HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 9, 2447–2455
http://dx.doi.org/10.1080/21645515.2016.1176652

Taylor & Francis
Taylor & Francis Group

REVIEW

Intradermal vaccination for infants and children

Akihiko Saitoh and Yuta Aizawa

Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

ABSTRACT

Intradermal (ID) vaccination induces a more potent immune response and requires lower vaccine doses as compared with standard vaccination routes. To deliver ID vaccines effectively and consistently, an ID delivery device has been developed and is commercially available for adults. The clinical application of ID vaccines for infants and children is much anticipated because children receive several vaccines, on multiple occasions, during infancy and childhood. However, experience with ID vaccines is limited and present evidence is sparse and inconsistent. ID delivery devices are not currently available for infants and children, but recent studies have examined skin thickness in this population and reported that it did not differ in proportion to body size in infants, children, and adults. These results are helpful in developing new ID devices and for preparing new vaccines in infants and children.

ARTICLE HISTORY
Received 22 January 2016
Revised 21 March 2016
Accepted 6 April 2016

KEYWORDS
child; device; intradermal vaccination; intramuscular vaccination; infant; needle length; subcutaneous vaccination; skin thickness; ultrasonography

Introduction

The skin is very important as a barrier against the external environment and contains plentiful immune cells, including Langerhans cells and dermal dendritic cells in the epidermis and dermis, respectively. These cells have crucial roles in presenting antigens and inducing immune responses.[1] Recent research in skin immunology has established the concept of a dermal immune system,[2] and studies indicate that antigen delivery into the epidermis and dermis better stimulates these cells.[3] Thus, intradermal (ID) vaccination is a promising method for eliciting a potent immune response. Dose sparing refers to achieving an equivalent immune response with a dose lower than that used in intramuscular (IM) and subcutaneous (SC) vaccines.[4] The advantages of ID vaccination may contribute to cost saving, vaccine volume reduction, easier access to vaccines in areas with limited resources, and better supply during epidemics of emerging or re-emerging infectious diseases.[4,5]

Some vaccine-preventable diseases (VPDs) remain a significant concern, particularly in developing countries.[6] The World Health Organization (WHO) estimates that, in 2008, there were 1.5 million deaths attributable to VPDs among children younger than 5 years, which corresponds to 17% of worldwide mortality for this population.[7] ID vaccination could increase opportunities to protect vulnerable infants and children from VPDs, especially those in developing countries and during epidemics such as the 2009 A/H1N1 influenza virus pandemic.

The idea of ID vaccination was first proposed long ago. In 1796, Edward Jenner inoculated cowpox virus into the skin as a vaccine for smallpox,[8] and this vaccine prototype was the basis for vaccines developed later. ID administration is now the standard technique for tuberculin skin testing, which is performed by means of the Mantoux technique and requires skill to create a wheal indicating successful injection.[8] Because of advances in skin immunology and the advantages of ID vaccination (discussed above), novel devices for antigen delivery into the skin have been developed,[9] and accumulating evidence indicates that ID vaccination is effective for both adults and children.[5] However, existing devices were developed by using data on adult skin thickness,[10] and the use of such data could result in suboptimal immune response in children if the needle is too long or too short to reach the SC layer of infants and children. To assist in the development of effective ID vaccinations, recent studies have measured skin thickness in specific pediatric populations.[11,12] These data could improve ID devices and lead to clinical trials of the efficacy and safety of an ID device specifically intended for infants and children. This article will review current findings regarding ID vaccines and offer a perspective on future development of ID vaccines, particularly those targeting infants and children.

ID vaccination in infants and children

The immunogenicity and efficacy of ID vaccination have been well documented in adults. The dose-sparing effect of ID vaccines[3] has been confirmed for various vaccines, including those for trivalent inactivated influenza virus,[13-19] inactivated poliovirus,[20,21] rabies,[22-26] yellow fever,[27] and modified vaccinia Ankara.[28] In contrast, far fewer studies have evaluated ID vaccination in infants and children than in adults, even though infants and children require more vaccines to ensure protection against VPDs, and need a greater number of vaccines that require multiple dosing. Existing data indicate that ID vaccination is advantageous for infants and children; however, the results of studies have been inconsistent. The advantage of ID vaccination in immunogenicity varies by vaccines, which could limit the dose-sparing effect. Differences between study

CONTACT Akihiko Saitoh, MD, PhD asaitoh@med.niigata-u.ac.jp Department of Pediatrics, Niigata Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku Niigata, 951-8510, Japan.

populations might result in variability in immune response. Thus, the optimal dose of an ID vaccine may differ in relation to the vaccine used and study population.[3] Furthermore, the quality of ID vaccination performance should be confirmed when assessing the efficacy of ID vaccination in infants and children. Table 1 summarizes the findings of studies comparing ID vaccination of infants and children with vaccines delivered by conventional routes.

Efficacy and safety of ID vaccines in infants and children

Inactivated split influenza vaccine

For adults, an ID trivalent influenza vaccine (Intanza®/ Fluzone® Intradermal, Sanofi Pasteur, Lyon, France)[14,18] is currently approved and commercially available in over 40 countries, including the United States, Canada, Australia, Korea, and a number of European countries.[12] In Europe, Intanza® 9 μg was approved in 2009 for seasonal influenza in adults aged 18–59 y.[14] Intanza® 15 μg is another product licensed for adults older than 60 years, because of its superior immunogenicity as compared with the same standard dosage delivered by IM administration.[29] In the United States, Fluzone® Intradermal was introduced during the 2011/2012 influenza season for adults aged 18–64 y.[30] As marketed ID influenza vaccination, the Soluvia® microneedle delivery device (Becton Dickinson, Le Pont de Claix, France) is used in combination because it makes ID vaccination technique easier and safer.[15,31] The length (1.5 mm) of the needle for this device was determined on the basis of data on adult skin thickness, which is approximately 2 mm.[10] An ID influenza vaccine was effective in an elderly population[32] and for immunocompromised patients.[33] Furthermore, an ID quadrivalent inactivated influenza vaccine was found to be noninferior to an ID trivalent inactivated influenza vaccine.[30]

For children, overall, ID vaccination was favorable to IM[34-36] or SC[37] injection with respect to immunogenicity and/or dose sparing, although subject age and antigen dose differed among the studies. Two studies showed comparable efficacy for ID vaccination, with a dose reduction of 80%[34] or 60%.[35] The extent of dose sparing was diminished in the study of infants,[35] most likely because of a weaker increase in hemagglutination-inhibition antibody in this young population.[38] Regarding the method of ID vaccination, the latest study used a microinjection system (Soluvia®) and Intanza® (9 μg and 15 μg)[36] and found that ID influenza vaccines already licensed for adults were also efficacious in children aged 3–11 y. Further evaluation, especially for children younger than 3 years, is warranted because the efficacy of influenza vaccines is limited in this specific population.

Poliovirus vaccine

In September 2015, type 2 wild poliovirus was declared eradicated by the Global Commission for the Certification of Poliomyelitis Eradication.[39] Furthermore, no cases of type 3 wild poliovirus have been reported since a 2012 case in Nigeria, although type 1 wild poliovirus is still circulating in Pakistan and Afghanistan.[39] Replacement of oral poliovirus vaccine (OPV) with IPV seems to be essential for global eradication of polio,[21] because OPV has the potential to regain pathogenicity and cause vaccine-derived poliovirus paralysis.[40] Indeed, the globally synchronized withdrawal of type 2 OPV in April 2016 was reaffirmed by the WHO Strategic Advisory Group of Experts on Immunization.[39] However, developing countries have considerable economic burdens; IPV requires syringes and needles for injection and costs approximately 20 times as much per dose as OPV.[41] In 2007, the Advisory Committee on Poliomyelitis Eradication proposed a strategy to make IPV use potentially affordable for developing countries,[42] and the dose-sparing effect of ID vaccination may help reduce the burdens on these countries.

The first studies of ID poliovirus vaccination began in the 1950s in the United States, Denmark, Iceland, and Italy,[21] and the first published report was by Salk, who invented IPV.[43,44] Since 2010, a number of randomized controlled trials have been performed (Table 1). Jet injectors are needle-free devices that use a gas propulsion system to deliver vaccine by an ID, IM, or SC route.[21] Needle-free devices, which were used in five (71%) of these seven studies, may reduce costs when switching from OPV to IPV in resource-limited areas.[45] Some reports showed similar seroconversion rates but lower antibody titers after ID delivery, as compared with IM injection;[41,46] other studies showed that a one-fifth dose ID vaccination was inferior to a full-dose IM vaccination.[47-50] One study reported that a fractional ID dose of IPV was useful in inducing priming and seroconversion in more than 90% of immunized infants, although seroconversion rates after dose-sparing ID vaccination were lower than those for standard IM vaccination.[51]

IPV can be affected by maternally delivered antibodies and results in suboptimal immune response if administered with a needle-free jet injector during early infancy.[47] In contrast, the same primary-series vaccination, except when delivered by the Mantoux technique, was noninferior to the IM route.[46] In a discussion of the inconsistencies in the results of these studies, the authors of the latter study suggested that the discrepancy may be attributable to differences in the criteria used to define noninferiority (≥4 -fold increase in titers vs. antibody titers ≥8) and serological assays (Sabin strains vs. Salk strains, which are antigenically different[52]).

The immune response induced varies in relation to the type of needle-free jet injector used.[49] The components of the needle-free jet injector differed between the studies conducted in Oman[41] and India,[48] which might explain the inconsistent conclusions. In fact, inadequate injection—defined as a wheal <3 mm or a small drop of vaccine on the skin—was in part responsible for a weaker immune response.[48] Device selection is likely to be critical for successful ID injection. Because the findings regarding the ID route for IPV have not been consistently favorable with respect to immunogenicity, as compared with IM vaccination, further studies are warranted.

Rabies vaccine

Children are at high risk for dog bites and rabies.[53] The efficacy of ID administration of rabies vaccine is well established,[54-56] and a WHO position paper calls for ID administration of rabies vaccine for pre- and post-exposure prophylaxis.[24] Indeed, ID

Table 1. Summary of efficacy and dose-sparing effect of ID vaccination, as compared with IM or SC vaccination, in infants and children.

Vaccine	Country	Year	Age	No. of subjects	ID injection		Comparison	Efficacy*	Dose sparing	Reference
					Method	Dose				
Trivalent inactivated influenza	China	2007	3 to <18 years	112	Mantoux	3 μg[#]	15 μg IM	Comparable Seroprotection rates, fold increase in HAI GMT (95% CI) H1N1; 98% vs. 98%, 12.9 (7.9–21.4) vs. 11.1 (7.2–17.1) H3N2; 100% vs. 100%, 2.6 (2.1–3.4) vs. 4.5 (3.4–5.9)[§] B/Shanghai; 96% vs. 93%, 4.3 (3.2–5.8) vs. 4.4 (3.3–5.8)	Yes	34
	Japan	2008	6–12 months	34	Mantoux	3 μg	3 μg SC	Superior Positive titer rate, HAI titer $\geq$ 10 No. (%) H1N1; 14 (93.3) vs. 8 (47.1)[§] H3N2; 14 (93.3) vs. 14 (82.3) B/Shanghai; 11 (73.3) vs. 6 (35.3)[§]	N/A	37
	China	2009	2–3 months	123	Mantoux	3 μg	7.5 μg IM	Comparable Fold increase in HAI GMT (95% CI) H1N1; 1.21 (1.02–1.43) vs. 1.13 (0.96–1.34) H3N2; 1.26 (1.07–1.46) vs. 1.26 (1.06–1.50) B/Malaysia; 1.15 (0.99–1.32) vs. 1.07 (0.94–1.22)	Yes	35
	Italy	2011	3–11 years	112	Microneedle device	9 μg, 15 μg	15 μg IM (with adjuvant)	Superior Seroprotection rates, fold increase in HAI GMT[**] H1N1; 92.1% vs. 94.6% vs. 86.5%, 7.9 vs. 10.9 vs. 14.9 H3N2; 97.4% vs. 97.3% vs. 94.6%, 3.2 vs. 4.9 vs. 3.6 B/Brisbane; 55.3% vs. 62.2% vs. 32.4%[§], 2.4 vs. 8.6 vs. 1.9[§]	Yes	36
Inactivated poliovirus	Oman	2010	2, 4, 6 months[¶]	373	Needle-free jet injector	0.1 mL	0.5 mL IM	Similar seroconversion rates but lower titers Seroconversion rates, median titers (95% CI) Type1; 97.3% vs. 100%, 228 (144–287) vs. 724 (575–912)[§] Type 2; 95.7% vs. 100%[§], 287 (228–456) vs. 1149 (912–1,149)[§] Type 3; 97.9% vs. 100%, 362 (287–456) vs. $\geq$1,448 ($\geq$1,448-$\geq$1,448)[§]	Yes	41
	Cuba	2010	6, 10, 14 weeks	364	Needle-free jet injector	0.1 mL	0.5 mL IM	Inferior Seroconversion rates, median titers (95% CI) Type1; 52.9% vs. 89.3%[§], 19 (19–22) vs. 85 (54–99)[§] Type 2; 85.0% vs. 95.5%[§], 45 (45–54) vs. 214 (178–295)[§] Type 3; 69.0% vs. 98.9%[§], 32 (24–45) vs. 295 (214–355)[§]	Yes	47
	Philippines	2012	6, 10, 14 weeks, 15–18 months	224	Mantoux	0.1 mL	0.5 mL IM	Similar seroprotection rates but lower titers Seroprotective rates, GMT (95% CI) Type 1; 100% vs. 100%, 2,833 (2,392–3,356) vs. 6,666 (5,613–7,916) Type 2; 100% vs. 100%, 3,210 (2,672–3,857) vs. 6,522 (5,540–7,678) Type 3; 100% vs. 100%, 4,498 (3,608–5,607) vs. 11,952 (10,046–14,220)	Yes	46
	India	2012	6–9 months	869	Needle-free jet injector	0.1 mL	0.5 mL IM	Inferior Seroprevalence (95% CI), median titers (95% CI) Type 1; 100% (98–100) vs. 100% (98–100), $\geq$1,448 ($\geq$1,448-$\geq$1,448) vs. $\geq$1,448 ($\geq$1,448-$\geq$1,448[§] Type 2; 89% (83–93) vs. 99% (97–100)[§], 724 (455–910) vs. $\geq$1,448 (1,176-$\geq$1,448)[§] Type 3; 70% (62–76) vs. 95% (90–97)[§], 202 (28–724) vs. 455 (181–910)[§]	No	48
	Cuba	2013	4 and 8 months	310	Needle-free jet injector	0.1 mL	0.5 mL IM	Inferior Seroconversion rates, median titers (95% CI) Type1; 93.6% vs. 100%[§], 450 (357–566) vs. $\geq$1,448 ($\geq$1,448-$\geq$1,448)[§] Type 2; 98.1% vs. 100%, 898 (713-$\geq$1,448) vs. $\geq$1,448 ($\geq$1,448-$\geq$1,448)[§] Type 3; 93.0% vs. 99.3%[§], 71 (36–113) vs. 898 (566-$\geq$1,448)[§]	Yes	51

(*Continued on next page*)

Table 1. (*Continued*)

Vaccine	Country	Year	Age	No. of subjects	ID injection		Comparison	Efficacy*	Dose sparing	Reference
					Method	Dose				
	Cuba	2015	12–20 months	728	Needle-free jet injector	0.1 mL	0.5 mL IM	Inferior Seroprevalence, median titers (95% CI) Type 1; 98% vs. 98.6%, 1,423 (1,130–1,423) vs. 4,499 (3,573–5664) Type 2; 98.7% vs. 100%, 1,130 (898–1,130) vs. 2,839 (2,255–3,573) Type 3; 95.4% vs. 99.3%, 1,423 (898–1,791) vs. 4,499 (3,573–4,499)	N/A	49
	Bangladesh	2015	6, 14 weeks	308	Microneedle device	0.1 mL	0.5 mL IM	Inferior Seroconversion rates Type 1; 87.5% vs. 94.9% Type 2; 80.9% vs. 91% Type 3; 88.8% vs. 97.4%	N/A	50
Rabies virus	Thailand	1998	5–12 years	118	Mantoux	0.1 mL	0.5 mL IM	Similar seroprotection rates but lower titers Seroprotection rates, GMT (95% CI) 100% vs. 98.3%, 1.6 (1.2–2.0) vs. 3.5 (2.5–4.8)§	Yes	60
	Thailand	2009	12–18 months	177	Mantoux	0.1 mL	0.5 mL, 1 mL IM	Similar seroprotection rates but lower titers Seroprotection rates, GMC (95% CI)***100% vs. 100% vs. 100% vs. 100%, 13 (8–20), 25 (16–38), 161 (103–251), 190 (121–299)	Yes	61
Hepatitis B virus	United States	1994	Neonates	173	Mantoux	2 μg	2 μg, 10 μg IM	Inferior Seroprotection rates, GMC****91% vs. 97% vs. 100%§, 312 vs. 317 vs. 2,248§	No	65
	Turkey	1998	Neonates, 3–6 years	367	Mantoux	2 μg	10 μg IM	Similar seroprotection rates but lower titers Seroprotection rates, GMT Neonates; 94% vs. 98%, 621 vs. 935 Children; 100% vs. 98%, 804 vs. 1,393	Yes	66
Hepatitis A virus	Thailand	2005	8–12 years	75	Mantoux	0.1 mL	0.25 mL IM	Similar seroprotection rates but lower titers Seroprotection rates, GMT (95% CI)100% vs. 100%, 542 (390–753) vs. 834 (664–1047)	Yes	69

#Amount of hemagglutinin antigen per strain in influenza vaccine
¶Multiple ages in inactivated poliovirus vaccine category indicate multiple vaccinations at each time point for the same subjects
*ID vaccination vs. the comparison (IM or SC)
**ID 9 μg vs. ID 15 μg vs. IM ***ID 2 doses vs. ID 3 doses vs. 0.5 mL IM vs. 1 mL IM ****ID vs. 2 μg IM vs. 10 μg IM
§Statistically significant
Abbreviations: ID, intradermal; IM, intramuscular; SC, subcutaneous; HAI, hemaggulutination inhibition; GMT, geometric mean titer; GMC, geometric mean concentration; CI, confidence interval; N/A, not available

vaccination has been widely used in developing countries because of its dose-sparing advantage.[8] ID vaccination is immunogenic in children,[57-59] although antibody titers after ID administration were lower than those after IM administration.[60,61]

Hepatitis B virus vaccine

The evidence is favorable from studies of dose-sparing ID vaccination with hepatitis B virus (HBV) vaccine,[62,63] although a meta-analysis of data from adults showed a slight inferiority of ID vaccination to IM vaccination.[64] The findings of randomized studies of infants and children were inconsistent. A study using plasma-derived HBV vaccine at birth, 2 months, and 4 months reported that ID vaccination was inferior to IM vaccination.[65] In contrast, a study using recombinant HBV vaccine at 0, 1, and 6 months reported comparable rates of seroprotection, although antibody titers were not significantly lower after ID vaccination ($P > 0.05$).[66] Comparable seroprotection rates were confirmed using recombinant HBV vaccine for children with human immunodeficiency virus infection[67] and celiac disease.[68]

Hepatitis A virus vaccine

Seroprotection rates were similar for reduced-dose ID vaccination and regular-dose IM vaccination for school-aged children, although antibody titers were lower after ID vaccination than after IM vaccination.[69]

Measles vaccine

Several studies investigated the immunogenicity of ID measles vaccines in children, all of which were performed before 1994.[70] The results were similar or inferior, as compared with IM or SC vaccines.[3,70]

Conjugated polysaccharide vaccine

There are no published data on conjugated polysaccharide vaccines, such as those against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.[3,5] The potential benefits of ID administration of these vaccines are considerable, as infants receive them simultaneously during early infancy and childhood.

Safety profile

Most relevant studies assessed both the adverse events and immunogenicity of ID vaccination.[36,37,41,46-49,51,60,65,66,69] Local reactions such as erythema, swelling, induration, hyperpigmentation, and pain were more often reported in the ID vaccination group than in IM and SC vaccination groups, although the local reactions were mild and resolved spontaneously within a few days. Systemic reactions such as fever or irritability were uncommon. Because the target injection site for ID vaccination is very close to the skin surface, local reactions are more apparent.[12] All but one[65] of these studies described local reactions as tolerable and acceptable because they were mild and transient and because ID vaccination had benefits that outweighed the drawbacks. Indeed, after the licensure of ID vaccination, the majority of adult vaccinees were satisfied with the ID influenza vaccine with dedicated devices because of less preinjection anxiety, quick administration, and less pain.[71-75] However, in general, acceptability of ID vaccination needs to be evaluated carefully, because post-marketing situation might be different from that in prelicensure settings and any issues thing that might reduce acceptance of vaccines should be taken very seriously.

Potential drawbacks of ID vaccination

As shown in Table 1, several studies reported similar seroconversion rates and lower antibody titers elicited by ID vaccination compared to IM vaccination.[41,46,60,61,66,69] For poliovirus vaccine, ID vaccination elicited similar[46] or lower[49] antibody titers as a booster. As a primary series, all but one[46] showed negative data for ID vaccination; antibody titers were lower,[41,51] and furthermore less seroconversion rates in 2 studies.[47,50] For a program such as Global Polio Eradication Initiative, providing IPV to all children is challenging; one modeling suggests that the demand after eradication of polioviruses could increase from the current level of 80 million doses to 450 million doses per year and that a possible transient peak in demand is prominent in low- and middle-income countries for approximately 5 y following cessation of OPV.[45] This increasing demand may lead to the situation that many children will receive less than the optimal 2–3 doses.[45] If children receive only one ID vaccine dose, both seroconversion rates and antibody titers elicited will be lower than IM vaccination,[51] which poses a problem for short- and long-term seroprotection, especially in a world where polioviruses are eradicated, because of lack of natural boosting.

Challenges of ID vaccines in clinical settings

Because vaccines applied for ID vaccination have been so far limited and it might be impossible for all vaccines to be given by ID route. Thus there will be programmatic challenges in having some vaccines given by ID route and some given by IM route. In this case, it may be confusing for providers given vaccines either routes. A prefilled syringe for ID vaccination such as Soluvia® may help avoid the erroneous vaccine injection. In case of an erroneous injection of IM vaccine by ID route, local reactions may be more apparent; however, antibody titers may increase more, which could be beneficial to protect vaccinees from VPDs. In case of an erroneous injection of ID vaccine by IM route, protective antibody titers may not be produced because of insufficient antigen dose. In summary, more attention is required after introducing ID vaccines in clinical settings.

Skin thickness in infants and children

Use of needles of the appropriate length is critical. In adults, wheal formation, an indicator of successful ID injection, was confirmed in 99.2% of vaccinations performed using the MicronJet600® device (NanoPass Technologies Ltd, Israel) with a 0.6-mm-long needle, but in only 46% of vaccinations performed using the Soluvia® device with a 1.5-mm-long needle.[76] However, the MicronJet600® resulted in more frequent leakage of vaccine fluid, indicating injection failure.[76] Dedicated devices

Table 2. Skin thickness in infants and children measured for intradermal vaccination by ultrasonography.

Authors	Country	Year	Age of subjects	No. of subjects	Skin thickness				Reference
					Deltoid	Suprascapular	Upper back	Lumbar	
Ploin, *et al.*	France	2011	4–7, 12–18, 54–66 months	373[#]	1.22 (1.01–1.41)	1.30 (1.08–1.49)	1.39 (1.20–1.57)[*]	1.31 (1.15–1.48)[*]	11
Saitoh, *et al.*	Japan	2015	2 months	78	1.67 (1.16–2.39)	1.83 (1.24–2.60)	N/A	N/A	12
			6 months	11	1.84 (1.52–2.29)	1.79 (1.57–2.14)			
			13–15 years	82	1.81 (1.25–3.00)	2.43 (1.51–3.95)			

Skin thickness is shown as mean (range) (mm).
[#]Study subjects were infants aged 4–7 months (N = 118), children aged 12–18 months (N = 131), and children aged 54–66 months (N = 124). [*]Skin thickness at the upper back and lumbar sites was measured only in some children aged 54–66 months (N = 43).
Abbreviations: N/A, not available

for ID injection do not require the Mantoux technique and thus might lead to stable and reliable performance, even for young infants, for whom the skin is thin.

Only two published studies assessed skin thickness for the purpose of ID vaccination of infants and children (Table 2).[11,12] Skin thickness corresponds to the combined depth of the epidermis and dermis. These two studies measured the same 2 body sites routinely used for intradermal vaccination: the deltoid and suprascapular regions. A French study showed relatively unchanged skin thickness in infants and children aged 4–66 months (N = 373; mean 1.22 mm, range 1.01–1.41 mm at the deltoid region).[11] In contrast, our study of Japanese infants and children showed a significant increase in skin thickness from age 2 months (N = 78; mean 1.67 mm, range 1.16–2.39 mm at deltoid region) to age 13–15 y (N = 82, mean 1.81 mm, range 1.25–3.00 mm at deltoid region).[12] No factor was consistently associated with skin thickness, including gender, age, and body mass index.[11,12] Another study of skin thickness in children but not infants showed that skin thickness at the interscapular region increased over time, from a mean of 1.48 mm at age 2–3 years, to 1.72 mm at age 4–10 years, to 1.97 mm at age 11–13 y.[77] Skin thickness seems to increase with age, although the discrepancy between the French study and our study is yet to be explained. Interestingly, the difference in skin thickness between infants and adults was not proportional to weight or height. Future studies of skin thickness should enroll larger numbers of participants and investigate children of different races and ethnicities. The available data suggest that the 1.5-mm-long needle, which is currently commercially available for ID delivery devices for adults, may be too long for infants and children and may result in SC rather than ID injection. Thus, a shorter needle, preferably one less than 1.2 mm in length, should be used with ID injection devices for infants and children, as indicated by our previous findings for infants and children.[12]

Future directions

Recent technical advances in the measurement of skin thickness in infants and children might partially explain the inconsistent results for ID vaccination in this population. Previous negative data for the Mantoux technique and ID delivery devices for adults should thus be re-evaluated. Additional efforts to promote the development of ID delivery devices for infants and children would be beneficial, as such devices could increase the benefits of ID vaccination and improve new vaccines yet to be studied in infants and children.

Methods

We searched Medline (1990 through 2015) for publications included in clinical studies, clinical trial, reviews and systematic reviews. A literature search in PubMed was performed with the following search terms: "intradermal" [All Fields] AND ("intramuscular" [All Fields] OR "subcutaneous" [All Fields]) AND ("infants" [All Fields] OR "children" [All Fields]) AND "vaccine" [All Fields]. Two reviewers involved in the study search, which resulted in a total agreement. In addition, relevant articles identified in textbooks were hand-searched. The eligibility criteria for inclusion in the present analysis were that the study (1) was a randomized controlled trial, (2) compared the efficacy of ID vaccines and IM/SC vaccines, and (3) enrolled healthy infants or children. The exclusion criteria were follows; the study (1) was not randomized, (2) evaluated the efficacy of ID vaccines without the comparison to other vaccine routes, and (3) enrolled infants or children with underlying diseases.

Abbreviations

ID	intradermal
VPDs	vaccine-preventable diseases
WHO	World Health Organization
IM	intramuscular
SC	subcutaneous
IPV	inactivated poliovirus vaccine
OPV	oral poliovirus vaccine
HBV	hepatitis B virus

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. Nat Rev Immunol 2004; 4:211-22; PMID:15039758; http://dx.doi.org/10.1038/nri1310
[2] Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol 2009; 9:679-91; PMID:19763149
[3] Zehrung D, Jarrahian C, Wales A. Intradermal delivery for vaccine dose sparing: overview of current issues. Vaccine 2013; 31:3392-5; PMID:23176978; http://dx.doi.org/10.1016/j.vaccine.2012.11.021
[4] Weniger BG, Glenn GM. Cutaneous vaccination: antigen delivery into or onto the skin. Vaccine 2013; 31:3389-91; PMID:23684830; http://dx.doi.org/10.1016/j.vaccine.2013.05.048

[5] Hickling J, Jones R. Intradermal delivery of vaccines: a review of the literature and the potential for development for use in low-and middle-income countries. Program for Appropriate Technology in Health (PATH). Ferney Voltaire 2009; 5–7.
[6] Levine MM. Can needle-free administration of vaccines become the norm in global immunization? Nat Med 2003; 9:99-103; PMID:12514720; http://dx.doi.org/10.1038/nm0103-99
[7] World Health Organization. Vaccine-preventable diseases. Available at: http://apps.who.int/immunization_monitoring/diseases/en/ (accessed 29 December 2015)
[8] Bruce GW, Mark JP. Cutaneous vaccination. In: Plotkin SA, Orenstein WA, Offit PA. Vaccines. 6th ed. Philadelphia: Saunders Elsevier; 2012. p. 1200-1212
[9] Kis EE, Winter G, Myschik J. Devices for intradermal vaccination. Vaccine 2012; 30:523-38; PMID:22100637; http://dx.doi.org/10.1016/j.vaccine.2011.11.020
[10] Laurent A, Mistretta F, Bottigioli D, Dahel K, Goujon C, Nicolas JF, Hennino A, Laurent PE. Echographic measurement of skin thickness in adults by high frequency ultrasound to assess the appropriate microneedle length for intradermal delivery of vaccines. Vaccine 2007; 25:6423-30; PMID:17640778; http://dx.doi.org/10.1016/j.vaccine.2007.05.046
[11] Ploin D, Schwarzenbach F, Dubray C, Nicolas JF, Goujon C, Trong MD, Laurent PE. Echographic measurement of skin thickness in sites suitable for intradermal vaccine injection in infants and children. Vaccine 2011; 29:8438-42; PMID:21821081; http://dx.doi.org/10.1016/j.vaccine.2011.07.111
[12] Saitoh A, Aizawa Y, Sato I, Hirano H, Sakai T, Mori M. Skin thickness in young infants and adolescents: Applications for intradermal vaccination. Vaccine 2015; 33:3384-91; PMID:25944297; http://dx.doi.org/10.1016/j.vaccine.2015.04.081
[13] Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. N Engl J Med 2004; 351:2295-301; PMID:15525714; http://dx.doi.org/10.1056/NEJMoa043540
[14] Leroux-Roels I, Weber F. Intanza ((R)) 9 microg intradermal seasonal influenza vaccine for adults 18 to 59 years of age. Hum Vaccin Immunother 2013; 9:115-21; PMID:23442585; http://dx.doi.org/10.4161/hv.22342
[15] Icardi G, Orsi A, Ceravolo A, Ansaldi F. Current evidence on intradermal influenza vaccines administered by Soluvia licensed micro injection system. Hum Vaccin Immunother 2012; 8:67-75; PMID:22293531; http://dx.doi.org/10.4161/hv.8.1.18419
[16] Young F, Marra F. A systematic review of intradermal influenza vaccines. Vaccine 2011; 29:8788-801; PMID:21968444; http://dx.doi.org/10.1016/j.vaccine.2011.09.077
[17] Gorse GJ, Falsey AR, Fling JA, Poling TL, Strout CB, Tsang PH. Intradermally-administered influenza virus vaccine is safe and immunogenic in healthy adults 18–64 years of age. Vaccine 2013; 31:2358-65; PMID:23499604; http://dx.doi.org/10.1016/j.vaccine.2013.03.008
[18] Frenck RW, Jr, Belshe R, Brady RC, Winokur PL, Campbell JD, Treanor J, Hay CM, Dekker CL, Walter EB, Jr, Cate TR, et al. Comparison of the immunogenicity and safety of a split-virion, inactivated, trivalent influenza vaccine (Fluzone(R)) administered by intradermal and intramuscular route in healthy adults. Vaccine 2011; 29:5666-74; PMID:21699951; http://dx.doi.org/10.1016/j.vaccine.2011.06.010
[19] Belshe RB, Newman FK, Cannon J, Duane C, Treanor J, Van Hoecke C, Howe BJ, Dubin G. Serum antibody responses after intradermal vaccination against influenza. N Engl J Med 2004; 351:2286-94; PMID:15525713; http://dx.doi.org/10.1056/NEJMoa043555
[20] Troy SB, Kouiavskaia D, Siik J, Kochba E, Beydoun H, Mirochnitchenko O, Levin Y, Khardori N, Chumakov K, Maldonado Y. Comparison of the Immunogenicity of Various Booster Doses of Inactivated Polio Vaccine Delivered Intradermally Versus Intramuscularly to HIV-Infected Adults. J Infect Dis 2015; 211:1969-76; PMID:25567841; http://dx.doi.org/10.1093/infdis/jiu841
[21] Nelson KS, Janssen JM, Troy SB, Maldonado Y. Intradermal fractional dose inactivated polio vaccine: a review of the literature. Vaccine 2012; 30:121-5; PMID:22100886; http://dx.doi.org/10.1016/j.vaccine.2011.11.018
[22] Wieten RW, Leenstra T, van Thiel PP, van Vugt M, Stijnis C, Goorhuis A, Grobusch MP. Rabies vaccinations: are abbreviated intradermal schedules the future? Clin Infect Dis 2013; 56:414-9; PMID:23042968; http://dx.doi.org/10.1093/cid/cis853
[23] Wongsaroj P, Udomchaisakul P, Tepsumethanon S, Khawplod P, Tantawichien T. Rabies neutralizing antibody after 2 intradermal doses on days 0 and 21 for pre-exposure prophylaxis. Vaccine 2013; 31:1748-51; PMID:23370149; http://dx.doi.org/10.1016/j.vaccine.2013.01.035
[24] Rabies vaccines. WHO position paper–recommendations. Vaccine 2010; 28:7140-2; PMID:20831913; http://dx.doi.org/10.1016/j.vaccine.2010.08.082
[25] Quiambao BP, Dimaano EM, Ambas C, Davis R, Banzhoff A, Malerczyk C. Reducing the cost of post-exposure rabies prophylaxis: efficacy of 0.1 ml PCEC rabies vaccine administered intradermally using the Thai Red Cross post-exposure regimen in patients severely exposed to laboratory-confirmed rabid animals. Vaccine 2005; 23:1709-14; PMID:15705476; http://dx.doi.org/10.1016/j.vaccine.2004.09.027
[26] Laurent PE, Bourhy H, Fantino M, Alchas P, Mikszta JA. Safety and efficacy of novel dermal and epidermal microneedle delivery systems for rabies vaccination in healthy adults. Vaccine 2010; 28:5850-6; PMID:20600481; http://dx.doi.org/10.1016/j.vaccine.2010.06.062
[27] Roukens AH, Vossen AC, Bredenbeek PJ, van Dissel JT, Visser LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. PLoS One 2008; 3:e1993; PMID:18431480; http://dx.doi.org/10.1371/journal.pone.0001993
[28] Wilck MB, Seaman MS, Baden LR, Walsh SR, Grandpre LE, Devoy C, Giri A, Kleinjan JA, Noble LC, Stevenson KE, et al. Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. J Infect Dis 2010; 201:1361-70; PMID:20350191; http://dx.doi.org/10.1086/651561
[29] Atmar RL, Patel SM, Keitel WA. Intanza((R)): a new intradermal vaccine for seasonal influenza. Expert Rev Vaccines 2010; 9:1399-409; PMID:21105776; http://dx.doi.org/10.1586/erv.10.134
[30] Gorse GJ, Falsey AR, Ozol-Godfrey A, Landolfi V, Tsang PH. Safety and immunogenicity of a quadrivalent intradermal influenza vaccine in adults. Vaccine 2015; 33:1151-9; PMID:25613721; http://dx.doi.org/10.1016/j.vaccine.2015.01.025
[31] Laurent PE, Bonnet S, Alchas P, Regolini P, Mikszta JA, Pettis R, Harvey NG. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. Vaccine 2007; 25:8833-42; PMID:18023942; http://dx.doi.org/10.1016/j.vaccine.2007.10.020
[32] Arakane R, Annaka R, Takahama A, Ishida K, Yoshiike M, Nakayama T, Takeshita F. Superior immunogenicity profile of the new intradermal influenza vaccine compared to the standard subcutaneous vaccine in subjects 65 years and older: A randomized controlled phase III study. Vaccine 2015; 33:6650-8; PMID:26519549; http://dx.doi.org/10.1016/j.vaccine.2015.10.088
[33] Pileggi C, Lotito F, Bianco A, Nobile CG, Pavia M. Immunogenicity and safety of intradermal influenza vaccine in immunocompromized patients: a meta-analysis of randomized controlled trials. BMC Infect Dis 2015; 15:427; PMID:26466898; http://dx.doi.org/10.1186/s12879-015-1161-z
[34] Chiu SS, Peiris JS, Chan KH, Wong WH, Lau YL. Immunogenicity and safety of intradermal influenza immunization at a reduced dose in healthy children. Pediatrics 2007; 119:1076-82; PMID:17545373; http://dx.doi.org/10.1542/peds.2006-3176
[35] Chiu SS, Chan KH, Tu W, Lau YL, Peiris JS. Immunogenicity and safety of intradermal versus intramuscular route of influenza immunization in infants less than 6 months of age: a randomized controlled trial. Vaccine 2009; 27:4834-9; PMID:19523908; http://dx.doi.org/10.1016/j.vaccine.2009.05.066
[36] Esposito S, Daleno C, Picciolli I, Tagliaferri L, Scala A, Prunotto G, Montinaro V, Galeone C, Principi N. Immunogenicity and safety of intradermal influenza vaccine in children. Vaccine 2011; 29:7606-10; PMID:21855592; http://dx.doi.org/10.1016/j.vaccine.2011.08.021
[37] Sugimura T, Ito Y, Tananari Y, Ozaki Y, Maeno Y, Yamaoka T, Kudo Y. Improved antibody responses in infants less than 1 year old using

intradermal influenza vaccination. Vaccine 2008; 26:2700-5; PMID:18436353; http://dx.doi.org/10.1016/j.vaccine.2008.03.016

[38] Kumagai T, Nagai K, Okui T, Tsutsumi H, Nagata N, Yano S, Nakayama T, Okuno Y, Kamiya H. Poor immune responses to influenza vaccination in infants. Vaccine 2004; 22:3404-10; PMID:15308365; http://dx.doi.org/10.1016/j.vaccine.2004.02.030

[39] Adams A, Salisbury DM. Eradicating polio. Science 2015; 350:609; PMID:26542542; http://dx.doi.org/10.1126/science.aad7294

[40] Jenkins HE, Aylward RB, Gasasira A, Donnelly CA, Mwanza M, Corander J, Garnier S, Chauvin C, Abanida E, Pate MA, et al. Implications of a circulating vaccine-derived poliovirus in Nigeria. N Engl J Med 2010; 362:2360-9; PMID:20573924; http://dx.doi.org/10.1056/NEJMoa0910074

[41] Mohammed AJ, AlAwaidy S, Bawikar S, Kurup PJ, Elamir E, Shaban MM, Sharif SM, van der Avoort HG, Pallansch MA, Malankar P, et al. Fractional doses of inactivated poliovirus vaccine in Oman. N Engl J Med 2010; 362:2351-9; PMID:20573923; http://dx.doi.org/10.1056/NEJMoa0909383

[42] Conclusions and recommendations of the Advisory Committee on Poliomyelitis Eradication, Geneva, 27–28 November 2007. Wkly Epidemiol Rec 2008; 83:25-35

[43] Salk JE. Recent studies on immunization against poliomyelitis. Pediatrics 1953; 12:471-82; PMID:13111847

[44] Salk JE. Studies in human subjects on active immunization against poliomyelitis. I. A preliminary report of experiments in progress. J Am Med Assoc 1953; 151:1081-98; PMID:13034436; http://dx.doi.org/10.1001/jama.1953.02940140013005

[45] Hickling J, Jones R, Nundy N. Improving the affordability of inactivated poliovirus vaccines (IPV) for use in low-and middle-income countries. An economic analysis of strategies to reduce the cost of routine IPV immunization. Program for Appropriate Technology in Health (PATH), Seattle 2010.

[46] Cadorna-Carlos J, Vidor E, Bonnet MC. Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines. Int J Infect Dis 2012; 16: e110-6; PMID:22153001; http://dx.doi.org/10.1016/j.ijid.2011.10.002

[47] Resik S, Tejeda A, Lago PM, Diaz M, Carmenates A, Sarmiento L, Alemañi N, Galindo B, Burton A, Friede M, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. J Infect Dis 2010; 201:1344-52; PMID:20350164; http://dx.doi.org/10.1086/651611

[48] Estivariz CF, Jafari H, Sutter RW, John TJ, Jain V, Agarwal A, Verma H, Pallansch MA, Singh AP, Guirguis S, et al. Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6–9 months in Moradabad, India: a community-based, randomised controlled trial. Lancet Infect Dis 2012; 12:128-35; PMID:22071249; http://dx.doi.org/10.1016/S1473-3099(11)70190-6

[49] Resik S, Tejeda A, Mach O, Fonseca M, Diaz M, Alemany N, Garcia G, Hung LH, Martinez Y, Sutter R. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. Vaccine 2015; 33:307-13; PMID:25448109; http://dx.doi.org/10.1016/j.vaccine.2014.11.025

[50] Anand A, Zaman K, Estivariz CF, Yunus M, Gary HE, Weldon WC, Bari TI, Steven Oberste M, Wassilak SG, Luby SP, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine 2015; 33:6816-22; PMID:26476367; http://dx.doi.org/10.1016/j.vaccine.2015.09.039

[51] Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemani N, Garcia G, Fonseca M, Hung LH, Kahn AL, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013; 368:416-24; PMID:23363495; http://dx.doi.org/10.1056/NEJMoa1202541

[52] Minor PD. Antigenic structure of picornaviruses. Curr Top Microbiol Immunol 1990; 161:121-54; PMID:2169382

[53] Chulasugandha P, Khawplod P, Havanond P, Wilde H. Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children. Vaccine 2006; 24:1478-82; PMID:16221511; http://dx.doi.org/10.1016/j.vaccine.2005.03.059

[54] Chutivongse S, Wilde H, Supich C, Baer GM, Fishbein DB. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. Lancet 1990; 335:896-8; PMID:1969993; http://dx.doi.org/10.1016/0140-6736(90)90488-Q

[55] Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S, Wasi C. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull World Health Organ 2000; 78:693-8; PMID:10859864

[56] Wilde H, Khawplod P, Khamoltham T, Hemachudha T, Tepsumethanon V, Lumlerdacha B, Mitmoonpitak C, Sitprija V. Rabies control in South and Southeast Asia. Vaccine 2005; 23:2284-9; PMID:15755612; http://dx.doi.org/10.1016/j.vaccine.2005.01.030

[57] Yang Y, Zhang J. An experimental study on the endurance of immunologic memory of intradermal micro-injection with rabies vaccine and boosting immune effect. J Epidemiol 1999; 9:209-15; PMID:10510577; http://dx.doi.org/10.2188/jea.9.209

[58] Kamoltham T, Thinyounyong W, Phongchamnaphai P, Phraisuwan P, Khawplod P, Banzhoff A, Malerczyk C. Pre-exposure rabies vaccination using purified chick embryo cell rabies vaccine intradermally is immunogenic and safe. J Pediatr 2007; 151:173-7; PMID:17643772; http://dx.doi.org/10.1016/j.jpeds.2007.02.044

[59] Kamoltham T, Thinyounyong W, Khawplod P, Phraisuwan P, Phongchamnaphai P, Anders G, Malerczyk C. Immunogenicity of Simulated PCECV Postexposure Booster Doses 1, 3, and 5 Years after 2-Dose and 3-Dose Primary Rabies Vaccination in Schoolchildren. Adv Prev Med 2011; 2011:403201; PMID:21991438; http://dx.doi.org/10.4061/2011/403201

[60] Sabchareon A, Chantavanich P, Pasuralertsakul S, Pojjaroen-Anant C, Prarinyanupharb V, Attanath P, Singhasivanon V, Buppodom W, Lang J. Persistence of antibodies in children after intradermal or intramuscular administration of preexposure primary and booster immunizations with purified Vero cell rabies vaccine. Pediatr Infect Dis J 1998; 17:1001-7; PMID:9849982; http://dx.doi.org/10.1097/00006454-199811000-00007

[61] Pengsaa K, Limkittikul K, Sabchareon A, Ariyasriwatana C, Chanthavanich P, Attanath P, Malerczyk C. A three-year clinical study on immunogenicity, safety, and booster response of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12- to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine. Pediatr Infect Dis J 2009; 28:335-7; PMID:19333080; http://dx.doi.org/10.1097/INF.0b013e3181906351

[62] Bryan JP, Sjogren MH, Perine PL, Legters LJ. Low-dose intradermal and intramuscular vaccination against hepatitis B. Clin Infect Dis 1992; 14:697-707; PMID:1532914; http://dx.doi.org/10.1093/clinids/14.3.697

[63] Bryan JP, Sjogren MH, Macarthy P, Cox E, Legters LJ, Perine PL. Persistence of antibody to hepatitis B surface antigen after low-dose, intradermal hepatitis B immunization and response to a booster dose. Vaccine 1992; 10:33-8; PMID:1531719; http://dx.doi.org/10.1016/0264-410X(92)90416-H

[64] Sangare L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. Vaccine 2009; 27:1777-86; PMID:19200451; http://dx.doi.org/10.1016/j.vaccine.2009.01.043

[65] Coberly JS, Townsend T, Repke J, Fields H, Margolis H, Halsey NA. Suboptimal response following intradermal hepatitis B vaccine in infants. Vaccine 1994; 12:984-7; PMID:7975851; http://dx.doi.org/10.1016/0264-410X(94)90332-8

[66] Egemen A, Aksit S, Kurugol Z, Erensoy S, Bilgic A, Akilli M. Low-dose intradermal versus intramuscular administration of recombinant hepatitis B vaccine: a comparison of immunogenicity in infants and preschool children. Vaccine 1998; 16:1511-5; PMID:9711797; http://dx.doi.org/10.1016/S0264-410X(98)80006-6

[67] Bunupuradah T, Ananworanich J, Pancharoen C, Petoumenos K, Prasitsuebsai W, Wongngam W, Wongngam W, Ubolyam S,

Sriheara C, Lange J, et al. Randomized study of intradermal compared to intramuscular hepatitis B vaccination in HIV-infected children without severe immunosuppression. Vaccine 2011; 29:2962-7; PMID:21329776; http://dx.doi.org/10.1016/j.vaccine.2011.01.114

[68] Leonardi S, Pratico AD, Lionetti E, Spina M, Vitaliti G, La Rosa M. Intramuscular vs intradermal route for hepatitis B booster vaccine in celiac children. World J Gastroenterol 2012; 18:5729-33; PMID:23155313; http://dx.doi.org/10.3748/wjg.v18.i40.5729

[69] Pancharoen C, Mekmullica J, Thisyakorn U, Kasempimolporn S, Wilde H, Herzog C. Reduced-dose intradermal vaccination against hepatitis A with an aluminum-free vaccine is immunogenic and can lower costs. Clin Infect Dis 2005; 41:1537-40; PMID:16231271; http://dx.doi.org/10.1086/497266

[70] Cutts FT, Clements CJ, Bennett JV. Alternative routes of measles immunization: a review. Biologicals 1997; 25:323-38; PMID:9325001; http://dx.doi.org/10.1006/biol.1997.0103

[71] Dhont PA, Albert A, Brenders P, Podwapinska A, Pollet A, Scheveneels D, Tihon F, Verheyden I, Victor J, Samson SI. Acceptability of Intanza(R) 15 mug intradermal influenza vaccine in Belgium during the 2010–2011 influenza season. Adv Ther 2012; 29:562-77; PMID:22678831; http://dx.doi.org/10.1007/s12325-012-0025-9

[72] Foy JE, Hendriksz T, Malouf P, Tobin A. Acceptability of fluzone intradermal vaccine to patients and vaccine administrators. J Am Osteopath Assoc 2013; 113:134-43; PMID:23412675

[73] Eizenberg P, Booy R, Naser N, Mason G, Stamboulian D, Weber F. Acceptance of Intanza(R) 9 mug intradermal influenza vaccine in routine clinical practice in Australia and Argentina. Adv Ther 2011; 28:640-9; PMID:21751080; http://dx.doi.org/10.1007/s12325-011-0042-0

[74] Prymula R, Usluer G, Altinel S, Sichova R, Weber F. Acceptance and opinions of Intanza/IDflu intradermal influenza vaccine in the Czech Republic and Turkey. Adv Ther 2012; 29:41-52; PMID:22228256; http://dx.doi.org/10.1007/s12325-011-0090-5

[75] Durando P, Alicino C, Alberti M, Sticchi L, Turello V, Marensi L, Caiazzo AL, Panico MG, Giugliano F, Parlato A, et al. Acceptance and safety of the intradermal influenza vaccine among the elderly in Italy: an on-field national study. Adv Ther 2012; 29:312-26; PMID:22529024; http://dx.doi.org/10.1007/s12325-012-0012-1

[76] Hung IF, Levin Y, To KK, Chan KH, Zhang AJ, Li P, Li C, Xu T, Wong TY, Yuen KY. Dose sparing intradermal trivalent influenza (2010/2011) vaccination overcomes reduced immunogenicity of the 2009 H1N1 strain. Vaccine 2012; 30:6427-35; PMID:22910287; http://dx.doi.org/10.1016/j.vaccine.2012.08.014

[77] Seidenari S, Giusti G, Bertoni L, Magnoni C, Pellacani G. Thickness and echogenicity of the skin in children as assessed by 20-MHz ultrasound. Dermatology 2000; 201:218-22; PMID:11096192; http://dx.doi.org/10.1159/000018491