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Clinical studies assessing immunogenicity and safety of intradermally administered influenza vaccines

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Importance of the field: Human influenza A and B are major respiratory pathogens and cause high mortality and severe morbidity, especially in at-risk populations. Most of the vaccines are administered intramusculary or subcutaneously. Owing to vaccine shortage and low vaccine coverage, intradermal administration of vaccines has gained renewed interest. In addition, higher immune responses with the same quantity of antigen have been elicited with intradermal vaccine administration, offering dose-sparing capacity.

Areas covered in this review: This review summarizes the immunogenicity and safety data accumulated from influenza vaccine trials where vaccines were administered intradermally. Clinical trials performed using reduced vaccine antigen doses in healthy volunteers or in at-risk populations and target groups are discussed as well as new devices for intradermal delivery of influenza vaccines. The studies addressed in this review were identified through a MEDLINE search.

What the reader will gain: The review provides insights into the potential of intradermal vaccines to overcome hurdles such as vaccine shortage in view of mass vaccination campaigns. Moreover, evidence is provided of improved immunological responses after intradermal vaccination when new intradermal devices are being used.

Take home message: In the authors' opinion, intradermal vaccination can be considered an equally immunogenic, safe and feasible alternative to intramuscular and subcutaneous vaccination. The future looks promising because of the recent development of new intradermal vaccine delivery devices.

Keywords: device, immune response, influenza, intradermal vaccine, review, safety

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1. Introduction

Influenza causes substantial mortality and morbidity especially in at-risk populations such as the very young, elderly and people with underlying chronic conditions. World Health Organization (WHO) estimates show that seasonal epidemics affect 3 million – 5 million people annually and result in 250,000 – 500,000 mortalities, mainly among people aged 65 or more [1]. Furthermore, morbidity due to influenza is high among young children, those < 6 months old [2,3]. Annually, influenza-related illnesses cause a substantial number of hospitalizations in children < 5 years of age [4-6], and especially for infants < 6 months of age hospitalization rates are high (104 hospitalizations for influenza per 10,000 infants < 6 months of age versus 4 hospitalizations per 10,000 children 5 – 15 years of age), approaching the

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Article highlights.

- Intradermal vaccination elicits comparable or even superior immunogenicity in different populations, including healthy adults, children, elderly and patients at risk, compared with intramuscular/subcutaneous vaccination.
- New devices, such as Soluvia and MicronJet, show promising results for the delivery of antigens in terms of immunogenicity, safety, reduced injection pain, ease of use and dose-sparing capacities.
- There is a need for studies comparing vaccines from different suppliers as well as comparing different populations, including healthy adults, children, elderly and patients at risk.
- Favorable immonological properties of the skin allow the use of reduced doses, which makes intradermal vaccination an attractive alternative to intramuscular/subcutaneous vaccination.

This box summarizes key points contained in the article.

hospitalization rates of the elderly > 65 years [5,7]. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) revisited its recommendations, thereby encouraging influenza vaccination in children aged 6 – 59 months [8]. The commercially available inactivated trivalent influenza seasonal vaccines are, however, not licensed for children < 6 months of age [9].

Also, the economic burden (direct and indirect costs) of seasonal influenza is considerable [10]. Next to reduction of the health costs, annual vaccination is the primary and single most effective strategy to control and prevent influenza. Vaccination could provide 70 – 90% protection for influenza occurrence in healthy adults and a protection rate of 30 – 70% in patients with underlying co-morbidities [11]. The WHO and the Council of the European Union aim to achieve vaccination coverage rates of 75% in the aged population by 2010 – 11 [12] and 2014 [13], respectively. In Western Europe, the vaccination coverage in the elderly population reached ~ 50% during the influenza season 2006 – 07 [14]. Vaccination coverage remains very low in adults between 18 and 60 years; vaccination rates as low as 10% have been reported in this age group in Western Europe [14], which are comparable to those in the US, Latin America, Eastern Europe and Asia [15]. One of the reasons for not getting vaccinated could be a dislike of needles, which could explain low vaccination coverage in adults aged 18 – 60 years. The use of alternative administration methods could therefore contribute to an increase in vaccination coverage in this population.

The route of administration of vaccines has interested clinicians for > 70 years. Vaccines are commonly administered intramusculary (i.m.) or subcutaneaously (s.c.) using large volumes (up to 1 ml), but other delivery methods are also possible. In 1931, Tuft [16] created controversy by indicating that a small dose of intradermally (i.d.) delivered typhoid vaccine was equally immunogenic and gave fewer systemic reactions than s.c. delivery of a larger dose. This study led to further research on administration of vaccines using the i.d. route.

The unique immunological properties of the skin make the epidermis and dermis attractive sites for prophylactic vaccination. Skin dendritic cells (DCs) are important professional antigen-presenting cells that have potent T-cell activating properties on pathogenic challenge [17]. In the skin, two types of DC are present: in the epidermis Langerhans cells (LCs) reside, whereas the dermis is populated by dermal or interstitial DCs (dDCs) [18]. Next to resident LCs and dDCs, recruitment of precursor DCs from the blood into the dermis is also important for efficient T-cell priming and differentiation [19]. Intradermal vaccination induces T-cell activation by triggering the activation and migration of dDCs on the one hand [20] and by favoring lymphatic drainage of free antigen and subsequent capture by lymph node-resident DCs on the other hand [21]. Therefore, i.d. vaccines have the potential for greater immunogenicity than i.m. vaccines with an equal content of vaccine antigen. Indeed, i.d. vaccines have shown promising results with rabies and hepatitis B vaccine antigen [22-24]. **Figure 1** gives an overview of the immune response induced by intradermal, intramuscular and transcutaneous vaccination. The latter refers to topical application of antigen onto intact or pretreated skin. Intramuscular vaccination delivers the influenza antigen into tissue without important antigen-presenting cells. Antigens are believed to be picked up by transient antigen-presenting cells or to circulate to the draining lymph node. By contrast, i.d. vaccination delivers antigens directly to the immune system of the skin and facilitates their exposure to antigen-presenting cells, such as dermal dendritic cells. Next, the immune response is amplified and antigens are presented to the T cells in the draining lymph nodes, thereby initiating an efficient cellular response [17].

Since 2006, recommendations by ACIP have stated that next to at-risk populations, children and household contacts of high-risk people should also be vaccinated against influenza, which could lead to a higher number of vaccines and antigens needed and consequently to potential vaccine shortage, mainly in the fall when the demand for influenza vaccines is highest [8]. In 1973, manufacturing difficulties led to vaccine shortage [25] and also in 2004 almost 50% of the vaccine supply in the US was declared unfit for use owing to contamination at a single production plant, again causing vaccine shortage [26]. After the turn of the century, renewed interest in intradermal vaccination was seen. Studies by Belshe *et al.* [27] and Kenney *et al.* [28] indicated that reduced dose or other strategies could provide an adequate answer to vaccine shortage.

In April 2009, human infections with a new influenza A (H1N1) virus were identified and as of June 2009 infections with this new strain were reported worldwide, which led

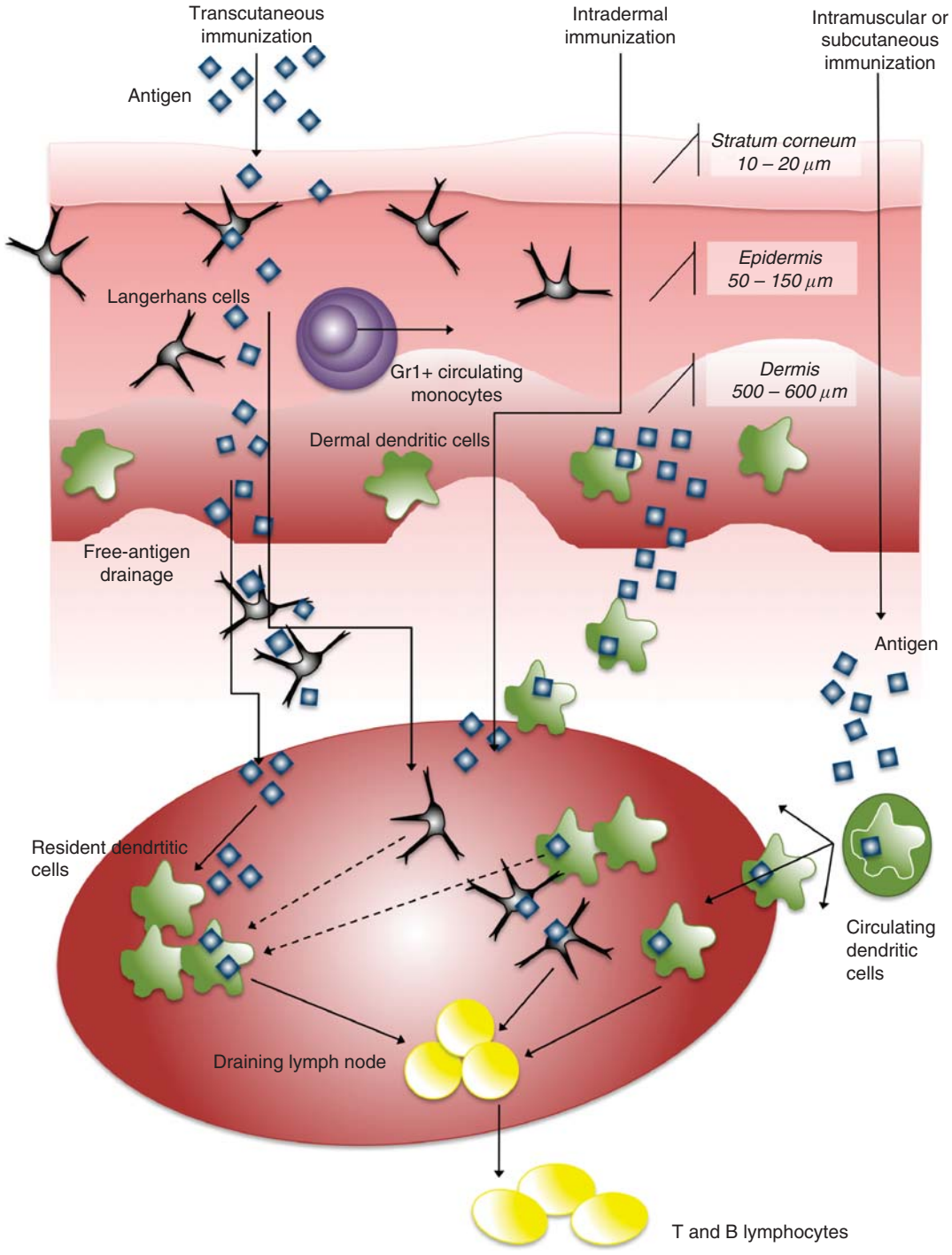

Figure 1. Immune response induced by transcutaneous, intradermal and intramuscular vaccination. Transcutaneous and intradermal vaccination deliver antigens directly to the immune system of the skin. They target antigen-presenting cells, such as Langerhans cells and dermal dendritic cells. After capture and maturation, they migrate to the draining lymph nodes and trigger T- and B-cell activation. Free antigens can migrate directly to the draining lymph nodes where they are captured by the resident dendritic cells who present the antigens to the lymphocytes. Intramuscular vaccination delivers the influenza antigen into tissue without important antigen-presenting cells. Antigens are believed to be picked up by circulating dendritic cells and migrate to draining lymph node or spleen through lymphatic drainage or general circulation. Next, the immune system is amplified and T- and B-cell activation is triggered.
Adapted with permission from [17].

the WHO quickly to raise the pandemic alert level to Phase VI [29]. Importantly, pandemic vaccines have the greatest impact as a preventive measure when administered before or near the peak incidence of cases in an outbreak [30]. The effectiveness of vaccination depends, however, on timely and sufficient supply of vaccine. WHO estimated worldwide production of vaccines at ~ 3 billion a year whereas the actual production in December 2009 was only 534 million doses, which is inadequate to cover a world population of 6.8 billion people [31,32]. Thus, this recent outbreak of H1N1 influenza virus highlights the urgent need to develop a more effective vaccine platform, vaccination method and dose-sparing strategies [32,33]. In this regard, if reduced dose i.d. vaccines were found to be as equally immunogenic, safe and effective as i.m. vaccines, the number of available doses would increase and more people could be offered vaccination, especially in times of shortage.

In people > 65 years, antibody responses to influenza vaccination have been shown to be significantly lower than in younger adults [34]. Goodwin *et al.* [34] estimated a clinical efficacy of only 17 – 53% in elderly depending on the circulating viruses. By contrast, clinical vaccine efficacy has been estimated at 70 – 90% in healthy adults by the CDC [35]. Importantly, the immune response to vaccination decreases with age because of immunosenescence. Antigen-presenting cells, such as macrophages and dendritic cells, show decreased capacity to present antigens. The macrophages also display reduced phagocytosis and increased release of pro-inflammatory cytokines, whereas the dendritic cells display impaired migration to the lymph nodes [36,37]. Next to immunosenescence, previous vaccination, pre-titers and living conditions also influence the antibody response significantly [34]. In this perspective, efficient i.d. vaccination has been suggested as an alternative route to increase the immunogenicity in not only the elderly, but also diseased people [38]. Next to administration of vaccines using alternative routes, improved protection against influenza could also be obtained by increasing the concentration of antigens, by adding adjuvants or by using attenuated vaccines. The latter three are not however, within the scope of this paper.

This review summarizes the clinical data accumulated from vaccination studies in which influenza vaccines were administered intradermally. The immunogenicity and safety data of trials conducted in healthy volunteers using standard and reduced doses are investigated. Also, clinical trials performed in at-risk populations and target groups are addressed and new devices for intradermal delivery of influenza vaccines are touched on briefly.

2. European guidelines for assessing immunogenicity, safety and reactogenicity

To measure vaccine protectiveness, the influenza hemagglutinin inhibition (HI) assay is the most established assay [39]. Owing to the change in viral structure of the seasonal influenza viruses, a new vaccine has to be manufactured yearly. The selection of three strains (one A/H1N1, one A/H2N3 and one B strain) included in the vaccine is done on a biannual basis by the WHO, once for the northern hemisphere and once for the southern hemisphere [40]. For the yearly relicensing of influenza vaccines in Europe, the guidelines published by the European Committee for Proprietary Medicinal Products (CPMP) have to be followed [9]. Furthermore, these also have to be taken into consideration when conducting clinical trials to evaluate influenza vaccines. The guidelines state that for adults aged 18 – 60 years at least one of the following requirements should be met: the number of seroconversions or significant increase in antihemagglutinin antibody titer must exceed 40% (equals seroconversion rate); the mean geometric increase must exceed 2.5 (equals seroconversion factor); and the proportion of subjects achieving an HI titer of ≥ 40 must exceed 70% (equals seroprotection). For adults aged over 60 years at least one of the following requirements should be met: seroconversion rate must exceed 30%, the seroconversion factor must exceed 2, and seroprotection must exceed 60% [9]. In all papers included in this review, antibody responses were measured before vaccination (pre-vaccination) and at 21 – 28 days after vaccination (post-vaccination).

In terms of safety and reactogenicity, CPMP guidelines state that within 3 days of vaccination the following reactions need to be assessed: injection site duration > 5 cm observed for > 3 days, injection site ecchymosis, body temperature of > 38.0°C for ≥ 24 h, malaise, and shivering [9].

The studies addressed in this review were identified through a MEDLINE search using the search terms 'humans', 'intradermal', 'influenza' and 'vaccine'. More articles were identified using the 'related articles' function in PubMed and based on the publication lists from the articles under review. Only articles published in English were reviewed. A selection of specific years to be included was not made.

3. Clinical studies evaluating reduced dose

Studies investigating the use of reduced dose vaccines have a long history. Early research on i.d. vaccines was performed between 1947 and 1980 using a mono- or bivalent influenza vaccine. In 1947, Van Gelder *et al.* [41] administered a bivalent influenza vaccine (A and B influenza), which showed protection using a lower dose. In 1948, Weller *et al.* [42] described fourfold antibody responses in most of the subjects who had received low doses of influenza antigen administered intradermally next to local redness and swelling in 90% of the subjects. During the pandemic of 1957 (Asian influenza), the possibility of using reduced doses of influenza vaccine by intradermal injection was investigated. The studies showed that in naive subjects who had no pre-immunization antibodies against the strain under study, one intradermal inoculation (1/5 to 1/10 the subcutaneous dose, 80 or 50 chick cell-agglutination units [CCA], respectively) of the

monovalent influenza vaccine (A2 Hong Kong variant) elicited lower antibody responses than one subcutaneous inoculation [43,44], whereas in primed subjects, due either to administration of two doses or to previous infection, equal antibody responses were seen with both administration routes [45,46]. By contrast, two studies reported a fourfold or even higher HI antibody increase after i.d. administration of a single dose containing one-fifth the s.c. dose (80 CCA) [47,48]. Pre-immunization titers, however, were not mentioned in these two studies.

The monovalent vaccine A/New Jersey/76 induced lower titers after i.d. vaccination of one-fifth of the i.m. dose (40 CCA/0.1 ml dose) compared with standard i.m. vaccination (400 CCA/0.5 ml dose) in 18 – 24-year-old people, whereas in people > 24 years of age, the serological response was equal after i.d. and i.m. vaccination. Systemic reactions were fewer after i.d. vaccination, whereas the opposite was true for local reactions [49]. These results seen in 18 – 24-year-old adults were not, however, confirmed in two other studies using the same strain. Halperin *et al.* [50] conducted a trial in the same age group (18 – 24 year olds) with a bivalent influenza vaccine (A/New Jersey/76 and A/Victoria/75, 40 CCA of each antigen for i.d. injection of 0.1 ml and 200 CCA of each antigen for s.c. injection of 0.5 ml), which showed that for the A/New Jersey/76 strain the i.d. and s.c. route led to an equivalent immune response, whereas for the A/Victoria/75 strain the intradermal route was superior. Also, Brooks *et al.* [51] reported satisfactory antibody responses in 6 different age groups after administration of a 0.1 ml i.d.-administered lower dose of the same bivalent influenza vaccine (2 A strains, 40 CCA A/New Jersey/76 and 40 CCA A/Victoria/75) combined with 0.1 ml of a monovalent (1 B strain, 100 CCA B/Hong Kong) influenza vaccine. The incidence of mild local reactions was high, but did not last > 1 day.

In 1977, the trivalent influenza vaccine (1 A/H1N1 strain, 1 A/H2N3 strain and 1 B strain) was introduced. Most of the influenza vaccines available at present are inactivated. Three subtypes can be distinguished: whole virion vaccines, split-virion vaccines and subunit vaccines [52]. Next to inactivated influenza vaccine, live attenuated vaccines have also been marketed, for example, Flumist™ (MedImmune, Gaithersburg, MD, USA), which is administered intranasally. It was not until the turn of the century that the i.d. vaccination route received renewed interest. Several major studies have been published since then evaluating an i.d.-administered inactivated trivalent influenza vaccine. In a study by Kenney *et al.* [28], immunogenicity of one-fifth (3 µg HA) of the standard i.m. dose administered intradermally to healthy adults (n = 100, 50 i.d., 50 i.m., < 40 years) was comparable or superior to the standard dose. Similar results were seen by Belshe *et al.* [27] using 40% (6 µg HA) of the i.m. dose in healthy adults (n = 130, < 60 years). Conversely, when the same dose was used in people > 60 years (n = 108), inferiority to the standard i.m. vaccine was seen. Also, in a study in 500 healthy subjects 20 – 50 years of age, post-vaccination geometric mean titers (GMTs) were significantly lower after i.d. administration of one-fifth of the dose (3 µg HA) of the standard i.m. adminstration [53]. However, CPMP criteria were still met.

All the studies described above using a trivalent inactivated influenza vaccine found similar results with respect to the safety of i.d. vaccination. Local reactions were more frequent after i.d. vaccination, whereas no significant differences were seen in the frequencies of reported systemic reactions.

Studies have been criticized in the past for not including an arm comprising i.m. vaccination in an equal reduced dose as i.d. vaccination. So far, only one study has compared three different doses of i.d. vaccine (3, 6, 9 µg HA) with equal doses i.m. as well as with the standard dose i.m. vaccine (15 µg HA) in 217 healthy adults (mean age of 30 years) [54]. Although the lowest i.d. dose (3 µg) was significantly inferior to the standard i.m. dose (15 µg), all i.d. doses were equally immunogenic to their respective control i.m. vaccine. None was found to be superior. Thus, in line with studies comparing reduced dose i.d. vaccine with standard dose i.m. vaccine, equal immunogenicity and safety was observed.

Although they are not commonly used for intradermal vaccines, adjuvants can be used to amplify immune responses or to reduce the vaccine dose. So far, one study has evaluated the intradermal administration of an adjuvanted influenza vaccine [55]. Healthy volunteers (n = 224, < 60 years) received a single dose of 3, 4.5 or 6 µg HA by means of i.d. injection or the full dose (15 µg HA) by means of intramuscular injection. The CPMP criteria were met in all study groups. However, seroprotection rates were significantly lower following i.d. vaccination compared with i.m. vaccination. Furthermore, GMTs and Geometric mean titer ratios (GMTRs) were significantly lower for the B strain after i.d. administration of the lowest dose (3 µg) compared with the full dose i.m. administration. Erythema was more frequent after i.d. vaccination whereas pain at the injection site was more frequent after i.m. vaccination.

Despite the fact that one study reported an inferior immune response after intradermal vaccination [53], it can be concluded that i.d. vaccination can be considered safe and immunogenic. Second, i.d. vaccination could be useful to increase not only vaccine availability because of dose-sparing ability but also vaccine coverage, as safety profiles comparable to i.m. and s.c. vaccination are seen. Finally, the immune response reported after i.d. vaccination was non-inferior or even superior compared with that elicited after i.m. or s.c. vaccination, which implies that protection capacity could be increased by i.d. vaccination. Overall, local reactions (erythema) were seen more often after i.d. vaccination, but were mild and transient. On the other hand, no significant differences were seen in systemic reactions after i.d., i.m. and s.c. vaccination. Safety profiles were similar for each of the vaccination routes and met the CPMP criteria. **Table 1** summarizes the studies performed using reduced vaccine antigen doses.

Table 1. Clinical studies using reduced vaccine antigen dose.

Authors	No. of subjects	Age range	Study year	Type of vaccine	Strains	Admin route	Dose	Safety	Immunogenicity	Pre-vaccination status	Remark
Boger and Liu [43]	90	> 70 years	1957	Monovalent	A2 Hong Kong	i.d. s.c.	50 CCA (0.1 ml) 500 CCA (0.5 ml)	Not tested	s.c. > i.d.	Naive subjects	
McCarroll and Kilbourne [46]	362	18 – 65 years	1957	Monovalent	A2 Hong Kong	i.d. s.c.	2 × 20 CCA (0.1 ml) 2 × 40 CCA (0.2 ml) 200 CCA (1.0 ml) 2 × 100 CCA (0.5 ml) 2 × 40 CCA (0.2 ml) 2 × 20 CCA (0.1 ml)	Not tested	s.c. = i.d. for two doses	Primed subjects (2 doses with interval)	
McElroy and Szwed [48]	16	Unknown	1968	Monovalent	A2 Hong Kong	i.d.	2 × 80 CCA (0.1 ml)	Not tested	Ninefold titer increase on average	Unknown	
Foy *et al.* [47]	271	Adults	1968	Monovalent	A2 Hong Kong	i.d.	2 × 80 CCA	Not tested	Fourfold titer increase in 50% of the subjects	Unknown	
Phillips *et al.* [44]	149	Students	1968	Monovalent	A2 Hong Kong	i.d. s.c.	80 CCA 400 CCA	s.c. = i.d.	s.c. > i.d.	Naive subjects	
Marks and Eller [45]	24	Young adults (25 – 39 years)	1970	Monovalent	A2 Hong Kong	i.d. s.c.	2 × 160 CCA (0.2 ml) 400 CCA (0.5 ml)	s.c. = i.d.	s.c. = i.d.	Primed subjects	Non-comparable control group (institutionalized children)
Brown *et al.* [49]	105	18 – 52 years	1976 – 77	Monovalent	A/New Jersey/76	i.d. i.m.	40 CCA (0.1 ml) 200 CCA (0.5 ml)	Systemic reactions i.d. < i.m. Local reactions i.d. > i.m.	18 – 24 years: i.d. < i.m. > 25 years: i.d. = i.m.	Naive subjects	
Brooks *et al.* [51]	70	20 – 80 years	1976 – 77	Bivalent + monovalent	A/New Jersey/76 + A/Victoria/75 + B/Hong Kong	i.d.	40 CCA of each A antigen (0.1 ml) 100 CCA B antigen (0.1 ml)	Incidence local reactions high	Satisfactory antibody responses; A/New Jersey/76 + B/Hong Kong > A/Victoria/75	High and low pre-immunization titers	
Halperin *et al.* [50]	124	18 – 24 years	1976	Bivalent	A/New Jersey/76 + A/Victoria/75	i.d. s.c.	40 CCA of each antigen (0.1 ml) 200 CCA of each antigen (0.5 ml)	i.d. = s.c.	A/New Jersey/76: i.d. = s.c. A/Victoria/75: i.d. > s.c.	High and low pre-immunization titers	
Belshe *et al.* [27]	238	18 – 60 years + > 60 years	2004	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Panama/2007/99 (H3N2) + B/Victoria 504/2000 (i.m.) or B/Johannesburg 5/99 (i.d.)	i.d. i.m.	6 μg HA 15 μg HA	18 – 60 years: Local pain i.m. > i.d. > 60 years: i.m. = i.d. Local inflammation: i.d. > i.m.	18 – 60 years: i.d. = i.m. > 60 years: i.d. < i.m.	Different pre-immunization titers	

Table 1. Clinical studies using reduced vaccine antigen dose (continued).

Authors	No. of subjects	Age range	Study year	Type of vaccine	Strains	Admin route	Dose	Safety	Immunogenicity	Pre-vaccination status	Remark
Kenney *et al.* [28]	100	18 – 40 years	2004	Trivalent	A/New Caledonia/20/99 IVR-116 (H1N1) + A/Panama/2007/99 Resvir-17 (H3N2) + B/Shangdong/7/97	i.d. i.m.	3 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions i.d. > i.m.	GMTR: A/New Caledonia and B/Hong Kong: i.m. = i.d. A/Panama: i.d. > i.m. Serconversion and seroprotection: i.d. = i.m.	Different pre-immunization titers	
Auewarakul *et al.* [53]	500	20 – 50 years	2007	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wellington/1/2004 (H3N2) + B/Shanghai/361/2002	i.d. i.m.	3 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions i.d. > i.m.	Post-vaccination GMTs i.d. < i.m. CPMP criteria met	Different pre-immunization titers	
Belshe *et al.* [54]	217	18 – 49 years	2007	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wellington/1/2004 (H3N2) + B/Shanghai/361/2002	i.d. & i.m. i.m.	3, 6, 9 μg HA 15 μg HA	Local reactions i.d. > i.m.	i.d. = i.m. for equal doses i.d. < i.m. for 3 and 15 μg, respectively	Different pre-immunization titers	Equal doses i.m. and i.d.
Künzi *et al.* [55]	224	18 – 60 years	2007	Trivalent	A/Solomon Islands/3/2006 (H1N1) + A/Wisconsin/67/2005 (H3N2) + B/Malaysia/2506/2004	i.d. i.m.	3, 4.5, 6 μg HA 15 μg HA	Local reactions i.d. > i.m. Pain at injection site i.d. < i.m.	CPMP criteria met Seroprotection: i.d. < i.m. GMTR B strain 3 μg HA: i.d. < i.m.	Different pre-immunization titers	Adjuvanted vaccine

4. Clinical studies in people with high-risk conditions and in children

4.1 Immunocompromised patients

Annual influenza vaccination is recommended in immunocompromised patients [11]. Most studies in immunocompromised patients have focused on administration of higher doses intramuscularly to improve vaccination in these patients [56,57]. Only a few studies have investigated the effect of intradermal influenza vaccination on immunocompromised patients (**Table 2**). In 140 patients ranging in age from 18 to 82 years (50% ≥ 51 years) with chronic pulmonary diseases, bivalent inactivated whole virus influenza vaccine containing A/New Jersey/76 and A/Victoria/75 was administered intradermally (n = 70, 0.1 ml containing 40 CCA) or subcutaneously (n = 70, 0.5 ml containing 200 CCA) [58]. Antibody responses were significantly higher after subcutaneous vaccination for the A/New Jersey/76 for which preimmunization titers were high. For the A/Victoria/75, no significant differences were seen in antibody response between intradermal and subcutaneous vaccination. The authors concluded that in the case of limited exposure to the virus, subcutaneous vaccination should be chosen over intradermal. A very recent study by Chuaychoo *et al.* [59] evaluated the immunogenicity of reduced dose intradermal trivalent inactivated influenza vaccine in chronic obstructive pulmonary disease (COPD) patients. A total of 156 patients received either 0.2 ml (6 μg HA per strain) split into two-site i.d. injections or a single 0.5 ml (15 μg HA) i.m. injection. Antibody responses (GMTs, seroconversion factors, seroconversion and seroprotection rates) of the i.d. injection were less than those of the i.m. injection. Nevertheless, CPMP criteria were met for i.d. vaccination, indicating that reduced dose may be considered in COPD patients in the case of vaccine shortage. Interestingly, systemic reactions were higher in the i.m. group than in the i.d. group, although not significant. Khanlou *et al.* [60] demonstrated that in HIV patients (n = 88, 53 i.d. route and 35 i.m. route), reduced dose i.d. vaccination (0.1 ml) provided equal immunogenicity in comparison with the standard dose i.m. vaccination (0.5 ml). However, the exact dose administered by either route was not mentioned. Similarly, Gelinck *et al.* [61] compared standard dose i.m. vaccination with reduced dose i.d. vaccination (3 μg HA, i.e., one-fifth of the normal dose) in not only HIV patients (n = 80), but also two other groups of immunocompromised patients, rheumatological patients treated with anti-TNF (n = 50) and hematological stem cell transplantation patients (n = 26). In contrast to the study by Khalou *et al.* [60], a group of healthy controls (n = 41) was included for comparative reasons. Post-vaccination titers and protection rates were similar after intradermal and intramuscular vaccination in all study groups. The healthy controls demonstrated significantly higher post-vaccination titers and protection rates compared with the immunocompromised patients. Within the immunocompromised patients, the patients with the most severe immunodeficiencies showed the lowest antibody responses. As expected, local reactions (erythema) were more frequent after i.d. vaccination than after i.m. vaccination, but interestingly, they occurred significantly more frequently in healthy controls than in immunocompromised patients. In 60 lung transplant patients, a two-dose regimen was given, that is, a standard intramuscular trivalent influenza vaccine (15 μg HA, 0.5 ml) followed by a booster of the same vaccine given intradermally (3 μg HA, 0.1 ml) [62]. A total of 63% of the patients met the criteria for seroconversion. Although GMT increased significantly from the baseline, the i.d. booster did not enhance further the GMT. Unexpectedly, low rates of adverse effects were seen after i.d. vaccination, which might be due to the use of immunosuppressive agents in this patient population. Recently, a study was conducted in patients with solid cancer [63]. The patients (n = 113) received either a conventional dose of influenza vaccine (15 μg HA, n = 59) intramuscularly or half of the conventional dose (7.5 μg HA, n = 54) intradermally. No significant differences were noted in seroconversion, seroprotection and GMT between either routes, and both met the CPMP criteria. Thus, reduced dosage of intradermal vaccination elicited an immune response that was comparable to that elicited by the full dose of intramuscular vaccine. Similar to what was noted by Gelinck *et al.* [61] and Manuel *et al.* [62] in their immunocompromised patient population, local reactions were less frequent in solid cancer patients than in healthy controls. This might be due to the relatively weaker immune response seen in immunocompromised patients.

Overall, these studies indicate that dose-sparing intradermal influenza vaccination is safe and immunogenic and can be considered as an alternative to intramuscular vaccination in immunocompromised patients.

4.2 Children

Intradermal vaccination might elicit good immune responses in children, but few studies have been conducted to investigate immunogenicity and safety of influenza vaccination in children and infants (**Table 3**). The oldest study dates back to the 1960s in which 89 infants and children ranging in age from 2 months to 5 years received equal volumes of monovalent influenza vaccine (200 CCA/0.1 ml) either intradermally (n = 48) or subcutaneously (n = 41) [64]. No significant differences were seen in antibody responses between both administration routes. However, owing to the low antibody titers seen, the use of two doses was suggested in children < 5 years of age in order to induce high antibody levels after vaccination. Importantly, a higher incidence of febrile reactions was seen after intradermal vaccination. Based on the latter, the authors support the use of subcutaneous vaccination rather than intradermal vaccination in children < 5 years of age. In a more recent study, 112 children aged 3 – 18 years (mean age of 10 years) were administered an inactivated trivalent influenza vaccine at one-fifth (3 μg HA) of the standard dose, which elicited high post-vaccination GMT and equal

Table 2. Clinical studies in immunocompromised patients.

Author	No. of subjects	Age range	Study year	Type of vaccine	Strains	Admin route	Dose	Safety	Immunogenicity	Pre-vaccination status	Remark
Herbert *et al.* [58]	140	17 – 82 years	1978	Bivalent	A/New Jersey/ 76 + A/Victoria/75	i.d. s.c.	80 CCA (0.1 ml) 200 CCA (0.5 ml)	Local reactions i.d. > i.m. Systemic reactions: i.d. = i.m.	Antibody response s.c. > i.d.	High for A/New Jersey/76	Chronic pulmonary disease
Chuaychoo *et al.* [59]	156	36 – 91	2006 – 2007	Trivalent	A/New Caledonia/ 20/99 (H1N1) + A/California/7/ 2004 (H3N2) + B/Malaysia/2056/ 2004	i.d. i.m.	6 μg (0.2 ml) 15 μg (0.5 ml)	Local reactions i.d. > i.m. Systemic reactions i.m. > i.d.	GMT, seroconversion, seroprotection: i.d. < i.m.	Comparable pre-immunization titers i.d. and i.m.	COPD
Khanlou *et al.* [60]	88	26 – 69 years	2004 – 05	Trivalent	Unknown	i.d. i.m.	0.1 ml 0.5 ml	Local reactions i.d. > i.m.	i.d. = i.m.	Unknown	HIV patients
Manuel *et al.* [62]	60	Mean of 47	2006 – 07	Trivalent	A/New Caledonia/ 20/99 (H1N1) like + A/Wisconsin/67/ 2005 (H3N2) + B/Malaysia/2056/ 2004 like	i.m. followed by i.d. booster	15 μg (0.5 ml) 3 μg (0.1 ml)	Local reactions i.d. > i.m.	No impact of booster	High pre-vaccination status (2005 – 06 vaccine)	Lung transplant patients
Gelinck *et al.* [61]	156 (80 HIV, 50 anti-TNF, 26 HSCT) 41 HC	19 – 81	2008	Trivalent	A/New Caledonia/ 20/99 IVR-116 (H1N1) + A/New York/55/ 2004 NYMC X-157 (H3N2) + B/Jiangsu/10/03	i.d. i.m.	3 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. HC > patients	GMT + protection rates: i.d. = i.m. HC > patients	Different pre-immunization titers	HIV patients Rheumatological patients treated with anti-TNF HCST patients HC
Jo *et al.* [63]	113	19 – 64 years	2005	Trivalent	A/New York/55/ 2004 like (H1N1) + A/California/7/ 2004 like (H3N2) + B/Shanghai/361/ 2002 like	i.d. i.m.	7.5 μg HA (0.25 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. HC > patients	GMT, seroconversion, seroprotection: i.d. = i.m.	Immunized and naive subjects	Solid cancer patients

COPD: Chronic obstructive pulmonary disease; HC: Healthy controls; HCST: Hematological stem cell.

Table 3. Clinical studies in children.

Author	No. of subjects	Age range	Study year	Type of vaccine	Strains	Admin route	Dose	Safety	Immunogenicity	Pre-vaccination status	Remark
Klein and Huang [64]	48	2 months – 5 years	1960 – 61	Monovalent	A2 Hong Kong	i.d. & s.c.	200 CCA (0.1 ml)	Febrile reactions: i.d. > s.c.	i.d. = s.c.	Unknown	
Chiu *et al.* [65]	112	3 – < 18 years	2006	Trivalent	A/Caledonia/20/99 like (H1N1) + A/California/7/2004 like (H3N2) + B/Shanghai/361/2002 like	i.d. i.m.	3 µg HA (0.1 ml) 15 µg HA (0.5 ml)	Local reactions: i.d. > i.m.	i.d. = i.m.	High pre-vaccination titers for 3 – < 9 years	
Sugimura *et al.* [66]	34	6 – 12 months	2005 – 06	Trivalent	A/Caledonia/20/99 like (H1N1) + A/California/7/2004 like (H3N2) + B/Shanghai/361/2002 like	i.d. & s.c.	2 × 3 µg HA (0.1 ml)	Local reactions: i.d. > i.m.	Seroconversion and seroprotection: i.d. > i.m. CPMP criteria not met	Very low HI titers (< 10)	
Chiu *et al.* [67]	126	< 6 months	2007	Trivalent	A/Solomon Islands/3/2006 (H1N1) + A/Wisconsin/67/2005 (H3N2) + B/Malaysia/2056/2004	i.d. i.m.	2 × 3 µg HA (0.1 ml) 2 × 7.5 µg HA (0.25 ml)	Local reactions: i.d. > i.m.	i.d. = i.m. CPMP criteria not met for seroconversion	High pre-vaccination titers (maternal antibodies)	

immunogenicity compared with the standard dose (15 µg HA) intramuscular vaccine [65]. It must, however, be noted that pre-vaccination titers in the participating children were already high. Moreover, for children between 3 and 9 years of age, only those who had previously received influenza vaccination were recruited. Local reaction was, as expected, more common after intradermal vaccination. So far, two studies have investigated the effect of intradermal influenza vaccination in very young children (< 1 year of age). A recent Japanese study compared i.d. and s.c. administration in children 6 – 12 months old [66]. For both administration routes 2 doses of 0.1 ml (3 µg HA) trivalent influenza vaccine was given. It must, however, be noted that the number of infants studied was low (n = 34). Higher seroconversion and seroprotection rates (33 – 87 and 20 – 26.7%, respectively) were seen after i.d. vaccination, but they were insufficient according to the CPMP definitions, which state that the seroconversion must exceed 40% and the seroprotection rate must exceed 70%. Local reactions were more frequent in the intradermal group compared with the subcutaneous group, but all adverse events were mild and transient. The most recent study assessed the immunogenicity of a split-dose inactivated trivalent influenza vaccine in 126 infants < 6 months old [67]. The infants received 2 doses of either 0.25 ml (7.5 µg HA) of the vaccine intramuscularly, which is the recommended dose for infants aged 6 – 35 months, or 0.1 ml (3 µg HA) intradermally. The authors saw that 40% of the intramuscular dose given intradermally produced similar if not better immune responses compared with the full intramuscular dose. Although seroconversion was not sufficient in either group to meet the criteria, titers were above protective level. Importantly, almost all children had pre-existing antibodies. The lack of seroconversion in these studies in children up to 12 months could be explained by the particularities of the immune system at that age and the presence of maternal antibodies. Indeed, a recent study demonstrated that a reduction of influenza illness by 63% was seen in infants < 6 months whose mothers had received influenza vaccination [68].

Only the study by Klein and Huang [64] recommended the use of subcutaneous vaccination instead of intradermal vaccination. However, this study dates from the 1960s and a monovalent vaccine was used, whereas the more recent studies that used the more standardized and commercially available trivalent influenza vaccines did not draw the same conclusion. Therefore, in the authors' opinion it can be concluded that based on the few studies conducted in children, i.d. vaccination appears safe and immunogenic. Furthermore, the data available at present suggest that i.d. vaccination elicits a better immune response than i.m. and s.c. vaccination in children and infants.

5. Clinical studies using new intradermal delivery methods

Devices for intradermal vaccine delivery have recently been reviewed by Lambert and Laurent [69] and Mikszta and

Laurent [70]. Although it is not the purpose of this paper to review the literature on delivery devices, in light of the clinical trials conducted so far, the subject is touched on briefly. The review is limited to intradermal delivery devices that have been clinically evaluated for influenza vaccination.

Conventional intradermal injection techniques (Mantoux technique, **Figure 2**) are difficult to perform and require highly skilled and trained medical personnel. The injection depth and volume are not always consistent using conventional techniques and the injection is usually painful for the patient. Thus, a more user-friendly, convenient and reliable method to overcome these problems is needed. The studies described in the previous sections of this review used a (tuberculin) syringe to administer the influenza vaccine intradermally. Recent studies have evaluated new, innovative techniques for intradermal delivery of the influenza vaccine.

One of the recently evaluated techniques is the MicronJet™ microneedle device (Nanopass, IL; **Figure 3A**). A total of 180 healthy subjects aged 18 – 40 were assigned to receive either full dose standard i.m. injection (15 μg HA), or medium i.d. injection (6 μg HA), or a low dose i.d. injection (3 μg HA) of a trivalent inactivated influenza vaccine [71]. GMT, GMTR, seroconversion rates and seroprotection rates were similar for all groups. It is interesting to note that the lowest dose of 3 μg HA also elicited immune responses equal to the standard dose. Local reactions were significantly more frequent after intradermal injection but transient. Importantly, 'prick-pain' was significantly lower with the MicronJet.

A second technique under evaluation for influenza vaccination is the intradermal microinjection system, Soluvia™ (Becton-Dickinson, NJ, US; **Figure 3B**). In a Phase II study, healthy adults (n = 978, < 60 years) received either reduced dose (n = 588, 9 μg HA) inactivated trivalent influenza vaccine by means of the intradermal route or standard dose (n = 390, 15 μg HA) by means of the intramuscular route [72]. The immune response induced by the i.d. vaccine was non-inferior to that induced by the i.m. vaccine and was even superior for both A strains. The safety profile was comparable for both routes even though local reactions were more frequent after i.d. vaccination. The most recently published Phase II study evaluated two different dosages of a trivalent inactivated influenza vaccine over a period of three successive years [73]. Healthy adults (n = 1150, < 60 years) received a 3 μg HA dose or a 6 μg HA dose intradermally or the standard dose (15 μg HA) intramuscularly. However, because both i.d. dosages elicited immune responses inferior to those elicited by i.m. vaccination, a dose of 9 μg HA was given in years 2 and 3, which showed comparable immunogenic and safety profiles to i.m. vaccination. Local reactions were more frequently reported after i.d. vaccination, whereas injection pain was similar after i.d. and i.m. vaccination.

Two studies investigated the intradermal microinjection system (Soluvia) in elderly volunteers > 60 years of age. In a multi-center Phase II study, 1107 volunteers received either intradermal trivalent inactivated split virus influenza vaccine containing 15 μg (n = 370) or 21 μg (n = 369) HA or standard intramuscular vaccine containing an identical dose of 15 μg HA (n = 368) [74]. Post-vaccination, GMTs were significantly higher after intradermal vaccination compared with intramuscular vaccination for both doses. The 21 μg dose was not superior to the 15 μg dose. Seroconversion, seroprotection and GMTR were significantly higher, except for seroprotection against A/H1N1 in the 15 μg group. In a subsequent Phase III study, 3707 elderly volunteers were enrolled for 3 consecutive years [75]. The volunteers received the vaccine either intradermally (n = 2618, 15 μg HA) or intramuscularly/subcutaneously (n = 1089, 15 μg HA). The latter depended on the routine practice of the clinician. Similarly to the study by Holland *et al.* [74], GMTs, GMTR, seroconversion and seroprotection were significantly higher for intradermal vaccination in comparison with intramuscular vaccination, though in this study for all three influenza strains. One of the CPMP criteria, the seroprotection rate, was not, however, met for the B strain. In years 2 and 3 seroprotection rates were again consistently higher after intradermal vaccination for all 3 influenza strains. In both studies in the elderly, local reactions were more common after i.d. vaccination, whereas systemic reactions were comparable for both administration routes.

Overall, antibody responses to intradermal vaccination for both the Soluvia and the MicronJet systems were equal or even superior to intramuscular vaccination in young adults, and also in the elderly in whom high pre-vaccination titers have to be taken into account. Also, with the new injection systems for intradermal delivery, local reactions are, as expected, more frequent than for intramuscular delivery owing to the close proximity of the injected vaccine to the skin surface. Importantly, in all trials mentioned above the injection pain of intradermal administration was comparable to that of intramuscular injection. **Table 4** summarizes the studies performed using the MicronJet and the BD Soluvia techniques.

6. Conclusion

This review summarizes clinical studies that have been performed with influenza vaccines administered intradermally in (young) adults, elderly, children and patients with high-risk conditions. Also, new devices for intradermal delivery of influenza vaccines that have been clinically evaluated have been discussed. Human studies have focused on the use of i.d. vaccines for either dose-sparing strategies or for increased immunogenicity in elderly and non-responders. The studies under review investigated the non-inferiority of the immune response elicited after i.d. vaccination compared with i.m. or s.c. vaccination. In all studies immunogenicity and safety was assessed according to CPMP guidelines.

This study has several limitations. First, based on Medline searches, only articles in English were selected for the review. Second, several of the publications did not contain all

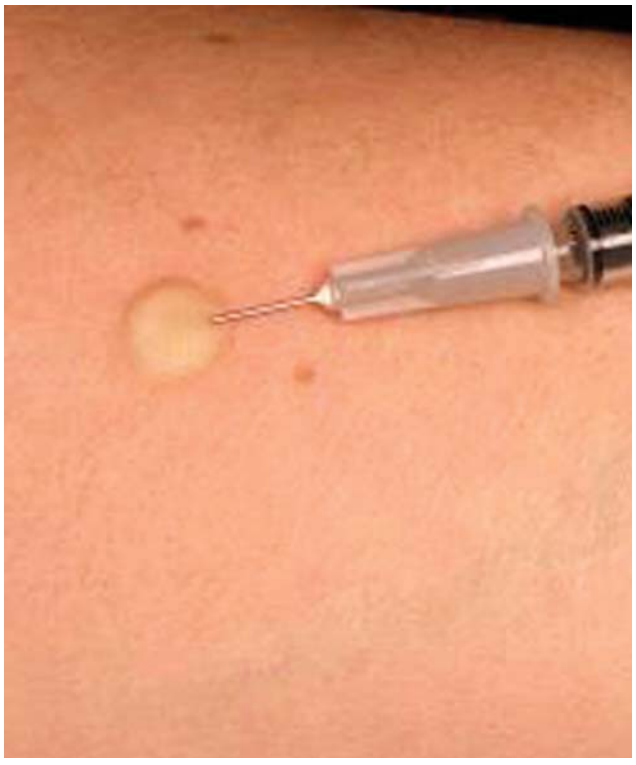

Figure 2. Intradermal injection using conventional needles (Mantoux technique).

necessary information, which made a thorough comparison in terms of safety and immunogenicity more difficult.

Although the number of studies that have been performed to date is low, intradermal vaccination can be considered safe and immunogenic in different age categories (young, adults, and elderly). The intradermal route appeared to have dose-sparing capacities as reduced antigen doses administered intradermally showed comparable or even superior immunogenicity to the standard i.m. or s.c. dose in healthy adults as well as in children. In immunocompromised patients, as well as in the elderly, intradermal vaccination could be useful to boost their weaker immune response. In most studies that evaluated i.d. vaccination, CPMP criteria, including seroconversion, seroprotection and GMTR, were met.

In all studies reported, injection pain and local reactions (erythema) at the injection site were higher for i.d. than for i.m. or s.c. injection. On the other hand, systemic reactions were usually lower or equal for i.d. than for i.m. and s.c. vaccination. Serious adverse effects were rarely reported, but if reported they were similar for each of the investigated administration routes and were unrelated to vaccination.

The new devices, such as Soluvia and MicronJet, showed promising results for delivery of influenza antigens. The CPMP criteria were met not only in young adults, but also in elderly volunteers. The immune response after intradermal vaccination was similar or even superior compared with intramuscular vaccination. Moreover, using these new devices injection pain was reduced compared with the conventional i.m. needle injection. The new i.d. devices are easy to use without the need for skilled personnel and could also be an alternative approach for people with needle phobia. In conclusion, the future of intradermal delivery looks promising for the administration of influenza vaccines.

7. Expert opinion

Thus far a limited number of studies have been performed that have assessed immunogenicity and safety of intradermal vaccination in humans. Importantly, a substantial number of these studies date back many years (1950 – 80) and evaluated monovalent or bivalent influenza vaccines, which were replaced by the trivalent influenza vaccine in the late 1970s. The older studies also used antigens in dosages that are not comparable to those available now. Therefore, results differ significantly between trials owing to differences in dosages and antigens utilized. Another weakness in most studies is that most were performed using only one supplier's vaccine. There is a clear need for studies that evaluate and compare vaccines from several suppliers. Also, studies that investigate and compare i.d. vaccine administration in different populations, including healthy subjects as well as children, elderly and patients at risk are lacking. Placebo-controlled studies are not feasible, because of the biannual change in vaccine composition, annually for the northern and southern hemispheres, respectively [40], thereby leaving little or no opportunity to conduct placebo-controlled trials. Also, based on the difficulty in administration and the high frequency of local side effects, the CDC discourages the use of intradermal influenza vaccination in its 2007 guidelines, especially in the elderly [76]. These guidelines stipulate that more studies are needed to investigate the immunogenicity and safety in risk groups and the elderly before intradermal vaccination can be recommended routinely. Nevertheless, intradermal vaccines provide an attractive and promising alternative to intramuscular injection, not only in case of vaccine shortage but also from an immunological perspective.

Several studies have been performed using reduced dose i.d. vaccines, which led to a similar or even superior immune response and were found to be as equally safe as the standard dose i.m. vaccine (**Table 1**). Unfortunately, in almost all studies that evaluated reduced dose i.d. vaccines, comparison with a similar dose i.m. or s.c. has not been performed, which makes independent conclusions on dose and route difficult. So far only one study has used this type of design, which showed that equal immunogenicity was seen for intramuscular doses that matched the intradermal doses [26,54]. Results from studies that used a dose as low as 20% of the standard dose (3 μg HA) are not clearcut. Some studies reported an inferior response compared with the standard dose of 15 μg HA [53-55], although not just our previous results

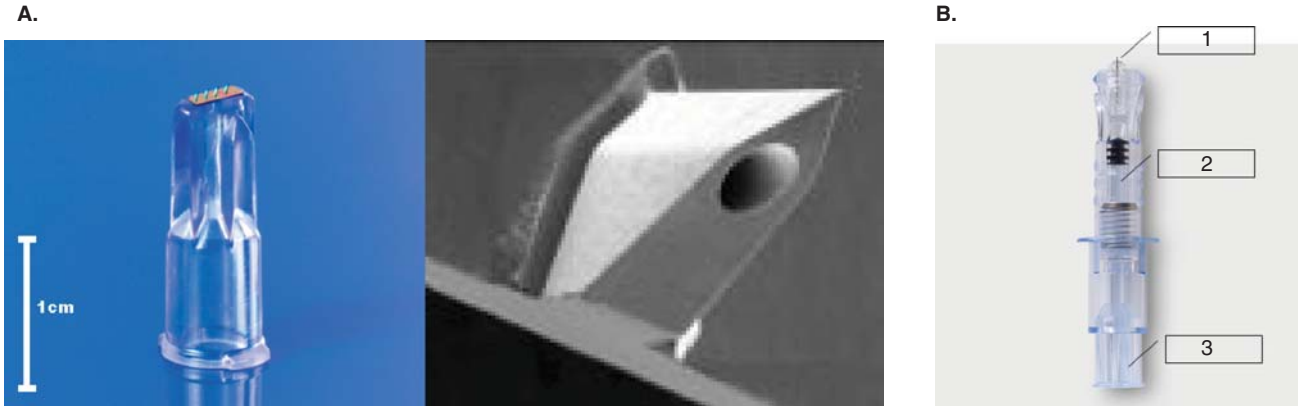

Figure 3. New intradermal delivery devices used for influenza vaccination. A. MicronJet™ device and scanning electron micrograph of a single microneedle. **B.** BD Soluvia™ microinjection system: (1) microneedle pre-attached in the tip of the syringe; (2) vaccine solution; (3) plunger rod.

demonstrated that the low dose was equally immunogenic as the standard dose [71], even in immunocompromised patients and children [60,61,65]. Reduced dose intradermal vaccines could be promising in pandemic situations and especially in the case of vaccine shortage, such as those encountered in 1973 [25] and 2004 [26] in the US, as well as to increase vaccine protection and coverage.

Notwithstanding the potential of i.d. vaccines, the classical i.d. administration method using conventional needles (Mantoux technique) requires experienced and trained personnel to inject the vaccine correctly intradermally. Moreover, injection depth and volume are not always consistent using the Mantoux technique and injection is experienced as painful for the patient [69]. Techniques such as Soluvia and the MicronJet device that do not require highly skilled personnel are essential to implement intradermal vaccination on a large scale. Two studies using the Soluvia technique demonstrated equal immunogenicity and safety of reduced dose i.d. vaccine compared with standard dose i.m. vaccine in adults [73] and even superior immunogenicity of standard dose i.d. vaccine in comparison with standard dose i.m. vaccine in the elderly [74]. Also, the MicronJet device using reduced dose i.d. vaccine was found to meet all CPMP criteria in terms of safety and immunogenicity [71], while other new innovative techniques, such as jet injection and topical patches, are under development or clinical evaluation, including those not being evaluated at present for delivery of the influenza vaccine [69,70]. The authors' own observations have, however, pointed out that a jet injection system was perceived as very painful by volunteers and the study was terminated because of the reported side effects [77]. Also, jet injectors have been criticized as the entire dose may not always be implanted into the skin [69]. The new devices described in this review have both a consistent and a reliable delivery of antigens and a standardized injection depth [71,78]. Moreover, these devices are less intimidating than needle-free systems and could increase the vaccination coverage in people dealing with needle phobia [71,78]. Needle-free intranasal vaccine delivery can be achieved using Flumist, as recommended by ACIP, although the vaccine has not been licensed for children younger than 2 years [11]. Also, serious side effects have been reported using an experimental intranasal vaccine [79]. Importantly, new devices should be tested not only in healthy populations, but also in people with high-risk conditions, children and the elderly. In addition, if the current demanding administration technique could be substituted by an easy-to-use technique, intradermal delivery of influenza vaccines could save up to 240 million of the 300 million doses distributed annually [80].

Intradermal immunization through the skin leads to a more potent activation of lymph node T cells compared with intramuscular immunization. Indeed, the skin is not only easily accessible, but also contains several potent antigen-presenting cells, including Langerhans cells in the epidermis and dermal dendritic cells in the dermis [17]. The favorable immunological properties of the skin make it attractive for vaccination and allow the use of reduced doses for intradermal vaccination. Another major advantage is the safety aspect. Even though local reactions (e.g., erythema) at the injection site are more frequent than for intramuscular vaccination, systemic reactions after intradermal vaccination are comparable to intramuscular vaccination or even less frequent (**Tables 1 – 4**).

In contrast to studies with rabies in which subjects are naive before vaccination, pre-immunization has to be taken into account when assessing the immune response of influenza vaccination. Subjects have either received vaccination in the past or have been exposed to influenza antigens via previous infection. Moreover, when investigating immunogenicity, along with analysis of the antibody titers, studies need to analyze the cellular and T-cell responses, especially influenza vaccination trials in the elderly because of immunosenescence

Table 4. Clinical studies assessing new devices for intradermal delivery.

Author	No. of subjects	Age range	Study year	Type of vaccine	Strains	Admin route	Dose	Safety	Immunogenicity	Pre-vaccination status	Remark
Van Damme *et al.* [71]	180	18 – 40 years	2007	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wisconsin/67/2005 (H3N2) + B/Malaysia/2056/2004	i.d. i.m.	3, 6 μg HA (0.1, 0.2 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. Prick pain: i.m. > i.d.	i.d. = i.m.	Comparable pre-immunization titers i.d. and i.m.	MicronJet™ device
Leroux-Roels *et al.* [72]	978	< 60 years	2005	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wellington/1/2004 (H3N2) + B/Shanghai/361/2002	i.d. i.m.	9 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m.	i.d. = i.m. A strains: i.d. > i.m.	Comparable pre-immunization titers i.d. and i.m.	Soluvia™ system
Beran *et al.* [73]	1150	18 – 57 years	2003 – 06	Trivalent	H1N1 + H3N2 + B Exact composition depended on the year (3-year trial)	i.d. i.m.	3, 6, 9 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. Injection pain: i.d. = i.m.	3 and 6 μg HA: too low 9 μg HA: i.d. = i.m.	Comparable pre-immunization titers i.d. and i.m.	Soluvia system
Holland *et al.* [74]	1107	> 60 years	2006	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wellington/1/2004 (H3N2) + B/Jiangsu/10/2003	i.d. i.m.	15, 21 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. Systemic reactions: i.d. = i.m.	GMTR, seroconversion, seroprotection: i.d. > i.m. Seroprotection for B strain: NS	Comparable pre-immunization titers i.d. and i.m.	Soluvia system Equal doses
Arnou *et al.* [75]	3707	≥ 60 years	2006	Trivalent	A/New Caledonia/20/99 (H1N1) + A/Wisconsin/67/2005 (H3N2) + B/Malaysia/2056/2004	i.d. i.m./s.c.	15 μg HA (0.1 ml) 15 μg HA (0.5 ml)	Local reactions: i.d. > i.m. Systemic reactions: i.d. = i.m.	GMTR, seroconversion, seroprotection: i.d. > i.m. CPMP criteria not met for seroprotection of B strain	Comparable pre-immunization titers i.d. and i.m.	Soluvia system

in this population. Regardless of the inferiority seen after intradermal influenza vaccination in the elderly in one study [54], which could be due to their high pre-immunization status, intradermal vaccination is also potentially applicable to this population. Indeed, a small number of studies that investigated the potential use of new delivery devices also included volunteers > 60 years of age in which even superior immunogenicity was seen for intradermal delivery [74,75].

In children, data have shown that young skin is superior to that of adults and elderly in antigen-presenting cells and migration response [81]. Intradermal vaccination might be more immunogenic in children than in adults, but too few studies have been performed in this population to make firm statements.

In conclusion, in the authors' opinion based on the available information, intradermal vaccines can be considered safe, immunogenic and feasible alternatives to intramuscular and subcutaneous vaccination. Also, the future looks promising because of the recent development of new injection devices. These devices clearly show non-inferiority or even superiority, and have proved to be dose-sparing even in the elderly. Although these interesting results need to be confirmed in further, well-designed studies in different age and patient groups, based on current knowledge, it is likely that intradermal vaccination will be recommended for routine use in the near future.

Declaration of interest

P Van Damme acts as chief and principal investigator for clinical trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers. V Vankerckhoven states no conflict of interest. P Van Damme and V Vankerckhoven have received no payment in preparation of this manuscript.

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