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Intradermal vaccination using the novel microneedle device MicronJet600: Past, present, and future

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Abbreviations: ID, intradermal; BCG, Bacillus Calmette–Guérin; PPD, Purified protein derivative; HBV, hepatitis B virus; WHO, World Health Organization; SAGE, Strategic Advisory Group of Experts; IPV, inactivated polio vaccine; SQ, subcutaneous; IM, Intramuscular; BD, Becton Dickinson; GMT, geometric mean titer; HIV, Human immunodeficiency virus; DTP, diphtheria, pertussis and tetanus; HPV, human papilloma virus; MEMS, Micro Electro Mechanical System; FDA, Food and Drug Administration; EMEA, European Medicines Agency; HA, hemagglutinin; AE, adverse event; CDC, Center of Disease Control; icddr,b, International Center for Diarrheal Disease Research, Bangladesh

Intradermal immunization has become a forefront of vaccine improvement, both scientifically and commercially. Newer technologies are being developed to address the need to reduce the dose required for vaccination and to improve the reliability and ease of injection, which have been major hurdles in expanding the number of approved vaccines using this route of administration. In this review, 7 y of clinical experience with a novel intradermal delivery device, the MicronJet600, which is a registered hollow microneedle that simplifies the delivery of liquid vaccines, are summarized. This device has demonstrated both significant dose-sparing and superior immunogenicity in various vaccine categories, as well as in diverse subject populations and age groups. These studies have shown that intradermal delivery using this device is safe, effective, and preferred by the subjects. Comparison with other intradermal devices and potential new applications for intradermal delivery that could be pursued in the future are also discussed.

A Brief History of Intradermal Vaccination

Intradermal (ID) immunization dates back to the advent of vaccines. Variolation (applying scabs or fluids from infected smallpox lesions onto healthy individuals) was practiced in many areas of the world for hundreds of years before the pioneering work of Edward Jenner, who used cowpox scarification for smallpox at the turn of the 19th century.[1-6]

Further major milestones were achieved over a century later by Calmette and Guérin,[7] who developed the BCG vaccine for tuberculosis circa 1921. Tuberculin (PPD) and the Mantoux technique[8] of intradermal injection, which typically uses a standard 25G-27G, 5/8-1.0 (16-25mm) needle for shallow (5–15 degrees) injection into the skin, were developed around the same time.

Importantly, the uptake of the standard ID Mantoux technique is still limited, some hundred years later, to a very narrow list of vaccines (**Table 1**). The Mantoux technique is neither simple nor reliable[9-11] and very often delivers the antigen too deep or it leaks out, failing on occasion to produce the typical 6–10 mm white bleb,[12] thereby limiting adoption of perhaps the most natural and physiological route of delivery of vaccines.

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Benefits of ID Vaccination

ID vaccination has primarily been explored for its ability to generate equivalent antibody responses at lower doses, a phenomenon typically described as "dose-sparing".[46] The importance of dose-sparing is most evident in high-surge situations, such as in pandemic[47] and seasonal flu,[48,49] where large populations are at risk and a new set of strains can be required each year.[50] Dose sparing is also important in increasing capacity and reducing the expense of a vaccine dose, especially in cost-sensitive global-health indications where the price of the vaccine limits its use and coverage, as in the case of polio.[51,52] Exploring the intradermal approach was recommended at a recent meeting of the World Health Organization Strategic Advisory Group of Experts (SAGE),[53] as a means to reduce dose prices to make injectable polio vaccines (IPV) affordable for successful eradication of the disease in the Polio End Game[54] A limitation of many of the studies, however, lies in the fact that they have not evaluated equivalent low-dose IM or SQ vaccination groups.[55]

The most recently registered indication for intradermal vaccination is influenza, where the ID approach has actually been pursued since the 1930's.[56,57] This vaccine (Intanza®, Sanofi

Table 1. Approved and pipeline vaccines delivered intradermally

Approved for ID delivery	Positive Clinical Data	Mixed Results
*BCG[13]	Hepatitis A[14,15]	HBV[16-21]
Rabies[22-26]	Pandemic influenza[27]	Measles[28-30]
Influenza[31-36]	Yellow Fever[37-39]	Inactivated Polio[40-43]
	Tick-Borne encephalitis[44]	
	Smallpox[45]	

* Intradermal delivery is the standard route for delivery for BCG.

Pasteur), is a 5-fold concentrated form of Fluzone[58] (inactivated influenza split-virus vaccine) delivered with an intradermal prefilled syringe (BD Soluvia™ Micro Injection System, Becton Dickinson and Company) that uses a 1.5 mm needle to provide a lower (9 μg HA/strain) or a standard dose (15 μg HA/strain), depending on the population and approved indication.[35,58] Another example of an ID vaccine is rabies. Rabies is a zoonosis that occurs in over 100 countries and is invariably fatal once symptomatic. The cost of a full-dose rabies vaccine limits its widespread use in many areas. ID administration of the vaccine offers an equally safe and immunogenic alternative that requires only 20% of the dose for post-exposure prophylaxis, which could reduce the direct cost of the vaccine by 60–80%. ID regimens have been successfully introduced for post-exposure rabies prophylaxis in India, the Philippines, Sri Lanka and Thailand.[59]

Despite limited clinical data, ID vaccination also holds the promise to enhance immune responses using equivalent, rather than fractional, doses. Efforts have been made to improve influenza immunization by concentrating the formulation and delivering an equivalent dose of 15 μg HA/strain. A Phase II study administering ID with the BD 30-gauge 1.5 mm short needle[60,61] demonstrated that an equivalent dose of 15 μg in elderly patients above 60 induced GMT ratios about 1.5-1.7-fold higher, compared with the same dose IM. This study was later confirmed in a Phase III study,[62] demonstrating that equivalent dose (15 μg HA/strain) given ID can produce superior GMT's and seroprotection at 21 d post-vaccination. However, Intanza15 has not yet been shown to have superior clinical efficacy in terms of reducing mortality and morbidity, although a large retrospective study suggests a reduction in influenza related hospitalizations.[63,64]

Improving immunogenicity of various vaccines in immunocompromised hosts via the intradermal route is extremely important. Hepatitis B virus (HBV) vaccine has a 3–5% failure rate of non-seroconversion and there is a significant improvement in this after ID injection.[65] Studies have demonstrated that in patients on dialysis or in patients with HIV, the intradermal route was more immunogenic than standard intramuscular delivery with the HBV vaccine. ID vaccine recipients had significantly better seroconversion rates compared with the standard dose intramuscular group,[66] which was also demonstrated in ID HBV vaccination of dialysis patients.[67]

Adverse Effects of ID Vaccination

Overall, intradermal vaccination has been demonstrated to be very safe. Studies have shown that ID vaccination may be associated with a greater incidence of local reactogenicity, including primarily mild pain, swelling, and redness, but not systemic adverse events. These events typically resolve quickly, as was noted in a meta-analysis[68] comparing the safety and immunogenicity of a large number of intradermal versus intramuscular influenza vaccines. ID vaccination was not associated with a greater incidence of any systemic adverse events examined and was associated with a lower incidence of myalgia. There was evidence of heterogeneity for most adverse events.

Devices for ID Vaccination

To address the unmet clinical and usability needs, various devices have been developed over the years. These are conceptually grouped into liquid delivery devices, including needles, mini-needles, and hollow microneedles, as well as needle adaptors and jet injectors, and solid delivery devices, such as solid microneedles, particle-injectors, and patches with coated microprojections or dissolvable needles (**Table 2**).

The most clinically advanced approach is the mini-needle technology, represented by the Intanza-Soluvia influenza vaccine combination (Sanofi Pasteur), which is commercially available. In its Intanza9 version, the 1.5 mm mini-needle demonstrated relative dose-sparing, at least non-inferior immunogenicity to standard unadjuvanted influenza vaccines, and high acceptability.[102-104] Another licensed ID vaccine delivery device that may have been used with the largest number of vaccine types is a disposable hollow microneedle (<1 mm) device known as the MicronJet600™, which is the focus of this review.

The MicronJet600 has 3 pyramid-shaped microneedles of 0.6 mm (600 μm) length (**Fig. 1**) and the device can be attached to any standard luer tip or luer-lock syringe. The needles are

Table 2. Devices for ID delivery of vaccines[69]

Type of delivery	Type of device	Vaccine fields evaluated clinically
Liquid administration	Needle and syringe (Mantoux)	Flu[46,70-74], Rabies[22-26,59], BCG[13], Polio[75,76]
	Hollow mini and microneedles	Flu[36,62], Rabies[77], Anthrax[78], Japanese encephalitis, DNA-encoding reporter genes (preclinical only)[79-83]
	Tattoo devices	HPV[84-89]
	Jet injectors	Smallpox[99], BCG[90], DTP[91], Polio[43,92], Tetanus[93], Typhoid[94-96], Rabies[97], Influenza[98], Yellow Fever[99]
Solid administration	Solid arrays	HPV[100]
	Dissolvable patches	Flu[101]

fabricated as a single 3-dimensional crystal silicon chip[105] that is etched in a pattern to produce micro-pyramid-shaped microneedles, each having a very sharp tip that penetrates the epidermis followed by a conduit or through-channel for liquid delivery, and is produced using Micro Electro Mechanical System (MEMS) fabrication technology[106] in a semiconductor fabrication house. The microneedle chip is integrated with a plastic hub or female luer that attaches to any male luer tip or luer lock syringe, thereby enabling the delivery of liquid formulations from any standard (prefilled or disposable) syringe directly into the skin. The integrated device forms a direct fluid channel from the syringe or container through the microneedles, in order to deliver a vaccine where the dendritic cells are most prevalent in the superficial dermis of the skin. Injection with the MicronJet600 is characterized by an intradermal bleb or wheal, which is the hallmark of an acceptable ID injection.[107] It is registered with the US FDA (510 k), the EMEA (CE Mark), Canada, Hong Kong, and in other countries.

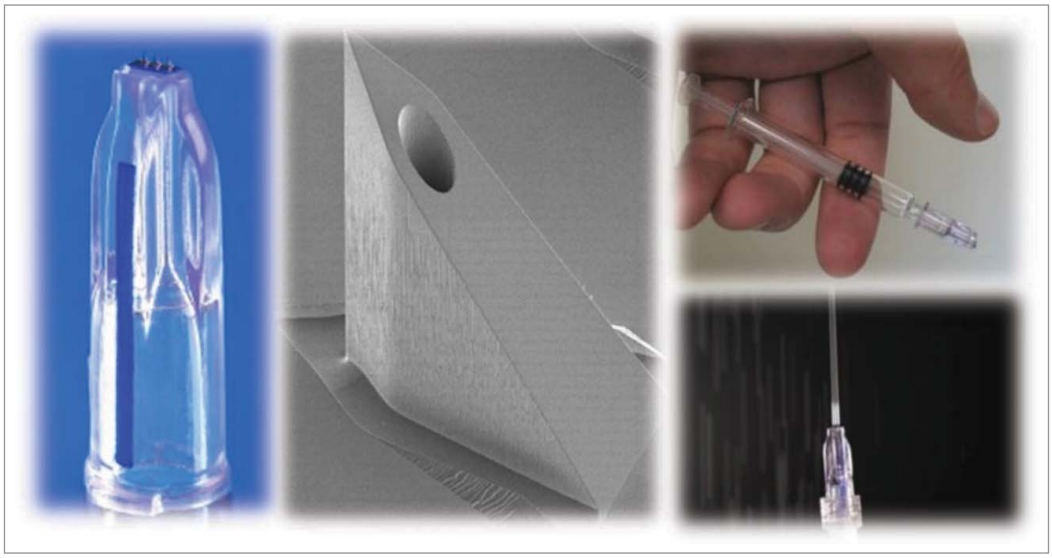

Figure 1. The MicronJet600 microneedle and attachment to a standard syringe. Left: Close-up of the MicronJet600; Middle: SEM picture (~×100) of a single microneedle prior to dicing, on wafer; Top Right: needle attached to a pre-filled syringe; Bottom Right: direction of injection flow.

Prior to the development and commercialization of the MicronJet600, an older (original) version of the MicronJet was used in the clinical trials conducted in 2007–2008. This device included 4 microneedles that were 450 μm in length, made in a very similar design. The performance characteristics of the original model were similar, but the insertion technique was less intuitive, requiring insertion at about 60 degrees and lowering the syringe while in skin to about 30 degrees. The MicronJet600 was developed to improve ease of use, requiring insertion at a more natural angle of about 45 degrees with no subsequent adjustment of position.

The Past: Clinical Results with the Original MicronJet Device

The MicronJet device was tested both in immune-competent healthy adults and in an elderly population that was considered to be relatively immunocompromised. A first-in-man study was conducted to demonstrate effective dose-sparing, safety, and user preference, using a commercially available influenza vaccine, Fluarix 2006/2007 (GSK, Belgium)[33] in healthy adults. This Phase I/II study used the original model MicronJet microneedle, described above. Groups received intradermal doses with 20% (3 μg HA/strain) or 40% (6 μg HA/strain) of the usual dose using the MicronJet device, or a 100% dose (15 μg HA/strain) given IM with a standard 26 G needle and syringe. Local reactogenicity was more frequent with ID vaccination, but was generally mild and transient. The low-dose ID groups had immune responses that were similar to those in the IM control group, demonstrating the potential for up to 5-fold dose-sparing. The regulatory criteria for re-licensure of seasonal influenza vaccines were met in full in all study groups. Recipient acceptance and discomfort was assessed using a questionnaire and demonstrated less pain and intimidation with the device compared to the IM injection (data on file).

A second study had a similar design using the A/2009/H1N1 strain and was the first intradermal vaccination study of pandemic influenza.[27] The study, which was conducted mostly in the elderly population in Hong Kong, demonstrated 5-fold dose-sparing as well, with a safety profile that was comparable to the previous study. There was a similar incidence of systemic adverse events (AEs) such as fever and arthralgia, and a higher incidence of local AEs such as erythema and edema, which is consistent with other ID influenza vaccine studies.[60,61,68]

A study in the elderly compared fractional-dose ID delivery to the full IM dose of the unadjuvanted influenza vaccine (Fluvirin™, Novartis), as well as to MF59-adjuvanted formulations with various antigen and adjuvant doses.[108] This study showed that the unadjuvanted ID approach yielded significantly higher immunogenicity at 6 μg HA/strain than unadjuvanted IM formulations at 15 μg or 30 μg HA/strain, in at least the A/H1N1 strain, with non-inferior GMTs in the other strains. One study arm (12 μg HA/strain ID) was also higher with the A/H3N2 strain compared to the unadjuvanted IM formulations. In addition, the study showed that formulations adjuvanted with

MF59 yielded significantly higher GMTs than the unadjuvanted ID formulation in the A/H1N1 and B strains, but not for A/H3N2. However, the adjuvanted formulation included 15 μg HA/strain (and 30 μg HA for A/H3N2), which was 2.5-fold higher than the unadjuvanted ID groups, so a direct dose-for-dose comparison of ID (unadjuvanted) with IM (MF-59-adjuvanted) was not established.

Another seasonal influenza study evaluated various ID or IM doses of a virosomal influenza vaccine (Inflexal V™, Crucell, BV).[36] This study was unique in that it included a head to head comparison of the use of the MicronJet device with the same formulation and dose using a 25 G 16 mm (5/8 in.) length needle and syringe with the Mantoux technique (typically using a 15 degree injection angle). This study showed that ID delivery of the low dose virosomal vaccine (3 μg HA/strain) with the MicronJet achieved statistically significant higher GMT fold-increases for the H1N1 and B strains as compared with the same dose ID using Mantoux (84.2 vs. 37.8 [$P < 0.05$] and 28.5 vs. 6.9 [$P < 0.01$], respectively). Superior immunogenicity was also demonstrated for the H3N2 strain compared to IM delivery of the full dose (15 μg HA/strain) vaccine, despite using 1/5th of the dose (39.9 vs. 16.9 [$P < 0.05$]). The improved immunogenicity results observed with the MicronJet600 could potentially be due to the consistent delivery of the influenza vaccine primarily to the superficial dermis and the epidermis, where Dendritic Cells (DCs), and Langerhans cells, (LCs) are respectively abundant. Injection site for all influenza studies was the deltoid area.

The Present: Demonstrating Improved Immunogenicity with the MicronJet600

Improving the immunogenicity of vaccines is an important unmet clinical need that might even be more important than mere dose-sparing. Theoretically, using higher or equivalent doses of an antigen intradermally (instead of reducing the dose due to volume constraints) may enhance such immunogenicity, and with it, potentially, vaccine efficacy. Intradermal delivery of high doses of the antigens may require concentration, which may result in some additional manufacturing costs.

A Phase II clinical study was conducted in 2010 at Hong Kong University to evaluate the ability of ID delivery to enhance the immunogenicity of seasonal influenza vaccines with Intanza9 2009/2010 as the source of antigen.[109] The study included 2 experimental ID groups using the MicronJet device to give either 20% (3 μg HA/strain) or 60% (9 μg HA/strain) of the usual IM dose and 2 control arms dosed ID with either Intanza9 (9 μg HA/strain) or IM with Fluzone (15 μg HA/strain). The doses selected for the study were based on the available vaccines on the market. A direct comparison between 3 μg using the MicronJet to the same dose with Intanza was not done, as this dose was not tested for Intanza and the 6 μg dose did not show non-inferiority in previous studies. The study demonstrated that the typical reduction in immunogenicity of the 2009 H1N1 strain could be overcome and was significantly higher with ID vaccination when compared with the IM vaccination, with the highest seroprotection rate and GMT fold increase value generated by the lowest dose of 3 ug (20%) HA vaccine delivered by the MicronJet600. The H3N2 strain seroconversion rates were also significantly higher in the ID groups compared with the IM group. There was no significant difference in immune response between the ID groups.

Additional promising results demonstrating very significant dose-sparing, as well as improved immunogenicity, have been recently released by Merck & Co, for live attenuated herpes zoster vaccine (NCT01385566). Further detailed information is pending publication.

Table 3 outlines various published clinical studies using the MicronJet device models for the delivery of vaccines, along with a summary of results, benefits and references.

The Future of ID Delivery of Vaccines and Immunotherapeutics: Promise and Challenges

Despite many years of clinical development and the very promising early-stage trials described above, there are still significant challenges facing the ID delivery approach, for the MicronJet600 or any other device. For instance, late stage clinical trials are still required to validate superior immunogenicity and vaccine efficacy, especially in challenging populations like the elderly.[110] In addition to having a low response to vaccination at a young age (below 6 months),[111] the pediatric population also poses specific mechanical challenges, due to their thin skin, making them unsuitable for immunization with certain delivery technologies.[112] However, the MicronJet600 device was recently utilized in a large Phase III inactivated polio vaccine (IPV) study in 6–14 week-old infants sponsored by the US CDC and the International Center for Diarrheal Disease Research, Bangladesh (icddr, b) (NCT01813604). The device performed very well in this setting (publication in preparation). Additional validation of ID delivery is required in order to expand the list of applicable

Table 3. Published clinical studies using the MicronJet and MicronJet600

Field	Study ID	Phase	N	Device used	Benefit demonstrated*
Seasonal Influenza	EudraCT number 2007-001160-77	Pilot	180	MicronJet	Dose sparing[33]
Seasonal Influenza	ISRCTN 33950739	Phase II	280	MicronJet	Dose sparing and superior immunogenicity[36]
Seasonal Influenza	NCT00848848	Phase I	450	MicronJet	Superior immunogenicity[108]
Pandemic Influenza	NCT01049490	Phase I	37	MicronJet600	Dose sparing[27]
Seasonal Influenza	NCT01304563	Phase II	282	MicronJet600	Dose sparing and superior immunogenicity[109]

*Compared to a standard dose of the unadjuvanted vaccine

vaccines beyond BCG, PPD, rabies, and influenza. Another phase I of ID iPV using Micronjet600 was conducted in HIV positive adults (NCT01686503).[113]

The use of ID delivery with immunotherapeutics holds future promise, coupled with unique challenges, in the settings of allergy (in Phase III clinical trials),[114] cancer immunotherapy, and Type 1 Diabetes (in preclinical studies).[115] Of most interest perhaps, is antigen-specific cancer immunotherapy, which despite past failures[116,117] is still the most vibrant vaccine field to undergo clinical evaluation of the ID approach. There are over 30 clinical programs today with ID delivery of cancer vaccines (at least one of which with the MicronJet600) and likely many more to come. The ability to enhance the skin's potent immune system with ID immunization, to directly target its Dendritic and Langerhans cells,[118,119] and to potentiate the response against cancer cells, remains one of the great challenges and promises of the 21st century.[120]

Disclosure of Potential Conflicts of Interest

Dr. Yotam Levin and Dr. Efrat Kochba are permanent employees of NanoPass Technologies, Ltd.

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