection groups. This is in contrast to previous studies[2,4,6,9] which showed that ID vaccination generated more local side effects than IM vaccinations, albeit in studies using antigen containing liquid and no saline solution. In terms of injection site, erythema was more frequently reported for ID injection in the forearm compared to the deltoid. This could partially be explained by the difference in skin thickness at both sites.[25]

As in previous studies[6,9] the incidence of systemic adverse events induced by ID was similar compared to IM. However the limited presence of systemic adverse events in any of our study groups could be explained by the saline solution that was injected. Importantly, Laurent et al.[22] also did not observe local and systemic adverse events after injection of saline solution except for some skin redness.

The vaccinators quickly learned how to use VAX-ID even without instructions or manual. They perceived VAX-ID as an easy-to-use tool. This is in contrast to the Mantoux method which requires ample training to allow for reliable injection in the dermis.[6] The low pain sensation the vaccinators observed in subjects during injection and the design were rated as highly beneficial in addition to their appreciation of the safety and simplicity of administration. However the virtual absence of any pain during ID injection required the need for proper feedback toward vaccinators and patients when using VAX-ID.

There were several limitations to this study. (i) Device performance was not evaluated via bleb formation, leakage and the quantity of injected fluid. (ii) The comparison with IM was performed with a 23G needle whereas a 25G is used in prefilled IM syringes for vaccines. (iii) The Mantoux technique was not used as a control comparator. These elements will be integrated in future studies with VAX-ID.

Safety was rated by the vaccinators as a very important aspect for an injection device in order to avoid needle-stick injuries as much as possible. The automatic safety mechanism, is thereby seen as a major added value compared to other routes of administration using a needle-based system (e.g. IM, ID and SC). The safety mechanism of VAX-ID is different to the one used by Soluvia[TM], whereas the latter has a safety-cap which covers the needle and VAX-ID retracts the needle into the housing.

The vaccinators suggested that self-administration would be possible by non-health care workers as well as by subjects themselves after 3 injections with VAX-ID. With respect to the latter, in a recent study using a microinjection device (Soluvia[TM]), self-administration was shown to be immunologically non-inferior and well-accepted.[26]

In conclusion, VAX-ID was shown to have a high degree of acceptability by the healthy subjects (i.e.: the future vaccinees)

and a high degree of usability for the healthcare workers (or vaccinators). Subjects were less anxious when seeing VAX-ID compared to seeing needle and syringe which were used for IM injections. Also, pain sensation was scored lower. Thus, VAX-ID could increase acceptability of vaccination, in particular in people with needle phobia and potentially in children.[27] Further national and international studies with VAX-ID or a next generation VAX-ID will be set-up using vaccine antigen to assess immunogenicity and safety. Moreover, assessment of usability by different categories of healthcare workers will be an added value in future studies. In addition, future studies will help to further improve VAX-ID including accuracy of delivered dose and feedback to the vaccinator.

Materials and Methods

Study method

During three study days in April 2012 an investigational study was conducted in healthy subjects aged 18 to 65 y to assess the acceptability and usability of VAX-ID. Enrolment was organized at the University of Antwerp as well as at the Artesis University College Antwerp.

Healthy subjects aged 18 to 65 y were enrolled in the study. Subjects were recruited through posters and direct mailings in the participating University and University College. People with regular exposure to needle injections, e.g., diabetic patients, as well as pregnant women were excluded from participation. Also, subjects had to be able to fill in an electronic diary for 5 d after the injections.

Nine nurses were recruited as vaccinators, i.e., to perform the IM and ID injections and evaluate the usability of VAX-ID. Brief instructions were given on how to use VAX-ID. To exclude potential bias, selected nurses were not informed on the development of VAX-ID. A 'licensed general nurse' was the only requirement for participation as a vaccinator (i.e. no extensive experience with vaccinations required).

To compare acceptability, subjects were, upon admittance to the study, allocated to 4 subgroups: 1) ID forearm × IM deltoid, 2) ID deltoid × ID forearm, 3) IM deltoid × ID forearm, 4) ID forearm × ID deltoid (**Fig. 1**). These subgroups allow for control of pain sensitization, as the first injection could be either in the forearm using VAX-ID or in the deltoid using VAX-ID or using needle and syringe for the IM injections. Next, subgroups 1 and 3 were combined as 'IM group' and subgroups 2 and 4 as 'ID group'. Each subject received their allocated injection on the day of enrolment. Injections were administered within a time frame chosen by the vaccinators varying from 1 to 3 minutes. The vaccinators did not receive any time constraints prior to delivering the injections.

The comparison between ID injection on forearm vs ID injection deltoid was to compare the injection site, the other comparison between ID injection forearm vs IM deltoid was to compare the injection technique, whereas the VAX-ID prototype device is intended to be used on the forearm.

Injections

All injections contained sterile, pyrogen free 0.9% NaCl solution (Mini-Plasco, B. Braun). The solution was injected at room temperature. For IM injections, a one-milliliter syringe and a 23G needle with a length of 1" or 2.5 cm was used to inject 0.5cc, while 0.1cc was injected via the ID route using VAX-ID. Syringes were filled prior to the experiment.

VAX-ID consists of: a foot, a double-pointed 31G needle in a needle hub protruding 1.0mm into the patient skin, a reservoir containing a volume of 0.1cc, a seal to close the reservoir, a spring and a plunger (**Fig. 2**). VAX-ID has 4 operation modes: 1) Inactive, 2) Active, 3) Administration, 4) Deactivation-locked. For detailed technical information please consult the patent file.[21]

VAX-ID is activated by rotating the foot after which the double-pointed needle penetrates the reservoir. Next, the foot is placed on the skin and the reservoir is emptied in the dermis by means of the plunger. VAX-ID has a unique mechanism of action: which includes (a) an activation mechanism, i.e., after rotating the foot the needle is able to penetrate the reservoir and to gain access to the liquid inside the reservoir and (b) a deactivation mechanism, i.e. after injection of the solution the needle is automatically retracted and is no longer accessible, thereby ensuring safety in term of needle-stick injuries for the vaccinators. VAX-ID is hence a pre-filled, disposable, single use ID device.

Assessment of acceptability of VAX-ID

Each of the subjects was asked to complete 2 questionnaires after the injections were administered: questionnaire one surveyed demographic parameters, including sex, age, health care related job or education, and number of vaccinations and blood samples taken during last 5 y, while questionnaire 2 surveyed the experience of ID and/or IM injection, such as anxiety, pain during injection and perception on the duration of injection. The second questionnaire was divided in 2 parts. The first part covered injections in the forearm, the second part covered injections into the deltoid. A 10 point Visual Analog Scale (1 = no agreement; 10 = full agreement) was used to score the statements.

Additionally, subjects were asked to fill in a daily electronic diary for 5 d after the injections. The diary surveyed the presence of local reactions (pain at injection site, redness, swelling, ecchymosis and hardening) and systemic adverse events (headache, malaise, chills, myalgia, arthralgia, weakness/fatigue and body temperature). In case of local reactions, subjects were asked to measure the size of the reaction (in mm). For this purpose, a transparent ruler was provided to the subjects on the study day.

Assessment of usability of VAX-ID

At the end of each study day, the vaccinators performing the injections received a questionnaire that assessed the usability of VAX-ID. The vaccinators were requested to rate the attractiveness, ease of handling, solidity, safety and ease of use. Some questions assessed their experience relating to pain, speed and injection sites. Also, vaccinators were asked their thoughts on the usability by non-medical staff (with or without any manual) and on self-administration by patients.

Similarly to the questionnaires used for the healthy subjects, a 10-point Visual Analog Scale was used. A panel (consisting of the investigators, the vaccinators and a coordinator) was organized to gather additional comments, remarks and proposed improvements on the use of VAX-ID through a group interview.

Statistical methods

SPSS 20.0 was used for statistical processing of the data. Comparisons between the different injection methods and between the 2 injection groups were performed using a Paired Samples t-test and an Independent Samples t-test, respectively. Power calculations have shown that, with the current sample size (51 subjects per group), 80% power is obtained to observe a mean difference in Visual Analog Scale of 0.64 between VAX-ID and IM (i.e. in case no significant Visual Analog Scale difference is observed upon significance testing, the mean difference between the 2 Visual Analog Scale scores is smaller than 0.64).

The descriptive data obtained from the questionnaires filled by the vaccinators served as input for obtaining additional information during an group interview. A cut-off value was set to analyze the Visual Analog Scale scores of the vaccinators, whereby a VAS-score between 1 and 5 was scored as negative and between 6 to 10 as positive. Data from the group interview was not statistically analyzed.

Ethical considerations

The study was approved by the Ethical Committee of the University Hospital Antwerp, Belgium (Belgian Registration Number B300201213376, 05/03/2012; Clinical Trial Registration, 10/2013, http://clinicaltrials.gov/ct2/show/study/NCT01963338). All subjects gave their informed consent prior to participation in the study. All collected data was anonymized.

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