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Immunogenicity and safety of intradermal delivery of hepatitis B booster vaccine using the novel drug delivery device VAX-ID™

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ABSTRACT

Background: Although intramuscular (IM) injection is still the most preferred method for vaccination, intradermal (ID) delivery may have several advantages over intramuscular and subcutaneous (SC), including an improved immune response and antigen dose sparing effect. However it is currently limited due to the difficulty in standardizing the injection technique often based on the Mantoux technique. Difficulties encountered using the Mantoux technique could be overcome by the use of alternative ID delivery systems that confer more uniform and standardized procedures.

The aim of this study was to evaluate the performance of a newly developed intradermal injection device, VAX-ID™, via a proof-of-concept to assess the immunogenicity of a commercially available hepatitis B booster vaccination in healthy hepatitis B pre-immunised subjects. Additionally, device safety and tolerability was evaluated.

Materials and methods: Three different routes of administration were compared over 4 groups, each receiving hepatitis B vaccine antigen: (1) standard IM injection in the deltoid region (HBVAXPRO® 10 μg/1 ml), (2) ID injection in the proximal posterior area of the forearm according to the Mantoux technique, (3) with VAX-ID™ in one forearm, or (4) with VAX-ID™ in both forearms. For ID injections 0.11 cc, of which 0.01 cc is overfill, was drawn from a vial containing HBVAXPRO® 40 μg/1 ml. Immunogenicity and safety were followed-up at day 0, 14, 30 and 210.

Results: A total of 48 subjects were included. All subjects showed an anamnestic response at 14 days post booster vaccination. Elevated titres persisted until end of follow-up at day 210. For the ID groups a 3 fold higher immune response at day 14 and day 30 was recorded compared to IM group. Local adverse events were more reported for ID compared to IM.

Conclusions: The investigated ID injection device VAX-ID™ proves to be a good alternative to offer ID vaccination.

1. Introduction

Although intramuscular (IM) injection is still the most preferred method for vaccination, intradermal (ID) delivery may have several advantages over intramuscular and subcutaneous (SC), including an improved immune response and antigen dose sparing effect [1,2].

The skin is considered as a desirable vaccination target since dermis and epidermis are rich sources of antigen–presenting cells which are known to participate in vaccine induced immune responses [2–4].

ID administration is currently limited due to the difficulty in standardizing the injection technique often based on the Mantoux technique which is considered the golden standard and is used for administration of the Bacille Calmette-Guérin vaccine [5]. There are several studies conducted to evaluate the effectiveness of ID delivery route using different commercially available vaccines including hepatitis B [6,7], influenza [2,8] and rabies [9].

Importantly, the Mantoux method is difficult to standardize, requires training and regular practice of healthcare workers [2,10–12]. Difficulties encountered using the Mantoux technique could be overcome by the use of alternative ID delivery systems that confer more uniform and standardized procedures [13–15].

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VAX-ID™ is a newly developed single use intradermal injection device designed to be user friendly and allow for accurate and painless ID drug and vaccine delivery. Previous data by Van Mulder et al. [16] has shown that the maximal penetration depth is mostly determined by the skin thickness in females, which should not exceed 1.0 mm.

To evaluate VAX-ID™ performance (e.g. successful vaccine delivery in the dermis which confers a sufficient immune response with acceptable side effects), a proof-of-concept was performed to assess the immunogenicity of a commercially available hepatitis B vaccine (HBVAXPRO®, MSD VACCINS [17]) administered as a booster vaccination intramuscularly or intradermally using the Mantoux technique or VAX-ID™ in healthy hepatitis B pre-immunised subjects. Additionally, device safety and tolerability was evaluated.

2. Materials and methods

2.1. Study design

To evaluate the immunogenicity and safety of a hepatitis B booster vaccination via VAX-ID, IM or ID by Mantoux technique in previously hepatitis B (HB) vaccinated subjects, the remaining anti-HBs concentration was measured in blood and compared with the anti-HBs response after vaccination, and local and systemic reactions were recorded.

Three different routes of administration were compared over 4 groups (Fig. 1), each receiving hepatitis B vaccine antigen: standard IM injection in the deltoid region (IM group) with a 23G × 1″ injection needle, ID injection in the proximal posterior area of the forearm according to the Mantoux technique (ID1 group) with a 25G × 5/8″, with VAX-ID™ in one forearm (ID2 group) or with VAX-ID™ in both forearms (ID3 group) (Fig. 1). For the IM injections HBVAXPRO® 10 μg/1 ml was injected, for the ID injections 0.11 cc, of which 0.01 cc is overfill, was drawn from a vial containing HBVAXPRO® 40 μg/1ml prior to injection. HBVAXPRO® is a recombinant hepatitis B virus surface antigen vaccine, absorbed on amorphous aluminium hydroxyphosphate sulfate marketed by MSD VACCINS for IM injections [17]. The ID3 group was added to the study to evaluate the dose sparing effect in contrast to the IM injection. All injections were performed in the non-dominant arm, except for ID3 group where one injection in each arm was given. The antigen dose for subjects in the IM group was 2.5 times higher than for subjects of the intradermal groups ID1 and ID2 (10 μg to 4 μg, respectively). Subjects of ID3 group received a double intradermal dose in two single injections (twice 4 μg).

2.2. Immunogenicity assessment

Primary objective was to demonstrate an antibody booster response to hepatitis B surface antigen (anti-HBs) in subjects completely vaccinated against hepatitis B at least 5 years earlier, after booster administration delivered according to the IM or ID routes (Mantoux or VAX-ID™). Blood samples were taken prior to vaccination (day 0), at day 14 and day 30 with a 2 day variation. Additionally a fourth blood sample was taken at day 210 with a 14 day variation. Serology testing of anti-HB levels were measured through a commercial immunoassay (ARCHITECT® Anti-HBs) and performed by a certified lab (A.M.L. bvba, Antwerp, Belgium).

An anti-HBs antibodies cut-off value of 3.3 mIU/mL was applied. Subjects were classified as seropositive when antibody concentration was greater than or equal to the cut-off value, seronegative when below the cut-off value and seroprotective when greater or equal to 10 mIU/mL.

Primary outcome was to achieve an anamnestic response in at least 90% of the subjects.

Anti-HBs anamnestic response to the booster dose was defined as: (1) anti-HBs antibody concentrations ≥10 mIU/ml at 14 days post-challenge dose in subjects seronegative at the pre-challenge time-point or (2) at least a 4-fold increase in anti-HBs antibody concentrations, at 14 days post-challenge dose in subjects seropositive at the pre-challenge time-point.

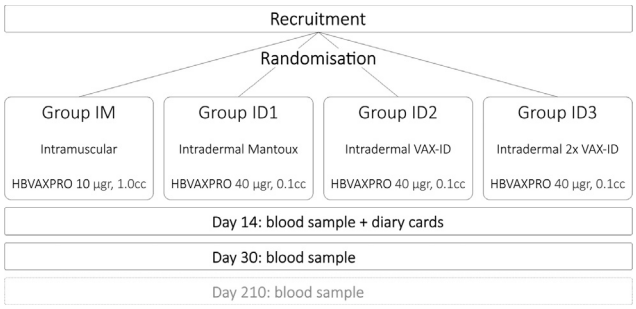


Fig. 1. Study design.

2.3. Safety assessment

Secondary objective was to evaluate the safety of a booster vaccination in previously HB vaccinated subjects, delivered according to the IM or ID routes (Mantoux or VAX-ID™) of administration. Safety was assessed by recording solicited local and systemic reactions, unsolicited adverse events (AE) and severe adverse events (SAEs). Occurrence, intensity and relationship to vaccination of all AEs were recorded on diary cards during a 14-day follow-up period after the booster dose. In case of ongoing local reactions on day 14, follow up was continued by means of a visit on day 30 and monthly telephone calls thereafter. The telephone calls had a range of ±14 days. The local reactions were followed up until disappearance or consolidation. For the local AEs pain and pruritus and the systemic AEs headache, malaise, myalgia and shivering the intensity was recorded by means of a Visual Analogues Scale (VAS; 1 = very low intensity, 10 = extremely high intensity). Other local AE's (erythema, swelling, induration and ecchymosis) were measured with a ruler (reported in cm). Temperature was measured orally in the first 7 days after vaccination and recorded in °C; >38 °C was considered as fever.

2.4. Novel intradermal drug delivery device VAX-ID™

VAX-ID™ consists of: a foot, a 32G needle in a needle hub protruding 1.0 mm into the vaccinee's skin. A 1.0 ml syringe (HSW Soft-Ject: Low Dead Space) is to be filled with 0.11 cc of vaccine to allow injection of 0.1 cc (Fig. 2).

VAX-ID™ is activated by twisting the foot one quarter turn. Next, the foot is placed on the skin, through the downward movement of the housing the needle will penetrate the skin, and the syringe is emptied by means of the plunger in the target area. VAX-ID™ is hence for single use (Fig. 2).

2.5. Study population

The study was conducted at a single trial centre in Belgium. Eligible subjects included Dutch speaking healthy, Caucasian adults aged 18–35 years. Subjects required to be fully vaccinated against hepatitis B at least 5 years earlier and to bring a proof of vaccination. Pregnant or lactating women were excluded, as well as people that received other vaccination(s) 4 weeks before study onset or planned to have other vaccinations during the study period. Recruitment took place from March 2016 to June 2016.

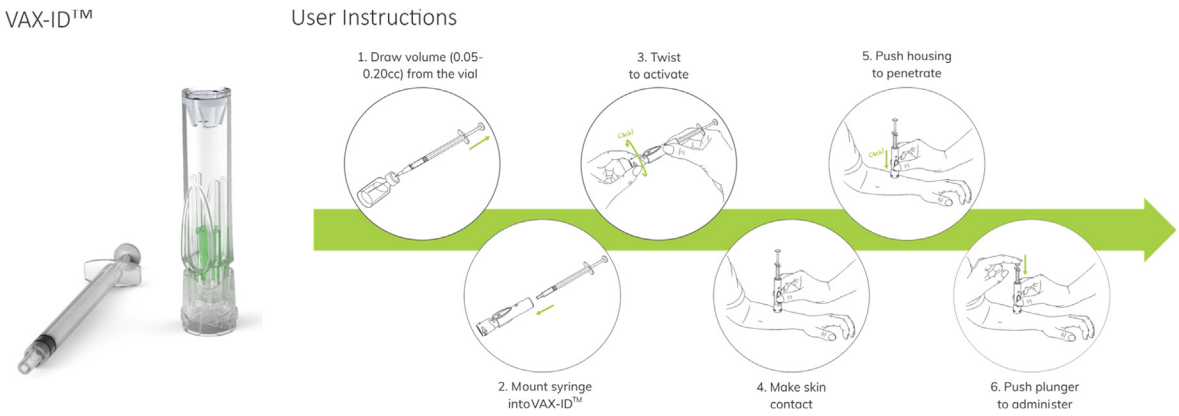


Fig. 2. VAX-ID™ and instructions for use.

Demographics, earlier vaccination details, regular medication use and medical history were surveyed via a questionnaire and anamnesis.

Subjects were allocated to a study group following a computer-generated list of random numbers.

2.6. Statistical methods

Demographics, logarithmic converted titers and solicited local and systemic adverse events were compared between groups using non-parametric tests (Kruskal-Wallis, Fisher-Freeman-Halton Test, and Spearman's rho test). Geometric Mean Concentration (GMC) were calculated per study group. The statistical software package IBM SPSS version 22 was used. A significance level of 0.05 and a confidence interval of 95% is maintained.

2.7. Ethical considerations

The study was approved by the Ethical Committee of the University Hospital Antwerp, Belgium and the Federal Agency for Healthcare Products and Medicines (EudraCT: 2014-002486-29), Belgium and registered at clinicaltrials.gov (NCT02186977). The study was conducted according to good clinical practice and Declaration of Helsinki. All subjects gave their informed consent prior to participation in the study. All collected data was coded.

3. Results

3.1. Subjects

A total of 48 subjects were included, resulting in 12 persons per group (Table 1). Overall 66.7% were female and the average age over all groups was 24 years (SD: 3.97; p = 0.270, Kruskal Wallis Test) with no difference per study arm. 1 subject was from Hispanic or Latino origin. Participants had received a hepatitis B vaccine on average 11 years prior to study onset (SD: 3.71; p = 0.256; Kruskal-Wallis Test). Importantly to note is that not all participants had a follow-up blood sample taken at day 210 (IM = 7, ID1 = 6, ID2 = 6, ID3 = 5), as this procedure was added after study onset, through a protocol amendment.

3.2. Immunogenicity evaluation

At baseline, 7 participants (5× IM, 1× ID1, 1× ID2) were anti-HBs seronegative. All subjects showed an anamnestic response at 14 days post booster vaccination. Elevated titres persisted until end of follow-up at day 210 (Fig. 3). Two participants, one of the ID1 and one of the ID3 group, were excluded for further analysis on anti-HBs concentration and GMC because of extreme values (eg. at day 14: 262558 and 190840, respectively). For the ID groups a 3 fold higher immune response at day 14 and day 30 was recorded compared to IM group (Fig. 3). However no statistical difference was found between all groups for all participants at different follow-up days (p-values, Kruskal Wallis Test; Day 0 = 0.061, Day 14 = 0.438, Day 30 = 0.555). For participants followed-up till day 210, the immune response was similar at all follow-up days between all groups (p-values, Kruskal Wallis Test; Day 0 = 0.583, Day 14 = 0.911, Day 30 = 0.840, Day 210 = 0.868).

No signification correlation was observed between the immune response at day 14 and the time since the last hepatitis B vaccination prior to the booster injection (r: −0.207; p = 0.167, Spearman's rho test).

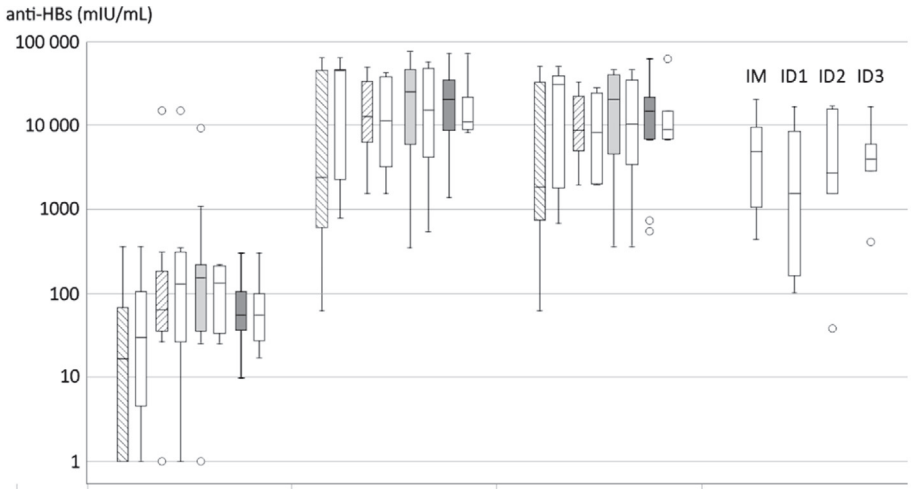
3.3. Safety evaluation

Overall pain after the injection was reported by 21.7% of subjects, and by participants of the IM group; the maximal pain score was 3 on a scale to 10 (Table 2). Pain was reported for maximum

Table 1
Demographics of the per protocol study population (N = 48).

Group	N	Age mean (SD)	Gender (n)		Last hepatitis B vaccine received (in years)
			Male	Female	Mean (min - max)
Intramuscular (IM)	12	23.5 (4.3)	6	6	12.8 (7 – 18)
ID-Mantoux (ID1)	12	22.4 (1.8)	1	11	9.3 (5 – 13)
ID VAX-ID (ID2)	12	25.4 (4.2)	3	9	10.7 (5 – 18)
ID 2x VAX-ID (ID3)	12	24.3 (4.6)	5	7	10.8 (7 – 16)
p-value		0.270*	0.138+		0.256*

* Kruskal-Wallis Test.
\+ Fisher-Freeman-Halton Test.



Study group	N	Day 0 GMC (95% CI)	Day 14 GMC (95% CI)	Day 30 GMC (95% CI)	Day 210 GMC (95% CI)
Intramuscular	12	11 (3- 44)	3682 (821- 16512)	3425 (845- 13884)	
	7	*22 (3 - 185)*	*12782 (2205 - 74080)*	*10207 (1763 - 59088)*	*3764 (931 - 15209)*
Intradermal Mantoux	11	89 (19- 427)	14750 (6755- 32211)	10752 (5373- 21513)	
	6	*125 (4 - 3607)*	*11371 (2487 - 51999)*	*8500 (2192 - 32953)*	*1503 (170 - 13292)*
Intradermal- VAX-ID 1x	12	129 (31- 532)	14921 (4757- 46817)	12235 (4123- 36299)	
	6	*105 (38 - 296)*	*12014 (1851 - 77965)*	*8702 (1302 - 58157)*	*2491 (239 - 25942)*
Intradermal- VAX-ID 2x	11	67 (33- 137)	15052 (6288- 36033)	10454 (3837- 28483)	
	5	*67 (17 - 270)*	*18910 (6170 - 57970)*	*14757 (4694 - 46398)*	*3819 (708 - 20597)*
p-value (Kruskal Wallis)		0.061	0.438	0.555	
		0.583	*0.911*	*0.840*	*0.868*

Boxplots are setup per follow-up day. The marked (stripes and grey) apply for all participants, within their respective study group, the white next to it is only applicable on the participants who followed-up till day 210. Numbers that are aligned left apply to all participants, numbers aligned right and in italics apply for participants follow-ed up till day 210.

Fig. 3. Geometric mean concentration of anti-HBs for 4 study groups (IM, ID1, ID2 & ID3) on day 0, 14 30 and 210.

9 days. Pruritus was mentioned more frequently and at higher scores in ID groups than in the IM group. For all ID groups pruritus reported with a maximum of 5 on a scale to 10.

Redness, swelling and induration were more frequent in ID groups compared to IM ($p < 0.001$, Fisher-Freeman-Halton Test), although no incidence difference was noted in between ID groups (p-value, Kruskal Wallis Test; 1, 0.890, 0.546, respectively). Ecchymosis was rarely reported (Table 2). Duration of redness was reported longer for ID injection via VAX-ID compared to Mantoux ($p = 0.011$; Kruskal Wallis Test). Intensity (VAS scores) of reported local adverse events did not differ in between the ID groups (Table 2)

3.4. Reactogenicity evaluation of systemic solicited AE

None of the subjects reported fever during 7 days post-vaccination (Table 3).

In six subjects headache was reported for 5 days (Table 3). Only for 7 subjects malaise was reported over the first 4 follow-up days. Maximum incidence was reported in the IM group, which was 5 on a scale to 10 at day 3. Myalgia was reported by 5 subjects over the first 3 follow-up days. The highest scored value, 3 on a scale to 10, was reported at 1 day follow-up for a subject in the ID1 group (Mantoux).

No shivering was reported.

3.5. Reactogenicity evaluation of unsolicited AE

Except for discoloration at injection site (max. 0.2 mm) in two participants of the ID groups which remained at least 30 days, no unsolicited nor serious adverse events were reported.

4. Discussion

The performance of the newly developed ID injection device, VAX-ID™, compared with the golden standard for ID administration, the Mantoux technique, and IM injection, shows promising results.

In the current study a booster vaccination with reduced dose recombinant hepatitis B vaccine administered via two different ID administration routes showed similar immune responses as full dose IM administration, and local side effects were mild. Although the small sample size limits generalisation of the results, the findings corroborate previous reports

Multiple studies investigated the immunogenicity and safety of ID vs IM vaccination in poor or non-responders and patients at high risk [6,7]. Despite the small sample size of the current study, higher anti-HBs levels were recorded for the ID groups compared to the IM groups, nevertheless those results were not statistically significant. Studies in non-responders or patients at high risk confirms higher seroconversion rates for ID injections compared to IM

Table 2
Local adverse events for the for 4 study groups (IM, ID1, ID2 & ID3) during the 14 days period after hepatitis B booster administration.

		IM N = 12	ID1 N = 12	ID2 N = 12	ID3 N = 24	p-value[a]	p-value[b]
pain	n (%)	10 (83)	5 (42)	6 (50)	9 (38)	0.065	0.810
pain - VAS[c]	mean (max)	0.26 (3)	0.11 (1)	0.18 (3)	0.12 (3)	0.136	0.624
pain - duration[d]	mean (max)	1.4 (4)	1.0 (3)	1.7 (9)	0.8 (5)	0.217	0.388
pruritus	n (%)	1 (8)	7 (58)	9 (75)	15 (62)	0.04	0.789
pruritus - VAS	mean (max)	0.01 (1)	0.62 (5)	0.63 (5)	0.54 (5)	0.04	0.721
pruritus - duration	mean (max)	0.1 (1)	2.2 (10)	2.9 (11)	2.5 (8)	0.05	0.788
redness	n (%)	0 (0)	11 (92)	12 (100)	23 (96)	< 0.001	1
redness - VAS	mean (max)	–	1.1 (5.5)	1.1 (5.3)	1.1 (3.2)	–	0.853
redness - duration	mean (max)	–	41.7 (90)	86.2 (120)	68.3 (120)	–	0.011
swelling	n (%)	1 (8)	9 (75)	10 (83)	20 (83)	< 0.001	0.890
swelling - VAS	mean (max)	0.1 (0.2)	0.7 (1.6)	0.8 (5)	0.7 (2.8)	0.261	0.462
swelling - duration	mean (max)	8(8)	23.1 (90)	30.0 (90)	35.0 (90)	< 0.001	0.671
induration	n (%)	0 (0)	11 (92)	10 (83)	23 (96)	< 0.001	0.546
induration - VAS	mean (max)	–	0.7 (1.6)	0.8 (5)	0.6 (2.6)	–	0.610
induration - duration	mean (max)	–	36.5 (90)	55.9 (120)	34.6 (90)	–	< 0.001
ecchymosis	n (%)	2 (17)	1 (8)	2 (17)	0 (0)	0.083	0.117
ecchymosis - VAS	mean (max)	0.7 (1.1)	0.2 (1.1)	0.4 (1.5)	–	0.819*	1
ecchymosis - duration	mean (max)	1.5 (10)	0.8 (9)	1.9 (14)	–	0.229*	0.143

For comparison 'n (%)' Fisher-Freeman-Halton Test was used and for comparison 'mean' Kruskal Wallis Test was used.
[a] p-value for comparison between all groups.
[b] p-value for comparison between ID groups.
[c] VAS = Visual Analogue Scale, 1 = very low intensity, 10 = extremely high intensity.
[d] Duration in days.
* Comparison only for IM×ID1×ID2.

Table 3
Incidence systemic solicited adverse events.

	Temperature (in °C)	Headache		Malaise		Myalgia	
	mean (SD)	N	max VAS*	N	max VAS*	N	max VAS*
IM group	37.0 (0.19)	2	4	2	5	1	1
ID Mantoux	37.0 (0.28)	1	1	1	2	1	3
ID VAX-ID 1x	36.9 (0.18)	2	2	1	1	1	2
ID VAX-ID 2x	36.9 (0.21)	1	2	3	2	2	2
	p = 0.243 Kurskal Wallis Test						

* VAS = Visual Analogue Scale, 1 = very low intensity, 10 = extremely high intensity.

injections [6,7,18,19], a trend that also was seen in the current study. One study with a very similar design as ours, by Ghabouli et al. [20], investigated the immunogenicity of a recombinant hepatitis B vaccine in young healthy adults whereby 4 μg was delivered ID and 20 μg IM, and found equal seroconversion rates for different administration groups.

The reported adverse events in the current study are comparable to other trials [7,18,20]. The frequency of local adverse events reported in the ID group is significantly higher compared to IM, but they were rather mild, which is also concluded by other researchers [18,20–22]. The used vaccine contains aluminium hydroxyphosphate sulfate which can explain the longer presence of local adverse events in the ID groups such as discoloration. Next to the enhanced immune response, following the adsorption of antigens to aluminum adjuvants, it provides a slower diffusion of antigens from the injection site resulting in more time for accumulation and related local adverse events [23]. As ID vaccination confers very effective qualitative immune response, there is actually no need for adding aluminum or other adjuvants [24]. However, we had no choice as no commercial hepatitis B vaccines are available vaccines without adjuvants. Nevertheless, the current research outcome contributes to a WHO defined challenge on ID delivery of vaccines and associated formulations and adjuvants [5].

The WHO suggest that ID administration of vaccines can be more efficient, by inducing protective immunity with smaller amounts of antigen [5,6]. In addition, the dose sparing can be cost saving, although the overall cost impact and use scenarios are to be evaluated to guarantee significant financial savings [4]. Moreover, the need for applications that are easy and that do not need training is highlighted by David MC et al. [6]. These important added values for ID vaccination are also supported by the earlier data on acceptability and usability from the previous study of Van Mulder et al. [12] and the immunogenicity and safety data from the current studies.

5. Conclusion

The investigated ID injection device VAX-ID™ proves to be a good alternative to offer ID vaccination. Additional research with larger sample size will be needed to confirm the immunogenic capacity of ID administration and to further emphasize the safety, ease of use and feasibility of VAX-ID™ as a ID-device for vaccine administration.

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Conflict of interest

Van Damme P. is chairman of the Board of Directors of Novosanis NV.

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