5. Preclinical studies of IDD of vaccines

It is possible that the vaccines most likely to benefit from IDD are those still relatively early in their development phases:

- They allow an opportunity to explore different routes of administration in preclinical and early clinical studies before committing to a final formulation and route of delivery.

- They might be technically more difficult to develop than existing vaccines and so might benefit more from efforts to enhance immunogenicity or target particular aspects of the immune system.

- Several of the vaccines in development for diseases such as TB, HIV, and malaria use live vectors (including viral vectors) or DNA, sometimes in heterologous prime-boost regimens. ID (or epidermal) delivery is possibly the optimal route for some or all of these components.

- Novel adjuvants to be developed specifically for use ID can be incorporated into the formulation at an early stage in development.

Preclinical studies of IDD can be broadly divided into two categories:

- **Vaccine-specific studies**: where the ID (and/or epidermal) route is being used or evaluated because it is believed to be the optimal route for delivery of the vaccine in question. The majority of these studies currently involve DNA vaccines, live viral-vector vaccines or a combination of both in a heterologous prime-boost regimen. Examples of these types of vaccines and regimens that have been used in clinical trials have been discussed in Section 3.6. A detailed summary of preclinical data obtained with all such vaccines is beyond the scope of this report; furthermore, the results would be subject to the limitations described in Section 5.1 below.

- **Preclinical studies of devices**: these studies generally employ model antigens such as ovalbumin or influenza HA to learn more about the performance characteristics of the device being developed. Data from this type of study are described in Section 6, according to the device used.

5.1. Limitations of preclinical studies

5.1.1. Skin anatomy

The thickness and flexibility of the skin are important parameters when studying IDD in animal models. Devices developed to deliver to the depth of the epidermis or dermis in humans might not target the same tissues in mice or non-human primates. Pigs, including mini-pigs, are often regarded as being the most representative models of human skin in terms of anatomy, although swine skin has been reported to be richer in collagen and less elastic than human skin (Laurent PE et al. 2007). Swine are, however, far less suited to immunological studies compared with small rodents, due to cost and the fact that their immune system is less well characterized than that of mice and rats.

An alternative approach is to use human skin explants obtained after skin-excision surgery. These can be maintained in a viable state for three to four days, allowing injection of antigen, analysis of the deposition of antigen, and immune cell activation and migration. It is also possible to study markers of reactogenicity.[6]

5.1.2. Immune responses

The immune responses seen following vaccination of mice and other small rodents are not always predictive of results obtained in clinical trials. This has certainly proved to be the case for DNA vaccines, which appeared to be very promising in small rodents, inducing potent CMI and antibody responses. Data from clinical trials, however, particularly with IM delivery of DNA, have been disappointing with relatively poor immune responses being induced even though 100- to 1000-fold higher doses of DNA have been administered (Fuller et al. 2006).

5.1.3. Adjuvants

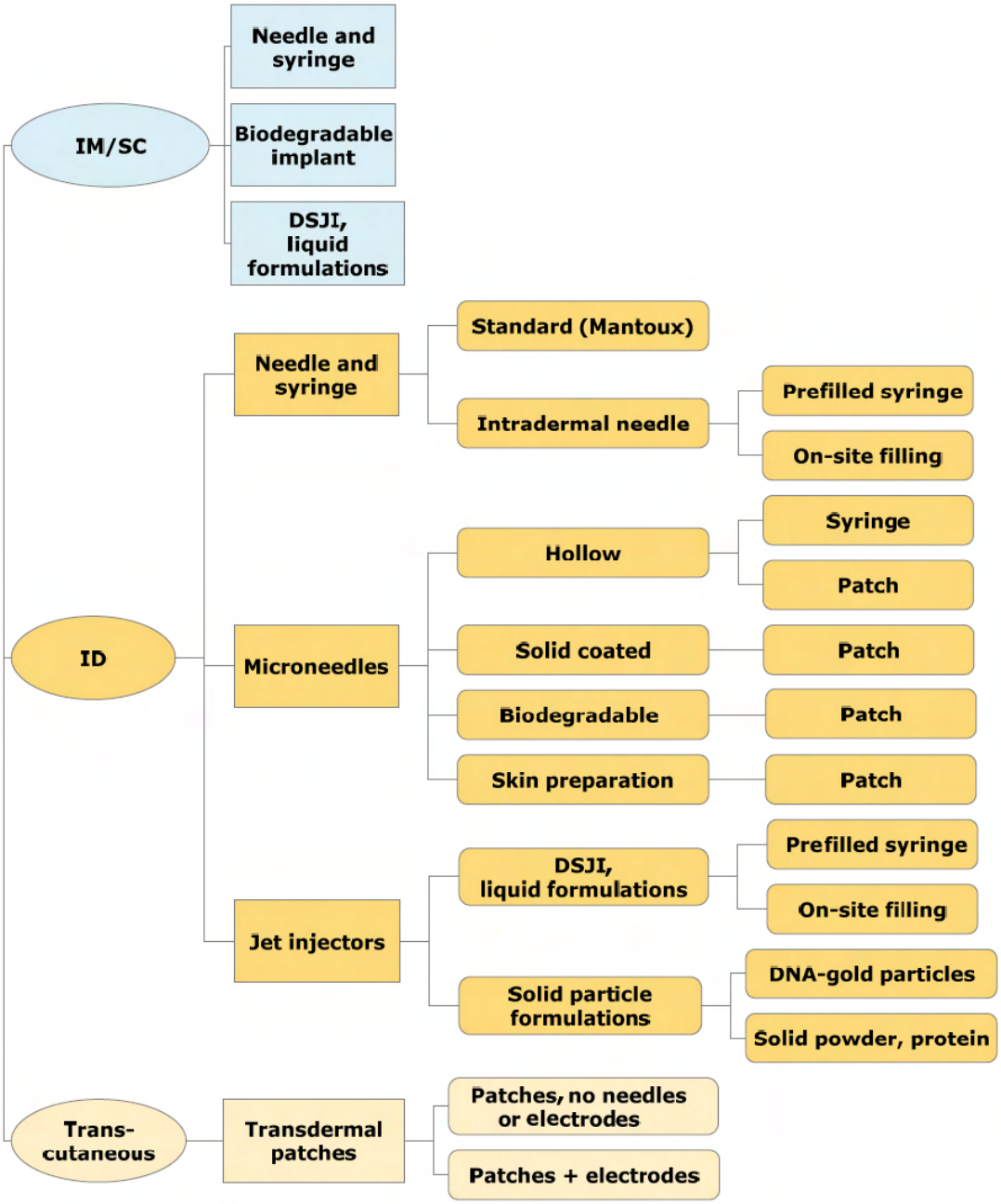
Some novel adjuvants have the same or similar immune-enhancing effects in animal models and humans. Others do not, and preclinical animal models (particularly inbred mice) are not always predictive of adjuvant effects in the clinic. This is of increasing importance as rationally designed adjuvants that stimulate immune responses via triggering of toll-like receptors (TLRs) are developed. There are however, differences between mice and humans in the patterns of expression of TLRs on APCs, and in the fine specificity of some of the receptors themselves (reviewed by Wagner 2004).

[6] James Birchall, Cardiff University, Wales, oral communication, March 17, 2009.

6. Review of IDD devices in development

A number of novel devices are being developed for the intradermal, epidermal, or transcutaneous delivery of vaccines. A taxonomy of devices relevant to IDD is provided in Figure 5. The key features of each class of device are summarized in the sections that follow.

Figure 5. Taxonomy of devices for intramuscular/subcutaneous (IM/SC), intradermal (ID), epidermal, or transcutaneous delivery of vaccines.



6.1. Jet injectors

The majority of jet injectors currently being developed for vaccine delivery are disposable syringe (sometimes referred to as "cartridge") jet injectors (DSJIs) consisting of a reusable hand-piece containing a propulsion system and a disposable, vaccine-containing needle-free syringe or cartridge (prefilled or end-user filled) that is replaced before each administration (see Table 11).

Single-use, disposable jet injectors (SUDJIs) are also being developed; these include devices for jet injection of DNA vaccines coated onto gold particles. SUDJIs are likely to be too expensive and occupy too much space in the cold-chain for LMIC use, and so are not discussed further in this report.

Jet injectors can be categorized according to whether they deliver solid or liquid vaccine formulations. Jet injectors for solid formulations (of protein or subunit vaccines) are not discussed further in this report because it is uncertain whether they are still being developed.

Table 11. Strengths and weaknesses of jet injectors

Strengths	Weaknesses
▪ Reduction of sharps, sharps waste, and needle-stick injuries and associated cost. ▪ Reformulation of existing liquid vaccines is (generally) not needed. ▪ Cartridges might have lower transportation costs than prefilled syringes. ▪ Potential for dose sparing via ID or IM delivery. ▪ Considerable clinical experience with several devices (particularly the Biojector 2000®).	▪ Relatively expensive compared with N&S. ▪ End-user filling reduces some of the potential benefits of DSJIs. ▪ Prefilling of cartridges by vaccine manufacturers will require reengineering of vaccine-filling lines. ▪ There is a risk that shearing forces might damage live virus or adjuvanted vaccines.

Note: DSJI, disposable syringe jet injector; ID, intradermal; IM, intramuscular; N&S, needle and syringe.

6.1.1. Disposable syringe jet injectors for delivery of liquid formulations

6.1.1.1. Leading devices

In response to earlier design requirements shared by WHO for low-cost, manually powered DSJIs (PATH unpublished data 2006)[7], a number of prototype and soon to be available commercial devices now meet these requirements (see Figure 6), including: Zetajet® (Bioject), E-Jet500® (Euroject), PharmaJet® (PharmaJet Inc.), and Lectrajet® M3RA (DCI).

[7] PATH. The Investment Case for New-Generation, Disposable-Cartridge Jet Injectors. PATH document for internal use.

The development status of the other devices is not known. The Zetajet® has the same performance characteristics as the Biojector 2000®, despite some differences in design such as the propulsion mechanism (manual spring vs. CO_2 propulsion, respectively).

Figure 6. Examples of disposable syringe jet injector (DSJI) devices.

Biojector® 2000 (Bioject)

Biojector® 2000 (Bioject) fitted with ID spacer

PharmaJet® (PharmaJet Inc.)[8]

Zetajet® (Bioject)[9]

6.1.1.2. Clinical experience and activities

The most widely used DSJI is the Biojector® 2000, which is used at a number of private, public, and US Navy and Coast Guard immunization clinics to administer approximately one million IM vaccine doses per year (Weniger and Papania 2008). Surveys have found its usage characteristics to be acceptable for adult and pediatric vaccinees. A study comparing the Biojector® 2000 with N&S for IM delivery of hepatitis A vaccine (Havrix®, Merck) found a better seroconversion rate following vaccination with the Biojector® compared with N&S (Williams et al. 2000). The Biojector® 2000 is not considered to be a suitable design for LMIC use, however.

In terms of IDD, the Biojector® 2000 has been used in Global Polio Eradication Initiative-sponsored ID dose-reduction studies with IPV in infants in Cuba and Oman (see Section 2.6) and with influenza vaccine in infants in the Dominican Republic. The Biojector® 2000 has also been used for the delivery of DNA vaccines for malaria in young adults (Wang et al. 2001, Epstein et al. 2002) and an HIV-vaccine candidate (Bioject 2009).

[8] Image used by permission from M Royals, PharmaJet Inc,

[9] Image used by permission from R. Stout, Bioject.

The PharmaJet device is being used in a trial comparing ID and IM delivery of HPV vaccines (see Section 2.7 and Appendix 1), is being evaluated in an ID trial of IPV in infants in India (started in April 2009), and is likely to be evaluated in a forthcoming trial of IDD of rabies vaccine (PATH and Indian Immunologicals Ltd).[10,11] Other vaccine trials with the PharmaJet device are being planned for diseases including measles, mumps, and rubella (MMR); varicella zoster virus; and yellow fever (see Appendix 1).[11]

Local adverse effects following jet injection appear to be dependent on the vaccine or medication involved. Delivery of insulin (for insulin-dependent diabetics) or non-adjuvanted vaccines is associated with equivalent or reduced pain compared with N&S, although IDD with Biojector® 2000 is associated with more injection-site erythema than N&S (Friede 2006). Vaccines that have aluminum-salt adjuvants tend to result in higher frequencies of delayed local reactions (e.g., soreness, edema, and erythema) when jet-injected (Weniger and Papania 2008, Williams et al. 2000).

6.1.1.3. Preclinical experience and activities

The Biojector® 2000 has been, and is still being used for delivery of DNA vaccines in a number of preclinical studies with several vaccines including: a model antigen coated onto cationic nanoparticles (Cui et al. 2003), herpes simplex virus type 2 (HSV-2; Meseda et al. 2006), and measles (Ramirez et al. 2008). The latter was conducted in rabbits before moving to Phase I clinical trials. The DNA vaccines were administered ID by Biojector® 2000; in some animals, DNA priming was followed by boosting with live-attenuated measles vaccine SC. Two immunizations with plasmid DNA, without a live measles vaccine boost, were sufficient to induce antibody titers in rabbits that were greater than the level believed to be protective in humans. The stated aim of the investigators was to progress this work to a Phase I clinical trial, although the current status of the work is not known.

6.2. Microneedles

There are a variety of vaccine delivery devices in development that employ some type of microneedle. These can be categorized according to type of microneedle, microneedle length, and whether or not the device is a patch or syringe-based. For the purposes of this report, microneedle devices are considered in four categories:

- Hollow microneedles, syringe-mounted or on patches, for the delivery of liquid vaccines.
- Solid, coated microneedles, in which the vaccine is dried onto metal, silicon, or polymer microneedles.
- Solid, biodegradable microneedles, composed of vaccine plus excipients.

[10] Darin Zehrung, PATH, oral communication, April 15, 2009.

[11] Michael Royals, oral communication, May 11, 2009.

- Solid, uncoated microneedles. In this format, the microneedles are used simply for skin preparation or perforation prior to application of vaccine either as a liquid or in a patch.

Devices such as Soluvia®, BD's "microinjector" in which the needle is >1 mm in length and designed to penetrate to the depth of the dermis are sometimes described as "mini-needles." For the purposes of this report, such devices are classified as ID needles (see Section 6.3).

Some of the strengths and weaknesses of microneedles are listed in Table 12. Examples are provided for illustration in Figure 7.

Table 12. Strengths and weaknesses of hollow, solid, and biodegradable microneedles

Strengths	Weaknesses
▪ Reduction of sharps, sharps waste, and needle-stick injuries and associated cost. Methods for "disabling" sharps after use are being developed. ▪ Potential for dose sparing via ID delivery. ▪ Patch-based microneedles might need less cold chain volume than standard presentations and are potentially compatible with solid, thermostable formulations. ▪ Syringe-mounted hollow microneedles use existing technology to ensure delivery of full-dose of vaccine. ▪ Likely to have high patient acceptability (due to causing less injection pain) and be simple to use.[12]	▪ Microneedles might have the potential to transmit blood-borne pathogens and so need to be treated as "sharps"; however, any risks are likely to be far less than for N&S, and might be mitigated by incorporating a retraction mechanism in the device. ▪ Considerable vaccine formulation development will be needed for some formats, particularly solid-coated or biodegradable microneedles. ▪ Confirming delivery of the full dose might be difficult. ▪ Engineering issues: ▪ Hollow microneedles can be prone to clogging and backpressure.[6] ▪ Might be difficult to load sufficient payload of vaccine onto patch (this is not seen as a problem by three opinion

[12] Yotam Levin, NanoPass Technologies Ltd., oral communication, March 5, 2009.

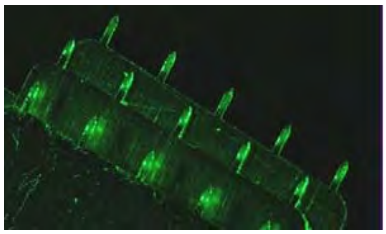
[13] Mark Prausnitz, Georgia Institute of Technology, oral communication, February 20, 2009. James Birchall, oral communication, March 17, 2009. Mark Kendall, Universtiy of Queensland, oral communication, March 18, 2009.

[14] Mark Kendall, oral communication, June 3, 2009.

Strengths	Weaknesses
	leaders).[13] ▪ Might be difficult to make biodegradable microneedles with sufficient structural strength, although this has been achieved in preclinical studies.[14]

Figure 7. Examples of different types of microneedle design.

Prototype patch of stainless steel microneedles



Stainless steel microneedles coated with green fluorescent protein

Micronjet (NanoPass Technologies Ltd.)[15]

Prototype dissolvable (biodegradable) microneedles

Images from Mark Prausnitz, Georgia Institute of Technology, unless labeled otherwise

6.2.1. Hollow microneedles

6.2.1.1. Leading devices

Engineering hollow microneedles that do not break, block, or require high pressure in order to deliver the vaccine is possible, but technically demanding (Kersten and Hirschberg 2007).[16] Hollow microneedle arrays can be applied to patches (such as Micro-Trans™,

[15] Micronjet image used by permission from Yotam Levin, NanoPass Technologies Ltd.

[16] James Birchall, Cardiff University, Wales, oral communication, March 17, 2009.

Valeritas) or, in some cases, can be fitted to the end of a syringe, e.g., Nanoject® (Debiotech) and Micronjet (NanoPass Technologies) (see Figure 7). This approach has the advantage of employing existing technology to ensure that the full dose of vaccine is delivered, and in the case of Micronjet employs a user-filled, rather than prefilled, syringe.[17] The Micronjet (needle length 450 µm) has recently been awarded CE (European Conformity) approval for marketing (NanoPass 2009).

6.2.1.2. Clinical experience and activities

The Micronjet device (NanoPass Technologies) has recently been tested for the IDD of reduced doses of inactivated influenza vaccine in healthy adult volunteers (Van Damme et al. 2009; see Section 2.1.4). In this study, the device consisted of an array of four silicon crystal microneedles, each 0.45 mm in length, fixed to an adaptor that could be mounted on a standard syringe (see Figure 7). The Micronjet device might be evaluated for the delivery of rabies vaccine as part of a PATH-coordinated clinical trial (see Section 6.3).

The Micro-Trans™ (Valeritas) device and Nanoject® (Debiotech) device are believed to be in preclinical development; data showing successful delivery of vaccines in humans are not available.

6.2.1.3. Preclinical experience and activities

Early studies with hollow microneedle arrays demonstrated that they were capable of delivering microliter quantities into the skin *in vivo* (McAllister et al. 2003). Delivery rates can be improved using active infusion methods (Roxhed et al. 2008), but these devices are likely to be too complex for use in LMIC settings.

Preclinical studies to investigate the use of hollow microneedles (Micronjet, NanoPass) for delivery of alum-adjuvanted vaccines (DTP) and a candidate malaria vaccine are underway (PATH unpublished data 2008).[18]

6.2.2. Solid, coated microneedles

6.2.2.1. Leading devices

In these devices, vaccine (e.g., protein or DNA) is coated by the manufacturer onto solid microneedles on a patch or array before application to the skin. The leading devices are probably the Macroflux® system (Zosano Pharma) and MTS® (3M) device, but other academic-based investigators are also developing solid, coated microneedles.

6.2.2.2. Clinical experience and activities

The Macroflux® system is believed to be in Phase I trials with influenza vaccine, but the only, limited, data available are on the company website (Macroflux 2009). No other clinical trials with solid, coated microneedles are known.

[17] Yotam Levin, NanoPass Technologies Ltd., oral communication, March 5, 2009.

[18] PATH. *HIP Microneedle Research Proposal*. Internal PATH document. February 2008.

6.2.2.3. Preclinical experience and activities

Work has been performed to develop formulations for coating solid microneedles with DNA (Chabri et al. 2004, Pearton et al. 2008, Chen In press) and proteins (Gill and Prausnitz 2007, Chen In press). Hydrophilic and hydrophobic proteins can be coated using formulations composed of US Food and Drug Administration approved excipients (Gill and Prausnitz 2007, Chen In press). It is estimated that a payload of 10–100 µg active protein could be coated onto a microneedle patch of 1 cm^2 or similar.[19,20] Investigators also believe that it is possible to control the position of coating of the microneedles to minimize losses of the coated antigen as it penetrates the skin to maximize the amount of antigen delivered to the target tissue.[21,22]At least one academic investigator has unpublished data showing that vaccines containing adjuvants such as alum, the saponin quil A, and CpG oligodeoxynucleotides can be coated onto microneedles.[19]

The effects of antigen load, depth of microneedle penetration, density of microneedles, and area of patch on the immune response to a model antigen (ovalbumin) have been described for microneedles 200–600 µm in length and with 140–662 microneedles per cm^2. The amount of antigen loaded onto a microneedle patch was found to influence the antibody response more than the length of the microneedles (Widera et al. 2006). Preclinical studies with model antigens have also been conducted with very closely spaced (20,000 projections per cm^2) microneedles, approximately 100 µm in length.[22]

Preclinical studies have been conducted, or are underway, with a number of vaccines including: influenza (split, unadjuvanted, whole inactivated virions, VLPs, and DNA); hepatitis B; HPV (Gardasil®, Merck); HSV-2 (DNA); malaria (viral vectors and possibly DNA); MMR; IPV; and BCG.[19,20]

6.2.3. Solid, biodegradable microneedles

6.2.3.1. Leading devices

In this configuration, microneedles are fabricated from the active vaccine plus generally-recognized-as-safe (GRAS) excipients. The feasibility of manufacturing biodegradable microneedles has been demonstrated (Park et al. 2005). The VaxMAT® technology from Theraject is possibly the most advanced approach, although other academic investigators are also pursuing this approach.

6.2.3.2. Clinical experience and activities

The technology is at a very early stage and clinical data showing successful delivery of a vaccine in humans are not yet available.

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[19] Mark Kendall, oral communication, March 18, 2009.

[20] Mark Prausnitz, oral communication, February 20, 2009.

[21] James Birchall, oral communication, March 17, 2009.

[22] Mark Kendall, oral communication, June 3, 2009.

6.2.3.3. Preclinical experience and activities

Studies to optimize the fabrication and formulation of biodegradable microneedles have been published (Park et al. 2005, Lee et al. 2008), but to date there are limited data on the use of this approach to deliver vaccines. Theraject has conducted preclinical experiments in mice with skin-penetrating dissolvable vaccine microneedles formed from lyophilized influenza vaccine. Satisfactory immune responses were induced, but it was noted that controlling the dose was difficult (Oh et al. 2006). Other investigators have used dissolving microneedles to deliver a viral vector encoding a malaria vaccine to mice.[23]

6.2.4. Solid, uncoated microneedles

6.2.4.1. Lead devices

In this scenario, the microneedles simply provide a means to prepare or abrade the skin, before the application of vaccine, typically in a patch (see Section 6.4).

The MTS® system (3M) can be used in this configuration or coated with vaccine. Control of the dose of vaccine delivered might be difficult using this uncoated approach, and there might be safety concerns with its use for live attenuated vaccines.

The Onvax® system (BD) employs a "microenhancer array" of silicon or plastic microprojections on a hand-held applicator. This is used to abrade the skin before or after topical application of liquid vaccine; the micro-projections can also be coated with vaccine. This device is no longer being developed, however.[24]

6.2.4.2. Clinical experience and activities

There are no published clinical studies with the Onvax® system.

Vaxinnate and 3M recently announced a collaboration to develop 3M's MTS® system for delivery of Vaxinnate's M2e "universal" flu vaccine (VaxInnate 2008).

6.2.4.3. Preclinical experience and activities

Preclinical experiments with Onvax® have demonstrated immune responses as good as those seen with IM injection, but not as good as those obtained with ID injection using a syringe-based microneedle (Mikszta et al. 2006).

[23] Mark Kendall, oral communication, June 3, 2009.

[24] Philippe Laurent, Becton Dickinson, oral communication, March 2, 2009.

6.3. Intradermal needles

The ID needle category includes devices that use a single needle designed to deliver to the dermis. See Table 13 for some strengths and weakness of these IDD devices.

Table 13. Strengths and weaknesses of intradermal (ID) needles

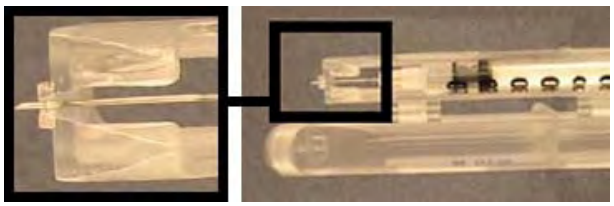
Strengths	Weaknesses
▪ Simple to use. ▪ Compatible with existing (or more concentrated) formulations of vaccines. ▪ Leading device is manufactured at scale and is commercially available.	▪ ID needles will still have the potential to transmit blood-borne pathogens. ▪ Some versions are prefilled and therefore are likely to require more cold chain storage space than multi-dose vials. ▪ There are some restrictions on availability of the Becton Dickinson (BD) device to vaccine manufacturers due to the license agreement with Sanofi Pasteur.

6.3.1.1. Leading devices

The Soluvia® device (BD),[25] also referred to as the "BD microinjection system" (Laurent PE et al. 2007, Laurent A et al. 2007) is a prefilled syringe with a single 30-gauge needle, 1.5 mm in length, designed to deliver 100–200 µl of fluid (Figure 8). The length of the needle means that simple injection, perpendicular to the skin, should deliver vaccine to the dermal layer. Because of the shallow depth of penetration, the sensation of injection is claimed to be almost imperceptible to the patient. The device is designed to protect the needle after injection, reducing risk of injury and preventing reuse and misuse of the system (Lambert and Laurent 2008).

Figure 8. Examples of intradermal (ID) needles.

Soluvia®, Microinjector (Becton Dickinson)



ID needle adaptor (SID Technologies and PATH)

[25] See www.bd.com/pharmaceuticals/products/microinjection.asp for example.

Although the BD Soluvia® device (Figure 8) might appear to be a relatively straightforward approach, a number of hurdles had to be overcome including the manufacture of very small needles, development of technologies for small-volume filling and addressing vaccine formulation issues such as density, viscosity, and propensity for foam formation (Picot 2008). The Soluvia® device is supplied prefilled. In this format the device currently has a particularly large packaged volume, about 200 cm^3.[26] It is understood that a plastic non-prefilled version compatible with multi-dose vials has been developed.[27]

PATH and SID Technologies are collaborating on an ID adaptor as an alternative approach to achieve a similar goal. A standard BD insulin/tuberculin syringe is fitted into a plastic adaptor that limits the depth and angle of needle penetration.[28]

6.3.1.2. Clinical experience and activities

In 2005, the BD microinjection device was licensed to Sanofi Pasteur (BD 2005). Use of the device in two trials with influenza vaccine in healthy younger adults (Leroux-Roels et al. 2008) and healthy older people (Holland et al. 2008) has recently been described (see Section 2.2). A marketing authorization application (MAA) for its use in the administration of influenza vaccine was submitted to the European Medicines Agency (EMEA) in February 2008 (BD 2008), following trials in >7,000 subjects. In December 2008, Sanofi Pasteur announced that the ID flu vaccine "Intanza® / IDflu®" had received a positive opinion from Europe's CHMP, the scientific committee of the EMEA (Sanofi Pasteur 2009). The version of the device used for the Intanza® vaccine has an anti-stick mechanism; after injection, further depression of the plunger covers the needle with a plastic shield (CHMP 2009).

6.3.1.3. Preclinical experience and activities

Preclinical studies with anthrax vaccine had shown that IDD using a prototype version of the BD microinjection device resulted in better immune responses than IM, SC, or topical delivery (Mikstza et al. 2006). The device has also been used for delivery of a live-recombinant Japanese encephalitis virus vaccine (Chimerivax™-JE, Acambis) to non-human primates and was shown to induce superior virus-neutralizing antibody titers compared with SC injection (Dean et al. 2005). The injection performance of the device as well as fluid distribution and reactogenicity following ID injection of human skin have also been described (Laurent A et al. 2007).

The PATH/SID Technologies ID adaptor is undergoing preclinical testing in pigs, guinea pigs, and mini-pigs, with the intention of being evaluated in a Phase I trial with rabies vaccine.[28]

6.4. Transcutaneous immunization

For TCI, some means of disrupting the stratum corneum (top layer of the skin) is usually required to allow large molecules to reach the dermal or epidermal layers. Use of

[26] Fiona Garin, Becton Dickinson, oral communication, March 11, 2009.

[27] Philippe Laurent, oral communication, March 2, 2009.

[28] Darin Zehrung, PATH, oral communication, February 16, 2009.

microneedles to abrade the skin has been described above. Other approaches to breach the stratum corneum are being evaluated, such as electromagnetic energy and skin stripping techniques to facilitate delivery of proteins to hair follicles (Vogt et al. 2008). It is, however, questionable whether these approaches will be appropriate for LMIC use, mostly due to complexity or cost (see Table 14).

Table 14. Strengths and weaknesses of transcutaneous immunization (TCI) patches

Strengths	Weaknesses
▪ Simple to use. ▪ No sharps. ▪ Potential for integrated vaccine and device, and with small volume.	▪ Patches might need to be worn for hours for delivery of full dose; therefore it might be difficult to ensure compliance. ▪ This approach might only be applicable to a very limited range of vaccines.

6.4.1.1. Leading devices

The most advanced technology for needle-free TCI is Iomai's transcutaneous immunization patch.[29] Vaxin Inc. is developing TCI patches for use with non-replicating bacterial vectors.[30]

6.4.1.2. Clinical experience and activities

Recent data from a Phase II clinical trial of a travelers' diarrhea vaccine based on TCI delivery of LT showed that the vaccine provided protection against severe disease (Frech et al. 2008); however, pretreatment with a mild abrasive is still required and the LT patches need to be worn for five to eight hours to ensure sufficient delivery of vaccine.

A Phase I trial of TCI with live attenuated measles vaccine reported induction of measles-specific salivary immunoglobulin A and measles-virus-specific interferon-γ–producing T cells. Serum antibodies with neutralizing activity were not induced, however (Etchart et al. 2007).

6.4.1.3. Preclinical experience and activities

Transcutaneous immunization with non-replicating bacterial vectors over-expressing tetanus toxoid or recombinant protective antigen (rPA) from anthrax resulted in protective or weakly protective immune responses, respectively (Zhang et al. 2006).

6.5. Comparison of properties of IDD devices

Some of the main attributes of IDD devices and their potential benefits are listed in Table 15. In order to compare the relative advantages and disadvantages of the devices, scores have

[29] Iomai was acquired by Intercell AG (Vienna) in August 2008.

[30] See the Vaxin Inc. company website www.vaxin.com/.

been subjectively assigned to each of the attributes and a series or radar charts have been plotted (Figure 9). At this stage, no weighting has been applied to the attributes. For comparison, N&S delivery for IM/SC administration has been included.

Table 15. Key attributes used for comparison of IDD devices (PATH unpublished data 2009)[31]

Attribute	Potential benefits	Comments
Potential for dose sparing.	Reduce vaccine costs. Improve vaccine availability.	Rated according to whether existing data suggests that delivery IM/SC or ID using the device is likely to be dose sparing.
Reduced volume in cold chain.	Reduce cold-chain volume , either by: ▪ reducing volume of vaccine required per dose, or ▪ by virtue of the small size of the device (e.g., microneedle patches).	Non-prefilled devices are assumed to be compatible with multi-dose vials.
Integrated vaccine and device.	Simplify distribution and administration.	Rated either: ▪ 0=separate device and vaccine. ▪ 4=integrated vaccine and device.
Ease of administration.	Reduce training required for health care workers. Possibility of self-administration.	Rated according to estimates of simplicity and speed of administration.
Patient acceptability.	Increase uptake of vaccine.	Rated according to pain and injection site reactions.
Sharps reduction.	Reduce risk of needle-stick injuries. Simplify waste disposal.	Microneedles are assumed to present some sharps hazard, but reduced compared with N&S.
Commercial availability.	Reduce time before benefits of device can be obtained.	Rated according to whether the device is currently manufactured commercially, or estimates of time required to reach the market.

[31] Unpublished data consists of attributes adapted from PATH Vaccine Delivery Framework Database, March 10, 2009.

Attribute	Potential benefits	Comments
Compatible with liquid formulations (existing).	Simplify introduction of new device.	Rated according to whether the device could be used with current liquid vaccine formulations. (Note: current liquid vaccines might require modification for use ID).

Figure 9. Radar charts illustrating the key attributes of IDD devices.