Intradermal Delivery of Vaccines

A review of the literature and the potential for development for use in low- and middle-income countries

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Authorship and purpose

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The purpose of the report is three-fold: 1) To summarize the clinical evidence supporting the intradermal route for vaccine administration and the devices being developed for this purpose; 2) to determine whether intradermal delivery broadly holds promise for vaccine applications for low- and middle-income countries (LMICs) in the future; and 3) to begin to prioritize vaccine targets and device strategies that best fit the public health needs in these countries and likely merit further investigation.

The authors hope this report will contribute to ongoing discussions of the role of intradermal delivery and devices for LMIC use, and welcome comments from interested parties.

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Executive summary

The dermis and epidermis of the human skin are rich in antigen-presenting cells. It has been proposed that delivery of vaccine antigens to these tissues (i.e., intradermal delivery) rather than to muscle or subcutaneous tissue could therefore induce superior protective immune responses and that smaller quantities of vaccine antigen could be delivered via the intradermal (ID) route, thus making it dose-sparing. These attributes might be particularly meaningful to immunization programs in low- and middle-income countries by potentially reducing the cost of vaccines, increasing vaccine availability where manufacturing capacity is limited, and providing more effective vaccination.

Over the past few decades, clinical trials have been conducted with vaccines against 11 different diseases to determine whether equivalent immune responses could be obtained through intradermal delivery (IDD) of reduced quantities of antigen in comparison to immune responses seen following standard intramuscular (IM) or subcutaneous (SC) injection. Data from these trials indicate that:

- IDD of reduced doses (typically 10% or 20% of the standard amount of antigen) of currently licensed influenza and rabies vaccines has been shown to induce immune responses equivalent to those seen with the standard dose and route. Seven of eight influenza trials and 22 of 30 rabies trials demonstrated that reduced-dose ID was equivalent to full-dose IM/SC delivery. Thus, for these vaccines, the majority of the study data suggest that dose-sparing can be achieved using the ID route.

- Studies assessing IDD of reduced doses (again usually 10% or 20% of the standard dose) of hepatitis B vaccines have shown more mixed results with only 9 of 20 studies reviewed for this report showing induction of equivalent immune responses by fractional doses delivered by the ID route compared to the full dose via the IM/SC route.

- A very limited number of trials have assessed reduced-dose ID delivery versus full-dose IM/SC delivery across seven other licensed vaccines (hepatitis A, inactivated polio vaccine, measles, diphtheria-tetanus-pertussis, tetanus toxoid, tick-borne encephalitis, and yellow fever). Additional studies of these and other vaccines will be required to fully understand the potential benefits of their delivery to the dermis and epidermis.

- Despite the considerable number of clinical trials investigating IDD of vaccines, relatively few have compared identical amounts of antigen delivered by ID and IM/SC routes; only 17 of the 91 trials reviewed were designed in this way. For this reason, data to demonstrate that dose-sparing is a phenomenon unique to the dermis or epidermis are limited; it is possible that some degree of dose-sparing might also be achieved using IM/SC delivery.

- Local injection-site reactions but not systemic events were generally higher following ID vs. IM/SC immunization, although reactions were generally mild and transient.

Several novel devices for IDD of vaccines are being developed; each offering a different set of benefits:

- Devices that use liquid formulations and are not prefilled (disposable-syringe jet injectors, hollow microneedles mounted on syringes, and ID needles) probably offer the fastest and lowest risk route to evaluating IDD in the clinic.

- Prefilled syringes with a single ID needle are commercially available, but their development and production requires the involvement of the vaccine producer.

- Solid microneedles coated with vaccine or composed of vaccine, offer additional advantages, but are further behind in development and are a higher commercial and regulatory risk due to the need to formulate the vaccine specifically for this presentation and because novel production methods are used.

For IDD of vaccines to progress, several key gaps in knowledge need to be addressed:

- **Adjuvants.** Aluminum-salt and oil-in-water adjuvants present in some vaccines might be too reactogenic locally when delivered by the ID route and might need to be reduced, removed, or even replaced with novel adjuvants designed specifically for ID use. Well-designed studies are needed to evaluate the reactogenicity of adjuvanted and non-adjuvanted vaccines delivered intradermally. Development of novel adjuvants designed to activate immune responses in the dermis and epidermis should also be undertaken because these could increase the dose-sparing potential of IDD.

- **Clinical trial design.** Further clinical trials are needed to assess the potential of IDD benefits such as dose-sparing to evaluate novel delivery device methods and to determine which vaccines are most suitable for IDD. Future trials should consider:

    - Comparing identical doses delivered by different routes (ID vs. IM/SC).

    - Testing more than one antigen dose so that information on the dose-response relationship for the different routes can be obtained.

    - Evaluating fractional doses other than 10% or 20% of the standard dose. Less-extreme dose reductions might still be beneficial and are more likely to be efficacious.

    - Assessing whether reduced doses of a vaccine are sufficiently immunogenic over the whole shelf life of the vaccine.

    - Including devices designed specifically for IDD in order to improve the reliability of administration compared with needle and syringe.

- **Vaccines.** Changing the route of delivery and formulation of existing vaccines for IDD will require investment and regulatory (re-)approval. It is important to understand the impact on vaccine prices and availability. Vaccines that are most appropriate for IDD in low- and middle-income countries will need careful economic and technical assessment, but are likely to include:

- Those for which there are strong drivers (e.g., high cost and limited availability) that could be addressed by dose-sparing.

- Future vaccines or vaccines that are currently in development (e.g., malaria, tuberculosis, HIV). IDD might induce superior immune responses, and early evaluation of IDD could save repetition of late-stage clinical trials.

1. Introduction

The vast majority of vaccines are delivered intramuscularly (IM) or subcutaneously (SC) using a needle and syringe (N&S).

Intradermal delivery (IDD) has been and is being used as the route of choice for only a very limited number of vaccines, such as Bacille Calmette Guérin (BCG) for tuberculosis (TB) and in at least some countries for post-exposure rabies vaccination. It has also been investigated in recent decades as an alternative delivery route for several other vaccines, including hepatitis B (HBV), measles, and influenza.

The past few years have seen renewed interest in the use of the intradermal (ID) route for the delivery of vaccines because this route is believed to offer several possible advantages compared with IM and SC, including dose sparing (and therefore reduced cost and improved access to vaccines with limited supply), improved safety, and improved logistics. Despite this renewed interest, the issue of whether IDD offers real benefits over IM or SC administration remains confusing and controversial.

To help assess the potential utility of IDD, this report aims to:

- Summarize the evidence from clinical studies of IDD for existing vaccines used in low- and middle-income countries (LMICs), focusing predominantly, but not exclusively, on the scientific literature from 1980 onward.
- Review the limitations of clinical trial data and the challenges for future testing of IDD.
- Review clinical and some preclinical data for IDD of recently introduced and future vaccines for LMIC use.
- Consider which devices being developed for IDD hold the most promise in the short-, medium- and long-term for use in LMICs.
- Consider which, if any, vaccines might be most suited for IDD in terms of potential benefits and also technical feasibility.
- Identify areas of research that the global health community could influence and promote in order to advance the implementation of IDD in LMICs.

1.1. Immunological basis for potential benefits of IDD

This report does not propose to discuss in detail the physiological and immunological properties of the skin that make it an attractive and efficient site for initiating immune responses. These aspects have been discussed in detail in a number of recent reviews (Nicolas and Guy 2008, Lambert and Laurent 2008). It is sufficient to note that the dermis and epidermis are extremely rich in various resident and recruited types of dendritic cells (DCs), a professional antigen-presenting cell (APC) capable of stimulating both innate and adaptive (i.e., antigen-specific) immune responses. Consequently, it has been proposed that the skin in

particular should be an anatomical site capable of stimulating potent immune responses. For these reasons:

- Delivery of antigens to the skin (i.e., the dermis, epidermis, or both), as opposed to the muscle or subcutaneous tissue, could result in quantitatively or qualitatively superior immune responses.

- An equivalent or non-inferior immune response to that seen following SC or IM injection might be induced by delivery of a smaller quantity of antigen to the dermis, i.e., be dose sparing.

1.2. Definition of terms

Although the terms used to describe vaccination into muscle (intramuscular, IM) or fat (subcutaneous, SC) are standardized by common and widespread usage, there is a confusing variety of semi- or fully-synonymous terms that have been used to describe vaccination into or onto the skin. Table 1 provides examples of some terms that have been coined or linked to particular methods of skin vaccination or that imply targeting either of the skin's two layers, dermis and epidermis. For purposes of this report, the terms ***ID*** and ***IDD*** are used broadly to encompass all vaccination into or onto the skin. When the dermis or epidermis is being specifically targeted for antigen delivery, these terms (ID and IDD) are used. The abbreviation IM/SC is used throughout this report to describe administration by either of these routes (i.e., intramuscular or subcutaneous).

Table 1. Definitions for parenteral routes[1]

Term (abbreviation)	Tissue targeted	Usual depth from skin surface	Types of devices
Transcutaneous (TC) delivery/ immunization	Surface of the skin (topical application)	10–20 µm	▪ TC patch ± pretreatment with microneedles or other abrasive. Note: if abrasion is used, the epidermis rather than skin surface is likely to be the target of delivery.
Epidermal (ED) delivery/ immunization	Epidermis	<200 µm	▪ Microneedle arrays, delivery of solid particles via some type of gene-gun.
Intradermal (ID) delivery/ immunization	Dermis	1.5–3 mm	▪ Standard or tuberculin needle and syringe (N&S) (Mantoux technique). ▪ Becton Dickinson (BD) microinjection system. ▪ Jet injector (configured for IDD).
Percutaneous delivery	Dermis and epidermis	~1 mm	▪ Usually refers to delivery of Bacille Calmette Guérin (BCG) via a multiple-puncture or multi-pronged device with 1 mm needles.
Subcutaneous (SC) delivery/ immunization	Hypodermis, i.e., the layer of loose connective tissue, elastin, and subcutaneous fat located immediately beneath the dermis	>3 mm	▪ Typically N&S. ▪ Historically, some jet injectors have probably delivered to this layer, even if targeted for ID.
Intramuscular (IM) delivery/ immunization	Muscle, usually underlying the subcutaneous layer	Variable	▪ Typically N&S. ▪ Jet injectors can be used to deliver antigen.

[1] Definitions adapted from Nicolas and Guy 2008, Picot 2008, Prausnitz and Langer 2008, and Lambert and Laurent 2008.

Other terms that are used in the field but are not used in this report include:

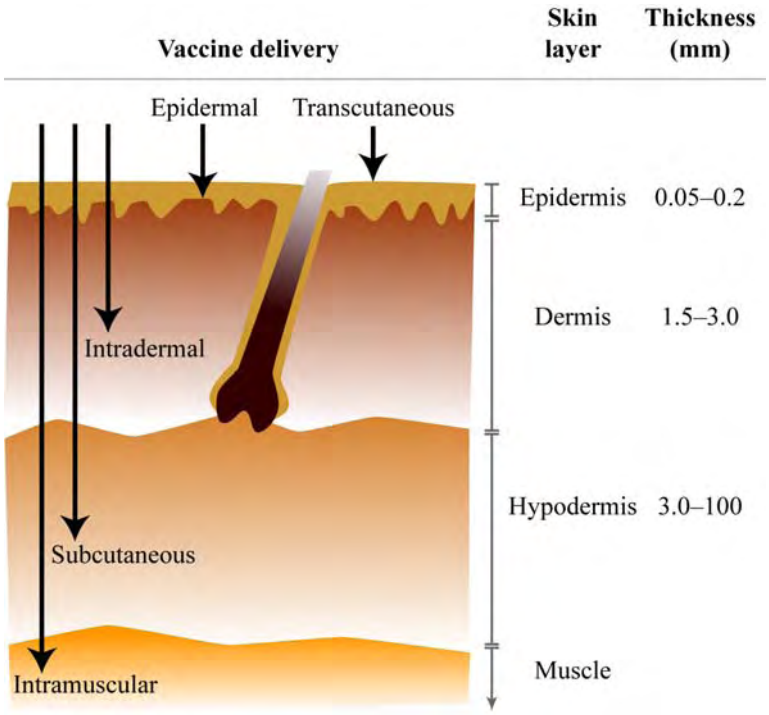
- **Cutaneous (or epicutaneous) immunization:** a general term used by some investigators for delivery via the skin, which includes epidermal, ID, and transcutaneous immunization.

- **Transdermal immunization:** some use this term as a synonym for transcutaneous immunization (Nicolas and Guy 2008), whereas others (Picot 2008, Lambert and Laurent 2008) use it to describe epidermal immunization. To avoid confusion, this term will be avoided in the report.

1.3. Skin anatomy

Figure 1 illustrates the different layers of the skin. Skin thickness varies significantly between different parts of the body; this variation between sites is greater than the variation in thickness between the same site on different individuals. The average thickness of skin also remains relatively unchanged between ages 18 to 70 years. In contrast, the amount of subcutaneous fat can vary greatly between individuals, in theory making ID and/or epidermal immunization a more consistent method than IM for vaccine delivery (reviewed in Lambert and Laurent 2008).

Figure 1. Schematic diagram of relevant features of the anatomy of the skin, and layers targeted by different methods of vaccine delivery (derived from Lambert and Laurent 2008).



1.4. Vaccines currently delivered by ID

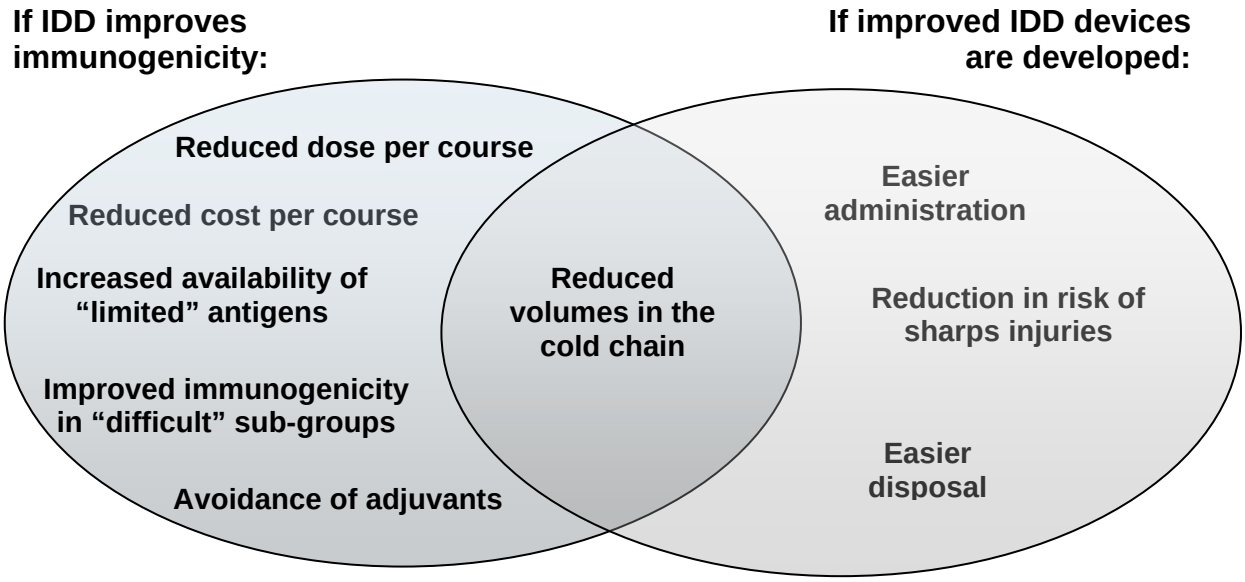
Only three currently-licensed vaccines are delivered ID: BCG, rabies (locally approved for this route in some countries), and smallpox (vaccinia). Table 1 includes IDD methods used for these licensed vaccines.

1.5. Potential benefits of IDD implementation

The current renewed interest in IDD has been largely driven by the perception or realization that IDD might offer a number of clinical (including vaccinee acceptability), immunological, safety, and/or logistical advantages compared with IM/SC delivery.

The advantages of IDD can be divided into those benefits that would be direct consequences of IDD being more immunogenic than IM/SC, by virtue of the fact that antigen is delivered to a tissue rich in APCs, and those that would result from the properties of novel devices that might be developed to deliver antigens intradermally (Figure 2).

Figure 2. Summary of potential benefits of IDD of vaccines.



If IDD enhances immunogenicity:

- **Reduced dose size and therefore cost:** might be achieved by delivering smaller amounts of antigen (e.g., 10% to 20%) than used for conventional IM/SC delivery.

- **Increased coverage of the population for antigens with limited manufacturing capacity:** might be achieved, by using a smaller amount of antigen per dose to induce an immune response equivalent to that generated by IM/SC injection.

- **Improved immunogenicity in "difficult" subgroups:** if IDD induces a qualitatively or quantitatively superior immune response to IM/SC, it might be possible to induce protective responses in populations that currently mount a poor response to some vaccines, e.g., influenza vaccine in older people and hepatitis B vaccine in patients with chronic renal disease.

- **Avoidance of the need for adjuvants:** if IDD is an efficient way to deliver antigen, it might avoid the need to develop or incorporate adjuvants in some vaccines (e.g., seasonal influenza), thereby reducing costs and possible reactogenicity; however, it is also possible that novel adjuvants for ID use would need to be developed.

If improved IDD devices are developed:

- **Easier and safer administration:** several novel vaccine delivery devices are likely to have ease of use as a key design criterion.

- **Reduction in risk of needle-stick injuries:** several of the IDD devices being developed are needle-free and could, therefore, reduce the risk of needle-stick injury or needle misuse.

- **Improved disposal:** safe and easy disposal is also likely to be built into the design criteria for novel IDD devices.

Other benefits:

- **Reduction in storage volumes in the cold chain:** use of fractional (reduced) doses for IDD would reduce the volume per dose required of existing vaccine formulations stored in the cold chain.

  In addition, some, but not all, novel IDD devices (e.g., microneedle patches) might have a smaller packaged volume of those components requiring refrigeration than existing vaccine presentations such as prefilled syringes. Thus, the demands for cold chain capacity needed to store vaccines could be reduced by developing alternative delivery devices, regardless of any dose-sparing impact.

2. Experience with IDD: evidence from clinical trials with licensed vaccines

2.1. Potential outcomes from clinical trials of IDD

When comparing IDD with IM/SC for dose-sparing potential in clinical or preclinical studies, several outcomes are possible:

- **Reduced doses delivered ID are more immunogenic than the same, reduced dose of antigen delivered IM/SC (ideally in the same volume):** In other words, the ID route is shown to be immunologically superior to IM/SC. Only a small minority of the clinical trials conducted to date have compared equivalent doses administered ID and IM/SC.

- **Reduced doses delivered ID are superior or equivalent (or non-inferior) to the standard full-dose IM/SC:** This is the comparison that is usually made in clinical studies of IDD to determine dose-sparing potential. In these cases, further evaluation of the reduced dose delivered IM might indicate that a reduced dose of the standard formulation via the standard route could be used. Switching to IDD of the reduced dose might still be advantageous, however, if other benefits can be obtained (e.g., reduction in sharps, smaller cold-chain volumes). Some of these benefits might also be achieved by using novel devices to deliver IM/SC.

- **IDD is inferior to IM/SC:** In this situation, switching to the ID route is unlikely to be justified unless the device-associated benefits are very significant.

We performed a non-comprehensive literature survey, aiming to identify key evidence from clinical trials of IDD of vaccines likely to be of interest to LMICs. We were aware of a systematic literature review by other parties, which has now been accepted for publication.[2] Although IDD has been studied (or used as the route of choice for some vaccines) for several decades, the collection of vaccines studied to date is not extensive. This literature review focused on work carried out using existing formulations of licensed vaccines, although there were occasional exceptions to this rule (Table 2).

Table 2. Number of clinical trials reviewed evaluating IDD of vaccines

Vaccine	Number of IDD clinical trials reviewed
Hepatitis A	3
Hepatitis B	26
Influenza (seasonal)	13
Measles	8
Inactivated poliovirus vaccine	3
Rabies virus	34
Tetanus toxoid	1
Tick-borne encephalitis	1
Yellow fever	1
Diphtheria-tetanus-pertussis	1

Key points from the literature review of each vaccine trial are described in the sections below. Each section includes a table summarizing the number of papers reviewed and the numbers of trials that demonstrated whether IDD was associated with dose sparing.

2.2. Influenza vaccine (seasonal)

Renewed interest in the dose-sparing potential of IDD for influenza vaccine has been triggered by a number of factors, including the seasonal influenza vaccine shortage in the United States in 2004–2005 and concerns regarding the global under-capacity for manufacture of pandemic influenza vaccines. Consequently, trials undertaken with influenza virus vaccines represent some of the most informative studies in this field. Additionally,

[2] Martin Friede, oral communication, April 8, 2009.

influenza vaccines have been used in some of the first published studies of new devices for IDD (Holland et al. 2008, Leroux-Roels et al. 2008, Van Damme et al. 2009). See Table 3 for a summary of results.

Table 3. Summary of results from clinical trials of IDD of influenza vaccine

Trials comparing equivalent doses delivered ID vs. IM/SC				**Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC**			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
5	**2**	**3**	**0**	**8**	**0**	**7**	**1**

2.2.1. Endpoints

The vast majority of the trials used serological endpoints, taking the European Committee for Medicinal Products for Human Use (CHMP) criteria as a measure of adequate immunogenicity. One study (Vogt et al. 2008) measured cell-mediated immunity (CMI) responses, rather than antibodies.

2.2.2. Dose comparisons

The majority of trials compared reduced-dose ID (usually 20% standard dose, i.e., 3 µg haemagglutinin [HA] per strain per dose) with the standard IM dose (15 µg HA per strain per dose). Of particular note are the trials conducted by Belshe et al. (2004 and 2007). The first of the studies (Belshe et al. 2004) reported that 6 µg HA per strain per dose was at least as immunogenic as the standard 15 µg of HA. For ID injections, this study used a tuberculin syringe fitted with a plastic disc to limit the depth of needle penetration (essentially a forerunner of BD's Soluvia™ device). The later study (Belshe et al. 2007) compared 3 µg, 6 µg, and 9 µg delivered by both ID and IM routes (as well as 15 µg IM). In this study, there was no difference in response when the equivalent amount of antigen was delivered by the two routes. Consistent with this are the findings of Treanor et al. (2002), who compared 100% and 50% doses of influenza vaccine, delivered IM. The 100% dose was marginally superior to the 50% dose in terms of antibody titers and seroconversion rate, but the differences were small, again suggesting a shallow dose-response curve.

2.2.3. Devices

Most of the trials have used N&S for ID and IM administration. Three recent trials, however, have used novel devices: Leroux-Roels et al. (2008) and Holland et al. (2008) used the BD micro-injector Soluvia® device for vaccination of healthy adults aged 18–57 years and for medically stable adults aged 60–85 years respectively.

- In the healthy adult population (aged < 60 years), ID injection of 9 µg (but not 3 µg or 6 µg) was found to be non-inferior to the standard IM dose (Leroux-Roels et al. 2008). In older people (aged 60 years or more), delivery of a more concentrated

formulation of the standard 15 µg dose stimulated improved immune responses compared with the same dose injected IM.

- Van Damme et al. (2009) used the Micronjet device (NanoPass Technologies), which is an array of four 0.45 mm microneedles mounted onto a standard syringe for ID injection. With this device, 3 µg or 6 µg per ID dose were equivalent to the standard 15 µg dose IM.

Arguably, both of these devices should have resulted in more accurate and consistent delivery of antigen than would be achieved with ID by N&S.

2.2.4. Trial populations

Most of the completed trials reviewed were conducted in healthy adults aged < 60 years. Two trials (Holland et al. 2008, Chi et al. 2008) have been conducted in older (≥ 60 years) subjects, who tend to mount lower immune responses following vaccination with standard, non-adjuvant influenza vaccines (American Geriatrics Society 2008). Chi et al. found no difference in response when 9 µg HA (i.e., 60% dose) was delivered ID or IM, but did not evaluate the 100% dose delivered ID to see if an enhanced response was seen.

Trials have also been conducted in healthy infants (Sugimura et al. 2008) and children (Chiu et al. 2007). Chiu et al. found that a 20% dose ID was equivalent to the 100% dose IM. However, in infants, two doses of a 20% dose ID was found to be superior to a 20% dose delivered SC (Sugimura et al. 2008).

It is reasonable to assume that in all the trials reviewed the subjects were already primed to influenza virus, either by natural exposure to the virus or by previous vaccination; the only exception being the trial conducted in infants (Sugimura et al. 2008) where the standard two doses of vaccine were given. Therefore, the trials with seasonal influenza vaccine might not provide a good indication of the efficiency of the ID route for priming immune responses, but rather reflect the ability of this tissue to boost pre-existing immunity. Trials with H5N1 or other avian-derived influenza vaccine strains should provide useful information on the relative ability of ID immunization to prime immune responses in naive individuals.

2.2.5. Tolerability

Local, injection-site reactogenicity, but not systemic events, were generally higher following ID versus IM/SC immunization, although reactions were generally mild and transient. It should be noted, however, that none of the influenza vaccines tested ID contained adjuvant.

2.2.6. Summary

Overall, there is a reasonable body of clinical data with seasonal influenza vaccine to suggest that:

- Reduced doses ID are non-inferior to the standard IM dose.
- Reduced doses delivered IM might be equally effective in healthy adults.
- IDD might lead to enhanced immunogenicity in the usually less-responsive older population.

2.3. Rabies vaccine

Investigation and adoption of reduced-dose IDD regimens for rabies vaccine has been driven by the high costs of the three cell-culture derived vaccines that were originally produced: PVRV (purified vero cell rabies vaccine, Verorab®, Sanofi Pasteur); PCECV (purified chick embryo cell vaccine, Rabipur®, Novartis); and HDCV (human diploid cell vaccine, Sanofi Pasteur). Cell-culture-derived vaccines are now available from other manufacturers including: Serum Institute of India (Rabivax®) and Indian Immunologicals Ltd.

Since 1991, WHO has recommended the ID route of administration for post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PREP), providing that the vaccines meet the same WHO requirements for production, control, and potency required for IM vaccines (WHO 2007). To date, WHO has recognized only a limited number of rabies vaccines and regimens as safe and efficacious for ID administration for PEP (WHO 2005), these include:

- PVRV (Sanofi Pasteur) and PCECV (Novartis) have been proven to be efficacious in the updated Thai Red Cross ID (2-2-2-0-2)[3] regimen (WHO 2005).

- HDCV (Sanofi Pasteur) and PCECV (Novartis) are considered safe and efficacious when administered according to the eight site ID (8-0-4-0-1-1) regimen.

2.3.1. Endpoints

The vast majority of the trials reviewed used virus neutralizing antibody titer as an endpoint; a concentration of 0.5 IU/ml was used as a correlate of protection (WHO 2007). Some studies also used prevention of rabies as an additional endpoint (Quiambao et al. 2005; Briggs et al. 2000; Jaiiaroensup et al. 1998).

2.3.2. Dose comparisons

The majority of trials compared a reduced-dose ID (usually 10% or 20% of the standard dose) with the standard IM dose. Because a serological correlate of protection has been defined (see above), many trials have tested reduced-dose ID schedules simply for their ability to induce antibody titers above this threshold, without running a comparator IM arm, with either the 100% or reduced dose. Data from these studies have been included in the summary in Table 4.

[3] PEP regimens are expressed in terms of the number of injections administered on days 0, 3, 7, 14, and 28. Six-dose regimens also include injection(s) on day 90.

Table 4. Summary of results from clinical trials of IDD of rabies vaccines

Trials comparing equivalent doses delivered ID vs. IM/SC				Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
4	**2**	**2**	**0**	**30**	**1**	**21**	**8**

Despite the considerable number of studies of IDD conducted, only a subset included an IM comparator arm and, of these, only four studies compared the same antigen dose given by the two routes:

- Fishbein et al. (1987): In addition to the full-dose IM, 10% and 3% of the full dose were given in the same volume either IM or ID. Although the full-dose IM induced the highest antibody titers, a 10% dose ID was significantly superior to a 10% dose IM, a 3% dose ID, or a 1% dose ID.

- Phanuphak et al. (1990): In order to assess the potential consequences of inadvertent injection of a reduced-dose SC rather than by the intended ID route, this trial evaluated the effect of two 0.1 ml immunizations given either ID (x 2), SC (x 2), or ID (x 1) plus SC (x 1) in a standard three-dose PREP schedule. There was no significant difference in the antibody levels induced by the ID (x 2) or SC (x 2) regimens, although interestingly, the ID (x 1) plus SC (x 1) regimen was significantly superior.

- Two studies by Bernard et al. (1982 and 1987) yielded slightly inconsistent data. In both cases, a full dose delivered IM was superior to reduced doses delivered ID or SC. In the first study, a reduced dose delivered ID was superior to the same reduced dose delivered SC, whereas in the second study this difference was not statistically significant. In all cases, protective levels of antibody were induced.

All the comparisons between ID and IM/SC delivery of rabies vaccines are further compromised by the fact that the ID immunizations are given in a smaller volume than IM/SC injections and in the majority of cases are given at multiple sites rather than the single site use of IM/SC.

2.3.3. Devices

Most of the rabies vaccine trials have used N&S for ID and IM administration. Some of the older studies used jet-injectors for ID delivery (Bernard et al. 1982, Bernard et al. 1987); these were not new-generation, disposable syringe (or cartridge) jet injector (DSJI) devices, however, and the authors noted that a significant proportion of the dose might have been delivered to tissue other than the dermis.

2.3.4. Trial populations and immunization regimens

Rabies vaccination is used in two temporal settings:

- PREP: used to immunize individuals at high risk of rabies, but before exposure. A number of regimens exist, but they typically consist of three doses at days 0, 7, and 28.

- PEP: administered to individuals who have been recently exposed to rabies risk. Multiple regimens exist, but all consist of vaccination on several occasions over a 90-day period.

The variety of regimens used is complicated further by the fact that three different vaccines are currently available and can be used with different regimens.

For this report, data from PREP and PEP trials, and from studies using each of the vaccine types described above, have been reviewed together.

2.3.5. Tolerability

As with seasonal influenza vaccination, local injection-site reactogenicity, but not systemic events, was generally higher following ID vs. IM/SC immunization; the reactions were generally mild and transient. HDCV, PVRV, and PCECV all contain inactivated virus particles and no adjuvant. In one study (Warrell et al. 1984), aluminum hydroxide adjuvant was added to the vaccine given SC to two of the groups; safety and tolerability were not, however, recorded in this study.

2.3.6. Summary

A large number of trials of IDD of rabies vaccines have been conducted. Interpretation is complicated by the different vaccines and the variety of regimens used for both PEP and PREP. Furthermore, the studies suffer from the common flaws of not comparing equivalent doses delivered by ID and IM/SC routes. Overall:

- The data show that reduced doses delivered using ID regimens induce protective titers and so could be considered to be at least “non-inferior” to IM.

- Only two trials suggest that ID is superior to IM when the same amounts of antigen are used (Fishbein et al. 1987, Bernard et al. 1982). Two further studies suggest that the two routes are equivalent (Phanuphak et al. 1990, Bernard et al. 1987).

2.4. Hepatitis B virus

IDD of hepatitis B vaccine has been the subject of many clinical trials (see Table 5), either with the aim of dose sparing, or in an attempt to induce enhanced immune responses in patient groups that would otherwise mount a poor immune response to the vaccine, such as patients with chronic renal disease. Analysis of the data is complicated by the fact that earlier studies used plasma-derived vaccines (PDVs) that were usually (but not always) non-adjuvanted, whereas later studies used recombinant vaccines, which usually include aluminum-salt adjuvants. The analysis and comments below include trials of PDVs and

recombinant vaccines, but do not include data from trials conducted specifically in immunocompromised patient groups.

Table 5. Summary of results from clinical trials of IDD of hepatitis B vaccines

Trials comparing equivalent doses delivered ID vs. IM/SC				**Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC**			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
6	**1**	**5**	**0**	**20**	**0**	**9**	**11**

2.4.1. Endpoints

All the trials reviewed used serological endpoints as a surrogate of efficacy. Typically, the proportion of subjects achieving the seroprotective antibody concentration of ≥10 mIU/ml, and geometric mean titers (GMTs) are reported.

2.4.2. Dose comparisons

The majority of studies have compared reduced-dose ID (either 10% or 20%) with full-dose IM/SC. Two meta-analyses of clinical trials of ID delivery of hepatitis B vaccine conducted in healthy subjects have been published relatively recently (Chen and Gluud 2005, Sangaré et al. 2009).

Chen and Gluud (2005) identified eight clinical trials that compared reduced-dose delivered ID vs. the full-dose IM/SC in health care workers. Overall, reduced-dose vaccine (1 or 2 μg/dose) delivered ID resulted in significantly more participants without protective anti-hepatitis B surface antigen (HBsAg) levels compared with high-dose (10 or 20 μg/dose) delivered by the IM route. Nevertheless, the authors commented that this route should still be evaluated in light of the potential cost savings. The ID route caused significantly more local adverse events, while the IM route caused significantly more systemic adverse events.

More recently, Sangaré et al. (2009) completed a meta-analysis of 33 clinical trials of IDD of hepatitis B vaccine. As with the Chen and Gluud (2005) analysis, ID hepatitis B vaccination was associated with a lower proportion of individuals achieving seroprotection compared with the IM/SC route. This difference was not, however, apparent in studies in school-aged children. It was also noted that females responded better to ID vaccination than males. A gender difference in antibody response (females greater than males) following vaccination by standard methods has been reported for at least 14 different vaccines, including hepatitis B vaccine (reviewed by Cook 2008), so the enhanced response in females reported by Sangaré et al. might not be specific to the ID route.

Six studies (Heijtink et al. 1989, Rahman et al. 2000, Milne et al. 1986, Ayoola et al. 1984, Coberly et al. 1994, Wahl and Hermodsson 1987) were identified that compared the same antigen dose delivered ID and IM. In all but one case (Wahl and Hermodsson 1987), the ID

route could be claimed to be equivalent but not superior to the standard IM route. Wahl and Hermodsson (1987) reported that 2 µg ID was equivalent to the full 20 µg dose IM, and superior to 2 µg SC. Interestingly, Rahman et al. (2000) delivered the full, standard 20 µg dose in 1 ml ID and IM and found that, while certain measures of CMI were enhanced following ID delivery, by the standard measure of serum antibodies the two routes were equivalent.

2.4.3. Devices

None of the studies reviewed used novel devices designed for ID delivery. In all cases, N&S were used.

2.4.4. Tolerability

As with other vaccines, injection-site reactions were more common with ID delivery. Several studies reported relatively long-lasting skin discoloration at the injection site. Although several of the studies use alum-adjuvanted recombinant hepatitis B vaccines, specific or serious adverse events due to the presence of the adjuvant were not noted. In one study (Rahman et al. 2000), a 1 ml dose containing 20 µg vaccine plus alum was delivered ID, and was reported to be well-tolerated.

2.4.5. Summary

Taken overall, the clinical data obtained with hepatitis B vaccine indicate that:

- The ID route and IM route are broadly equivalent in terms of inducing an immune response.
- Reduced doses delivered ID are less effective than the full dose delivered IM, but might still be sufficiently immunogenic to be protective.
- There is a suggestion that school-aged children and females might respond better to ID delivery, but it needs to be determined whether these differences are specifically related to the ID route.

2.5. Hepatitis A virus

There have been only three studies of IDD of hepatitis A virus vaccine (see Table 6). Two of these (Brindle et al. 1994, Carlsson et al. 1996) used alum-adjuvanted inactivated whole-virus vaccines. One study (Pancharoen et al. 2005) used a virosome formulation. None of the studies compared equivalent doses given by different routes, and all used standard N&S for IDD.

Table 6. Summary of results from clinical trials of IDD of hepatitis A vaccines

Trials comparing equivalent doses delivered ID vs. IM/SC				Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
0	**0**	**0**	**0**	**3**	**0**	**2**	**1**

Results from the three trials were inconsistent; in two cases (Carlsson et al. 1996, Pancharoen et al. 2005), reduced-dose ID induced similar immune responses to full-dose IM. However, Brindle et al. (1994) reported inferior immune responses following 1–3 doses of 0.1 ml Havrix® ID, compared with a single dose of 1.0 ml IM.

The studies with alum-adjuvanted Havrix® vaccine provide some information on potential reactogenicity issues. Brindle et al. (1994) reported short-lived injection-site tenderness as the only vaccine-related events. Carlsson et al. (1996) stated that a small local reaction resembling a mosquito bite was generally observed at the injection site, but that this could persist for several months. More severe reactions were reported in 2 out of 189 subjects.

2.6. Inactivated polio vaccine

In the 1950s, IDD was the standard route of immunization for inactivated polio vaccine (IPV) in some countries such as Denmark (Weniger and Papania 2008). Dose sparing of IPV is now of interest in order to make the vaccine more affordable and increase its use post-eradication of poliovirus, with the concomitant goal of phasing-out use of oral polio vaccine (OPV).

Three completed studies of IDD of IPV were found in the literature (Table 7), although others are underway. In two cases (Samuel et al. 1992, Samuel et al. 1991), satisfactory seroconversion rates were seen with reduced (20%) doses delivered ID, but no IM comparator arm was included. Nirmal et al. (1998) reported that two or three 0.1 ml doses ID were equivalent to two 0.5 ml doses delivered IM.

The limited data currently available, therefore, suggest that 20% doses delivered ID are likely to be non-inferior to the standard full-dose delivered IM.

Two Global Polio Eradication Initiative trials used the Biojector 2000® DSJI device to deliver a 20% dose ID compared with full-dose IM. Two different immunization schedules were tested, one in each of the two countries (Oman and Cuba) selected to run the study. Inferior seroconversion rates to each of the poliovirus types were seen when ID immunizations were given at 6, 10, and 14 weeks of age. When the vaccine was given at 2, 4, and 6 months however, the 20% dose ID resulted in >95% seroconversion to all three poliovirus types (Sutter 2008). The data from these trials have not been fully reported, and the reasons for the difference in results are unclear at this stage.

Additional WHO-sponsored studies of IDD of IPV are being initiated, including a follow-on study of the trial described above (using a Bioject device), and a trial to evaluate a single ID boost with IPV (using a PharmaJet DSJI device) following the standard OPV regimen (see Section 6.1 and Appendix 1).

Table 7. Summary of results from clinical trials of IDD of inactivated polio vaccine (IPV)

Trials comparing equivalent doses delivered ID vs. IM/SC				**Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC**			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
0	**0**	**0**	**0**	**3**	**0**	**3**	**0**

2.7. Measles

A small number of studies have been carried out to investigate IDD of measles vaccine. The rationale behind most of these was to reduce vaccine cost and simplify delivery. For these reasons, most of the trials compared SC injection with IDD by jet injector using multi-dose vials of vaccine, but not using devices from the current generation of DSJIs. Results were variable (see Table 8); in some studies (Whittle et al. 1984, Kok et al. 1983, Burland et al. 1969) reduced-doses delivered ID were equivalent to the standard SC dose. In others, this was not the case. The vaccine might not, however, have been delivered exclusively to the dermis by the older generation jet injectors; therefore, these results need to be treated with caution.

Table 8. Summary of results from clinical trials of IDD of measles vaccine

Trials comparing equivalent doses delivered ID vs. IM/SC				**Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC**			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
1	**0**	**0**	**1**	**7**	**0**	**3**	**4**

A more recent trial (Etchart et al. 2007) compared transcutaneous immunization (TCI) via a patch with SC injection. Although TCI resulted in good CMI responses and induced serum antibodies, it did not induce neutralizing antibodies in the serum and, as such, cannot be seen as a viable alternative to standard N&S delivery of measles vaccine.

2.8. Other licensed vaccines

Single studies of IDD have been conducted with other vaccines including: diphtheria-tetanus-pertussis (DTP) (Stanfield et al. 1972), tetanus toxoid (Dimache et al. 1990), yellow fever (Roukens et al. 2008), and tick-borne encephalitis (TBE) (Zoulek et al. 1986). In general, these studies are similarly designed and yielded broadly similar results to those listed above, i.e., a reduced dose (and volume) delivered ID induced a similar immune response to that seen with the standard dose delivered IM/SC (see Table 9).

Table 9. Summary of results from clinical trials of IDD of diphtheria-tetanus-pertussis (DTP), tetanus toxoid, yellow fever, and tick-borne encephalitis (TBE) vaccines

Trials comparing equivalent doses delivered ID vs. IM/SC				**Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC**			
Total	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	**Total**	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC
1	**1**	**0**	**0**	**3**	**0**	**3**	**0**

Two papers (Zoulek et al. 1984 and 1986), possibly describing the same trial with TBE vaccine, compared ID and SC delivery of the same antigen dose of the vaccine, although the TBE vaccine was split between four sites. In this case, a more rapid immune response was seen; however, it is not clear whether this is a consequence of delivering the antigen to four sites or of the ID route of delivery.

A Phase I trial is underway at the Chinese University of Hong Kong to evaluate the safety and immunogenicity of ID administration of two human papillomavirus (HPV) vaccines: Gardasil® (Merck) and Cervarix® (GlaxoSmithKline [GSK]) (Prince of Wales Hospital 2005). The standard (full) dose IM will be compared with a reduced (20%) dose delivered IM, ID by N&S, or ID by DSJI (PharmaJet). To date, a pilot reactogenicity study has been completed, but no immunogenicity data are available (see Appendix 1).[4]

[4] Tony Nelson, Chinese University of Hong Kong, oral communication.

2.9. Summary of data from IDD clinical trials

A summary of all of the above data is presented in Table 10. The limitations of the data and overall conclusions that can be drawn are discussed in Section 4.

Table 10. Summary of results from all IDD clinical trials reviewed for licensed vaccines

Vaccine	Trials comparing equivalent doses delivered ID vs. IM/SC			Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC			Number of trials
	ID **superior** to IM/SC	ID **equivalent** to IM/SC	ID **inferior** to IM/SC	RD ID **superior** to FD IM/SC	RD ID **equivalent** to FD IM/SC	RD ID **inferior** to FD IM/SC	
Influenza (seasonal)	**2**	**3**	**0**	**0**	**7**	**1**	**13**
Rabies	**2**	**2**	**0**	**1**	**21**	**8**	**34**
Hepatitis B	**1**	**5**	**0**	**0**	**9**	**11**	**26**
Hepatitis A	**0**	**0**	**0**	**0**	**2**	**1**	**3**
Polio (IPV)	**0**	**0**	**0**	**0**	**3**	**0**	**3**
Measles	**0**	**0**	**1**	**0**	**3**	**4**	**8**
YF[a], TBE, DTP, TT	**1**	**0**	**0**	**0**	**3**	**0**	**4**
TOTAL	**6**	**10**	**1**	**1**	**48**	**25**	**91**

a. YF, yellow fever; TBE, tick-borne encephalitis; DTP, diphtheria-tetanus-pertussis; TT, tetanus toxoid.

3. Evidence from clinical trials of vaccines in development

Clinical trials involving IDD have been completed for a number of novel vaccines or novel formulations of vaccines, including: enterotoxigenic *E. coli* (ETEC), hepatitis C virus, HIV, influenza (seasonal and pandemic), malaria, Rift valley fever, and TB. IDD is also being actively explored as a route for delivering certain vaccine platform technologies, such as DNA vaccines, live-virus vectors, and heterologous prime-boost strategies.

Delivery to the dermis (or possibly epidermis) might be the most appropriate route for some of these new vaccines and vaccine types due to their formulations. Also, there are major benefits in considering route of delivery early in the development of a vaccine. In most cases, however, it is hard to draw conclusions as to whether IDD is a superior route compared with conventional IM/SC in terms of dose sparing for novel vaccines, because:

- Many of the early-phase clinical trials of novel vaccines do not compare delivering the vaccine by different routes.
- For many of the vaccines (e.g., malaria, HIV) the correlates of protection are poorly understood, so it is difficult to determine whether IDD of the vaccine induced an adequate or protective immune response.

Nevertheless, some of the studies of novel vaccines add to the body of knowledge obtained from IDD of licensed vaccines.

3.1. Enterotoxigenic *E. coli*

Two clinical trials have been completed using transcutaneous patches to deliver the heat-labile toxin (LT) from ETEC. Neither study included comparison with other routes of delivery.

Transcutaneous immunization (TCI) with LT failed to protect individuals from disease in a challenge study, although disease severity was reduced (McKenzie et al. 2007). In a field trial conducted in travelers, TCI with LT reduced the incidence and duration of travelers' diarrhea in a Phase II trial, although the study was not powered to demonstrate efficacy (Frech et al. 2008).

LT and cholera toxin appear to be unusual in that they can be delivered by TCI, possibly because they are potent immune-stimulators with intrinsic adjuvant properties. Therefore, it is possible that these two proteins (or vaccines composed of other proteins fused to LT or cholera toxin) might be the only subunit vaccines suitable for administration by this method.

3.2. Hepatitis C

A small Phase I trial of virus-like particles (VLPs) composed of the E1 protein from hepatitis C found that ID delivery of a 20% dose of non-adjuvanted VLPs was inferior in terms of antibody production compared with levels seen in an earlier study of alum-adjuvanted VLPs delivered IM (Leroux-Roels et al. 2005). This vaccine is no longer being developed.

Intercell is developing a therapeutic vaccine for the treatment of hepatitis C virus infections, which consists of eight T-cell epitopes combined with a proprietary poly-arginine adjuvant (IC30®). The vaccine is delivered ID and interim results from a Phase II trial suggested that the vaccine induced a small but significant decrease in viral load (Intercell 2007). This vaccine is unlikely to be useful as a prophylactic vaccine and/or for use in LMICs. Overall, there are too few data to draw any conclusions regarding whether future hepatitis C vaccines will be suitable for IDD. However, the fact that the novel adjuvant appeared to be well-tolerated suggests that it might be suitable for use with other vaccines delivered ID.

3.3. Influenza (seasonal)

Seasonal influenza vaccine has been formulated and spray-dried to enable needle-free dry-powder jet injection into the epidermis (as epidermal powder injection). Delivery of a standard dose of trivalent inactivated influenza vaccine by this method was equivalent in terms of immunogenicity to IM/SC delivery by N&S (Dean and Chen 2004). This approach was originally developed by Powderject Ltd and was more recently pursued by Iaculor Injection Inc.[5] It is not known whether this technology is now being actively developed.

DNA vaccination for seasonal influenza was also investigated by Powderject and more recently PowderMed (acquired by Pfizer in 2006) (PowderMed 2009). An initial Phase I trial with a monovalent HA-based vaccine (consisting of DNA-coated gold particles) delivered by jet injection into the epidermis found the vaccine induced similar antibody titers to standard inactivated flu vaccines, but the kinetics of the immune response were slower (Drape et al. 2006). A recently published clinical study (Jones et al. 2009) tested epidermal delivery of a trivalent DNA vaccine and included a challenge with a single strain of influenza. The vaccine induced “modest antibody responses” to two of the three strains but will require further development before it meets CHMP criteria. It is not known if this vaccine or technology is still in active development.

Thus, there is no good evidence to suggest that novel formulations of influenza vaccine are being actively developed that are likely to be more appropriate for IDD than the currently licensed vaccine formulations (Section 2.2).

3.4. Influenza (pandemic)

Despite the interest in, and data from, trials using ID devices for delivery of seasonal flu vaccine discussed above (Holland et al. 2008, Leroux-Roels et al. 2008, Van Damme et al. 2009) and concerns about the global under-capacity for manufacturing pandemic influenza vaccines, IDD data are only available from a single study of a pandemic influenza vaccine (Patel et al. 2009). This study used a non-adjuvanted, split H5N1 vaccine formulation that is relatively non-immunogenic compared with similar-formulation seasonal flu vaccines. The trial compared 3 or 9 µg ID with 15 or 45 µg IM. There was some evidence for only modest dose sparing by ID delivery; 45 µg IM induced the best antibody responses, with 9 µg ID inducing similar responses to 15 µg IM. Therefore, it is too early to state whether IDD will be beneficial for pandemic influenza vaccines.

[5] See profile: http://investing.businessweek.com/research/stocks/private/snapshot.asp?privcapId=27827289.

3.5. Rift valley fever

ID delivery of a 0.1 ml booster dose of an unlicensed, experimental formalin-inactivated Rift-valley fever vaccine in subjects who had completed a three-dose primary vaccination course was found to be equivalent to a 1 ml SC booster dose and superior to a 0.1 ml SC booster dose (Kark et al. 1985). It is not known whether there are plans to develop this vaccine further.

3.6. DNA vaccines and heterologous prime-boost vaccinations

IM injection of naked DNA vaccines has proved to be inefficient in the clinic due in part, to the low numbers of cells that are actually transfected by the plasmid. To overcome this hurdle, investigators have used delivery methods that a) target tissues richer in APCs, namely the dermis and epidermis, and b) use particulate formulations that promote DNA-uptake by APC (Fuller et al. 2006). These approaches have resulted in induction of immune responses with 100- to 1000-fold lower doses of DNA than used for IM delivery when tested in preclinical models. Results to date from DNA vaccines in clinical trials have, however, continued to be disappointing, failing to live up to the promise of preclinical data. Nevertheless, devices or approaches that improve the intracellular delivery of DNA vaccines could still lead to enhanced immunogenicity.

Results from published studies that have compared IM and ID DNA delivery have not always found IDD to be more effective (Launay et al. 2007). In this case, DNA was delivered in a lipopeptide formulation.

It seems likely that ID will remain the delivery route of choice for DNA vaccines, but other issues including optimizing transfection efficiency, incorporation of adjuvants, and the formulation of the vaccine need to be resolved.

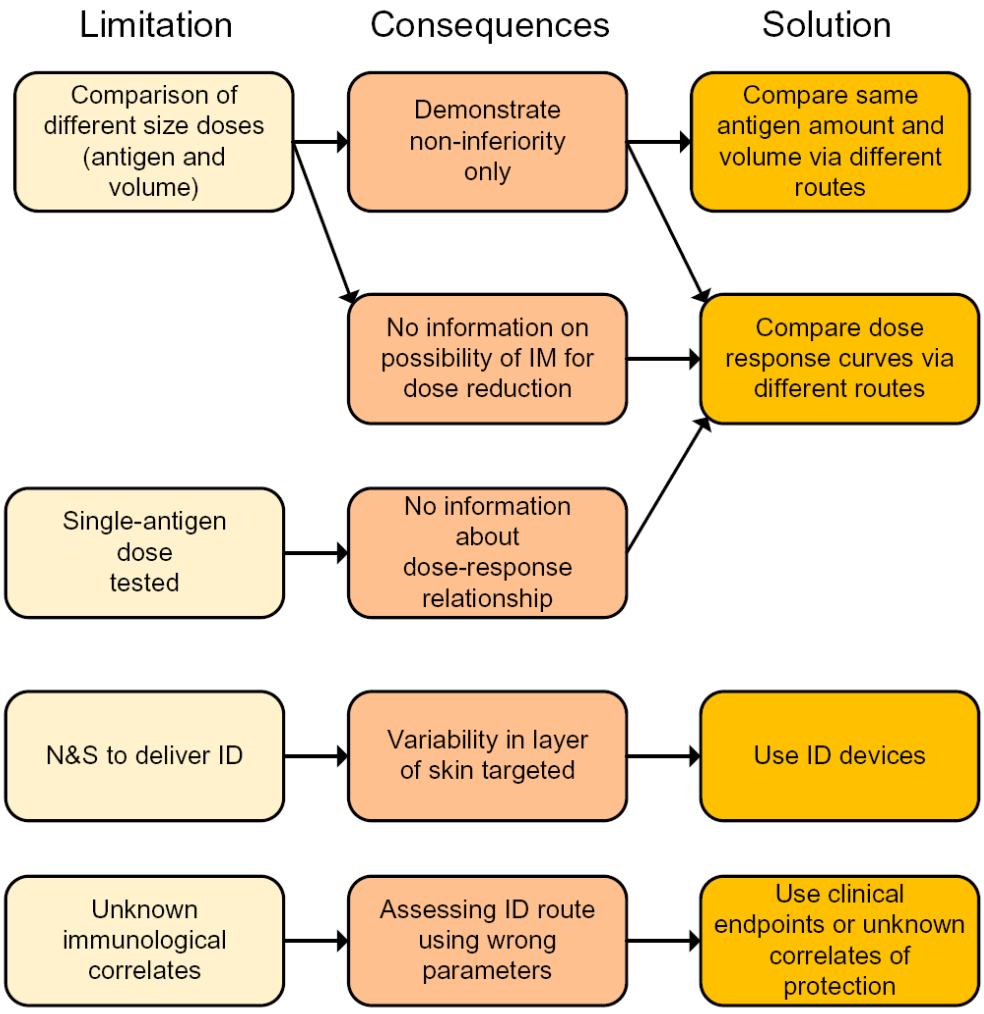
Heterologous prime-boost regimens in which priming (generally with DNA vaccines) is followed by booster immunizations of recombinant protein or a live virus vector encoding the gene of interest are also being investigated (e.g., for malaria and TB). The DNA component is often delivered ID; the boost might be delivered IM or ID depending on the type of vaccine or formulation. Few clinical studies have been completed comparing ID vs. IM for either or both of the components of the regimen. Bansal et al. (2008) delivered DNA encoding HIV proteins ID or IM followed by an IM protein boost, and found that ID was equivalent or inferior to IM for DNA vaccination.

It should also be noted that, from the data available to date, DNA vaccines are seen as being more appropriate for induction of cell-mediated rather than antibody responses. As such, these vaccines are likely to be most appropriate for infections such as HIV, TB, and persistent virus infections. Most of the trials of DNA vaccines and heterologous prime-boost regimens use measures of CMI as read-outs; these are suspected, but have not been shown, to be correlated with protection in the various diseases under investigation.

4. Limitations of the data from clinical trials

It is difficult to draw firm conclusions regarding the dose-sparing potential of IDD from the existing clinical trial data due to limitations in the design of the majority of studies. These are discussed below and summarized in Figure 3.

Figure 3. Summary of some of the limitations of existing clinical trials using IDD and possible solutions to be considered for future studies.



4.1. Comparison of antigen doses delivered

The majority of studies investigating IDD for dose sparing have compared a reduced dose (typically 10% or 20% of standard) with the full dose delivered by the standard IM/SC route, usually because it is convenient to reduce the standard 1 ml or 0.5 ml IM dose to 0.1 ml ID. An exception is seasonal influenza, where a wider range of doses has been tested. In the trials of licensed vaccines reviewed for this report, only 17 of 91 trials (19%) compared equivalent doses (in terms of antigen amount) in some part of the protocol.

Demonstration of a satisfactory or equivalent immune response following IDD of a reduced dose of vaccine indicates “non-inferiority” compared with IM/SC. This might still be

considered to be sufficient evidence to support further development of IDD for the vaccine in question and use of IDD devices. Data of this type, however, do not demonstrate that the dermis is an immunologically superior target for vaccine delivery compared with muscle or SC tissue. Results from trials of this type still leave open the possibility that similar dose-sparing benefits might also be achievable with IM/SC delivery.

4.2. Comparison of volumes of vaccine delivered

In the few cases where equivalent antigen doses are compared ID vs. IM/SC, it is very rare for equivalent volumes of vaccine to be delivered by the two routes. It is theoretically possible that delivery of the same antigen content in a smaller volume will be more efficiently captured and processed by APCs, resulting in an improved immune response. There are no published data to indicate how significant this effect might be.

4.3. Consistency of administration using IDD

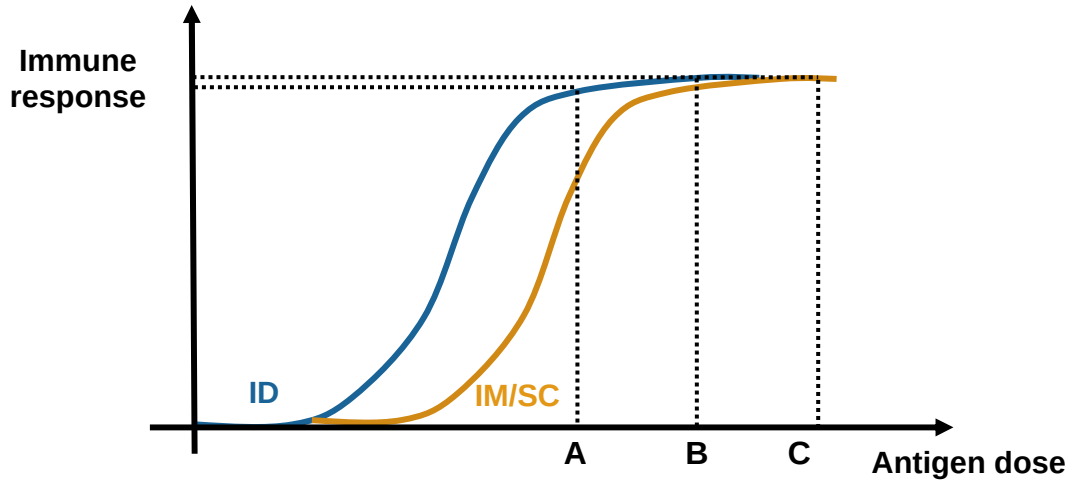
Nearly all of the studies of IDD of vaccines have used standard or tuberculin N&S and the Mantoux technique for ID immunizations; this is a technique that is generally regarded as being technically difficult and requiring training and practice to perform reliably (Weniger and Papania 2008). Although some studies (Chiu et al. 2007) have stated that a single individual administered all ID injections in order to overcome operator variability, it should be assumed that failure to achieve reliable, reproducible delivery of vaccine to the dermis is a potential problem in many other studies using N&S.

For this reason, more recent trials in which novel devices developed for IDD have been used might provide relevant and more-robust data (Van Damme et al. 2009, Leroux-Roels et al. 2008, Holland et al. 2008). Some earlier trials used jet injectors (DermaJet® and Medi-jector®) to deliver ID doses; however, it cannot be assumed that these older devices delivered all or most of the dose to the dermis. In at least one study, the investigators felt that the majority of the dose was delivered SC rather than ID (Bernard et al. 1982).

4.4. Dose-response relationships

Very few clinical trials have compared the same range of doses delivered ID and IM, and those that have found that there is often only a slight dose-response effect (Belshe et al. 2007), suggesting that the standard amount of antigen delivered is toward the top of the dose-response curve (see Figure 4). Similar results have been reported for Haemophilus influenzae type B (Hib) vaccine, either alone or in combination with DTP (Fernandez et al. 2000). In this case, reduced doses of 50% or 33% of the standard dose still resulted in equivalent seroprotection and antibody titers. Thus, there might be several vaccines for which reduced or fractional doses could be used, either IM or ID, without inducing a significant impact on immune response (Figure 4).

Figure 4. Schematic representation of vaccine dose-response relationships, illustrating the impact of comparing doses taken from different regions on the dose-response curves.



Comparing dose B (IM) with "reduced dose" A (ID) would suggest a non-inferior ID response. The same outcome would result from comparing dose C (IM/SC) with "reduced dose" B (ID). These scenarios reflect the type of design used in the majority of trials performed to date. If the reduced dose is delivered IM/SC as well as ID, then it is possible to determine whether only the ID route offers dose sparing (e.g., A vs. B) or whether dose sparing could also be obtained with IM/SC injection (e.g., B vs. C).

4.5. Immunological readouts and correlates of protection

The majority of clinical trials have used immunological rather than clinical endpoints as measures of vaccine efficacy. In most cases, such as for influenza, rabies, and hepatitis B vaccines, this is a reasonable approach; serological correlates of protection have been defined and accepted for these well-established vaccines and, in most cases, standardized assays exist. For novel vaccines, particularly DNA and other vaccines designed to act primarily via CMI, the exact immune parameters that are responsible for protection have not been defined, and assays are usually not standardized.

4.6. Overall conclusions from clinical data

1. The results from a small number of "appropriately-designed" studies are encouraging and suggest that IDD might be more efficient or more immunogenic than IM/SC. However, the majority of IDD trials performed to date have not been designed in a way that allows firm conclusions to be drawn regarding whether the dermis and epidermis are immunologically superior to muscle or subcutaneous tissue.

2. IDD of reduced doses (typically 10% or 20% of the standard IM/SC dose) for some vaccines (such as influenza, rabies, and IPV) can result in the induction of satisfactory, protective immune responses. Further trials are needed to define more precisely the amount of antigen needed for IDD to induce a non-inferior, reliably protective immune response.

3. It is also possible that additional, more appropriately-designed trials would show that reduced doses could be delivered IM and still induce satisfactory immune responses; this might entail less product development than IDD.

4. IDD of vaccines, with or without licensed adjuvants, is generally associated with increased local reactogenicity at the injection site. To date, these reactions appear to be mild and often (but not always) transient.

5. Additional appropriately-designed trials are needed to address points 1–4.

6. The majority of the studies analyzed suggest that a reduced-dose ID is “non-inferior” to the standard dose IM/SC dose. Therefore, the potential for dose sparing exists and the development of novel devices for ID (or IM) delivery that could also yield additional benefits is warranted.

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

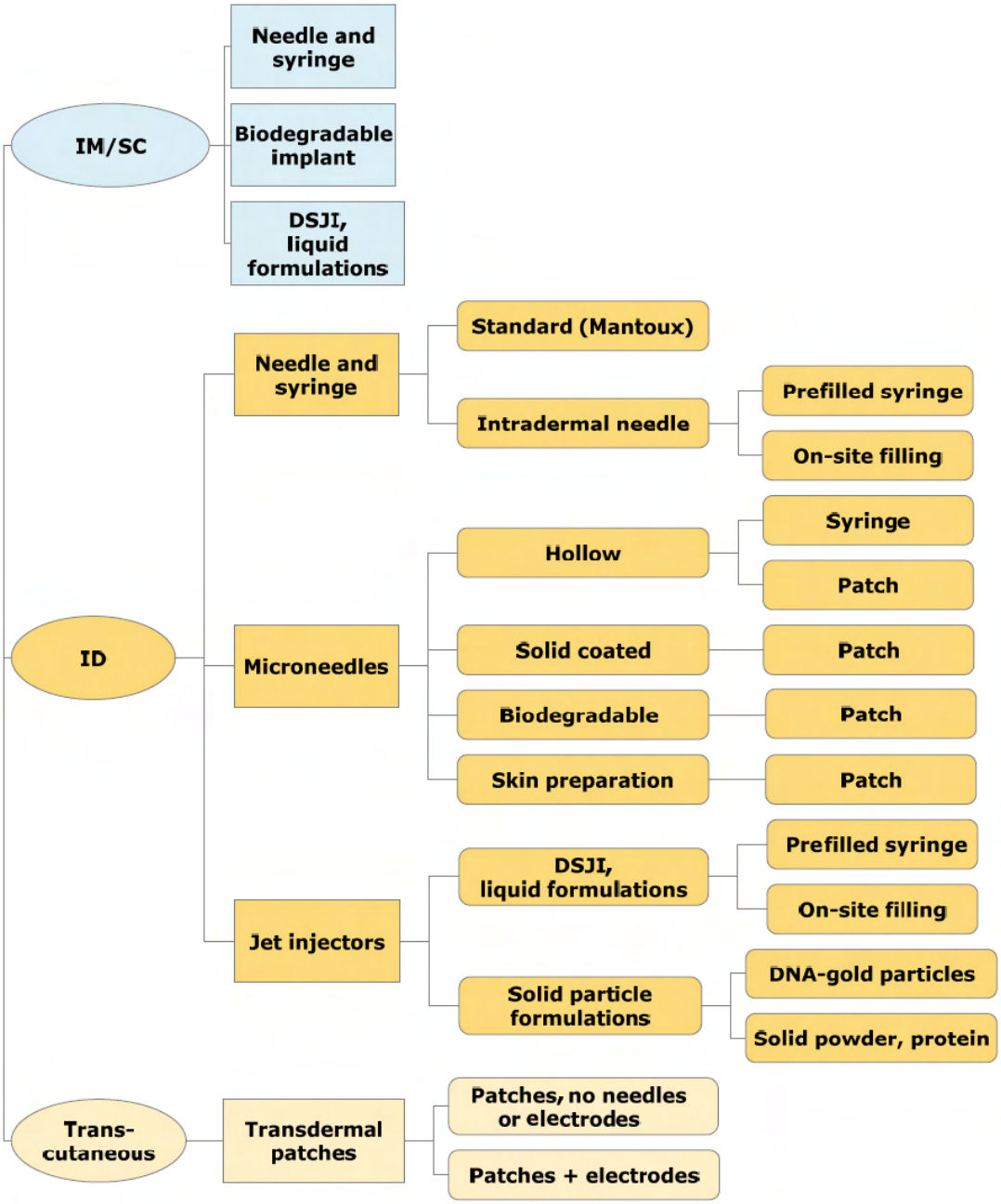
Some novel adjuvants have the same or similar immune-enhancing effects in animal models and humans. Others do not, and preclinical animal models (particularly inbred mice) are not always predictive of adjuvant effects in the clinic. This is of increasing importance as rationally designed adjuvants that 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.

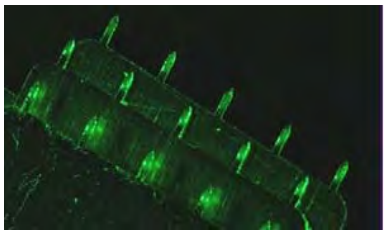
[13] Mark Prausnitz, Georgia Institute of Technology, oral communication, February 20, 2009. James Birchall, oral communication, March 17, 2009. Mark Kendall, Universtiy of Queensland, oral communication, March 18, 2009.

[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

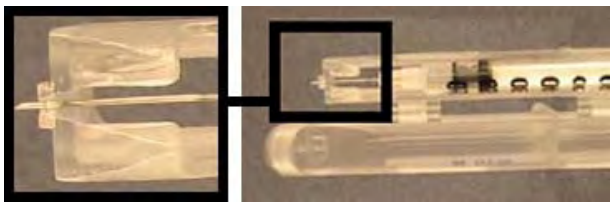
Strengths	Weaknesses
▪ Simple to use. ▪ Compatible with existing (or more concentrated) formulations of vaccines. ▪ Leading device is manufactured at scale and is commercially available.	▪ ID needles will still have the potential to transmit blood-borne pathogens. ▪ Some versions are prefilled and therefore 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.

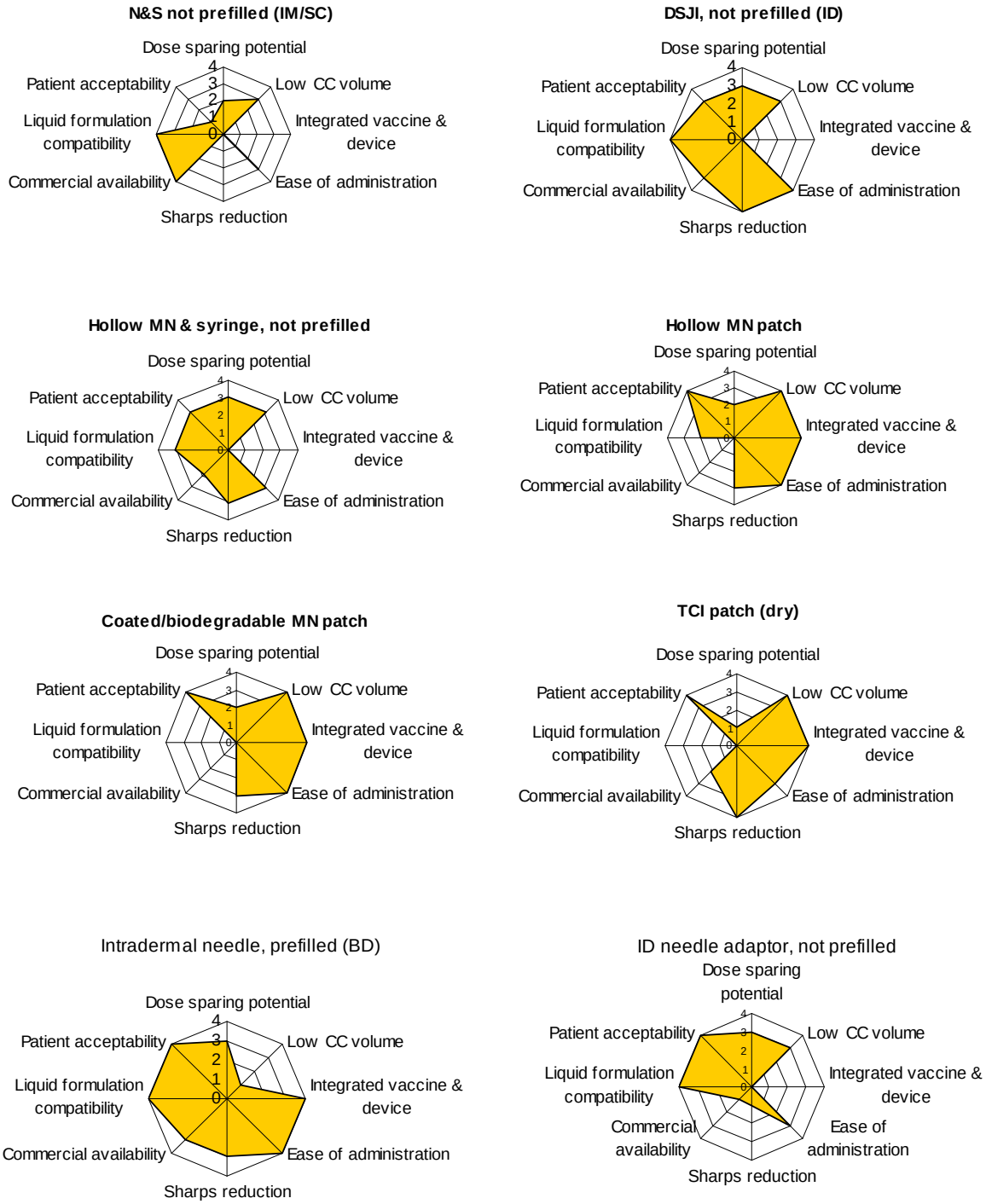
Table 15. Key attributes used for comparison of IDD devices (PATH unpublished data 2009)[31]

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.



7. Selection of vaccines for IDD

When assessing which vaccines might be suitable for IDD, the technical feasibility of (re)formulating a vaccine to be compatible with IDD and the device to be used needs to be considered in addition to the potential benefits that might be provided by IDD.

The following sections present some proposals or suggestions for which vaccines might be appropriate for IDD based on vaccine type, formulation issues, and prior experience. It should be noted, however, that at this stage the amount and quality of data to support some of the classifications used are very limited. The results of this analysis are, therefore, presented more as a starting point for discussion and as an attempt to identify gaps in knowledge, rather than as definitive recommendations.

7.1. Suitability of vaccine types and formulations for IDD devices

The compatibility of existing and novel vaccines with IDD devices will be a function of the vaccine type and formulation. Table 16 presents the compatibility of each of the IDD device types being considered, along with various generic vaccine types, and highlights any key formulation requirements or limitations imposed by the devices.

DSJIs used for SC/IM delivery have been included for comparison, and because they could confer some of the benefits associated with other ID devices.

Table 16. Summary of vaccine type and formulation requirements for various IDD and other devices

Route	SC/IM	IDD				Transcutaneous
Type of device	**DSJI (SC/IM use)**	**DSJI (ID use)**	**ID needle**	**Hollow microneedle (syringe or patch)**	**Solid microneedle (coated or biodegradable needles)**	**Transcutaneous patch (needle-free)**
Formulation requirement	Liquid.[b]	Liquid.[b]	Liquid.[b]	Liquid.[b]	Dry (coated onto or formed into needles).	Liquid or dry.
Vaccine type						
Subunit /inactivated whole organism	OK.	OK, some might need ID adjuvant.	OK, some might need ID adjuvant.	OK, some might need ID adjuvant.	OK, some might need ID adjuvant.	OK for a limited range of vaccines.
Live	OK.	OK, risk of	OK, risk of	OK, risk of	OK, risk of shedding[32]	OK, risk of shedding (stable,

[32] Preclinical studies have not detected inadvertent shedding from solid coated microneedles to date, according to Mark Kendall, oral communication, June 3, 2009.

Route	SC/IM	IDD				Transcutaneous
Type of device	**DSJI (SC/IM use)**	**DSJI (ID use)**	**ID needle**	**Hollow microneedle (syringe or patch)**	**Solid microneedle (coated or biodegradable needles)**	**Transcutaneous patch (needle-free)**
attenuated[a]		shedding.	shedding.	shedding.	(stable, viable dry formulation might be difficult).	viable dry formulation might be difficult).
Polysaccharide -protein conjugate	OK.	Possibly OK, might require re-formulation.[33]	Possibly OK, might require re-formulation.[33]	Possibly OK, might require re-formulation.[33]	Possibly OK, (might be difficult to achieve a dry immunogenic formulation).	Possibly OK, (likely to need potent ID adjuvant).
DNA	OK.	OK.	OK.	OK.	OK.	OK.
Adjuvant						
Alum	OK.	Possibly OK, might be too reactogenic.	Possibly OK, might be too reactogenic.	Possibly OK, might be too reactogenic.	Possibly OK, might be too reactogenic.	Possibly OK, might be too reactogenic (poor diffusion across skin likely).
Oil in water	OK.	Possibly OK; might be too reactogenic.	Possibly OK; might be too reactogenic.	Possibly OK; might be too reactogenic.	No (can't dry adjuvant).	Possibly OK; for liquid-compatible devices (might be too reactogenic).

a. Live attenuated virus or bacteria, including live-virus vectors (e.g., vaccinia virus, modified vaccinia Ankara, adenovirus).
b. Assumes that preservatives and other excipients that are currently in liquid vaccines will be compatible with DSJIs.
Note: DSJI, disposable syringe jet injector; IDD, intradermal delivery; IM, intramuscular; SC, subcutaneous.

Several key points can be made from the information in Table 16:

7.1.1. Adjuvants

Adjuvants are a critical formulation issue for IDD. Many subunit and non-live vaccines are likely to require an adjuvant in order to be sufficiently immunogenic, even when delivered by the ID route, although currently there are few data to demonstrate this formally.

There is a concern that existing aluminum-salt and oil-in-water adjuvants will be too reactogenic when administered ID. Long-term injection-site reactions have been reported in some (but not all) clinical trials that have delivered alum-adjuvanted vaccines ID (see Section

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

2), but these have not been described as severe adverse events or led to the withdrawal of subjects from studies.

The presence of adjuvants also imposes constraints that could limit the use of some IDD devices, for example:

- Alum adjuvants can lead to clogging of smaller bore diameter hollow microneedles.
- Although some drying processes, such as spray-drying, can be applied successfully to alum-containing vaccines, this might not apply to all drying techniques. Unpublished data from at least one investigator suggests that at least some adjuvant-vaccine combinations can be dried onto coated microneedles.[34]
- Oil-in-water adjuvants such as MF59® (Chiron) and the AS adjuvant series (GSK) will not be compatible with dried formulations.

Although subunit and inactivated whole-virus/bacteria vaccines have been treated as a single category in this part of this report, it is possible that there will be differences within this grouping in terms of whether an adjuvant is required.

Some inactivated whole-organism vaccines, such as rabies and influenza vaccines, do not require adjuvants when delivered either IM/SC or ID. This superior immunogenicity, compared with most subunit vaccines, might be due to the presence of TLR-agonists (which stimulate innate immune responses) derived from the virus or bacterium in the vaccine, as has been suggested for influenza (Geeraedts et al. 2008). But, if IDD is to be used with a range of subunit and inactivated vaccines, it is highly likely that novel adjuvants developed for ID use will need to be developed; this can be a lengthy and expensive process.

7.1.2. Live attenuated vaccines

Live-attenuated vaccines might be suited to IDD, in that they are unlikely to require an adjuvant; however:

- Development of stable, liquid formulations (where needed) is likely to be difficult.
- There are concerns that transcutaneous or IDD methods might leave residual vaccine on the surface of the skin, which could be inadvertently transmitted to a person who comes into contact with recently-vaccinated individuals. The significance of this risk will need to be assessed for each attenuated vaccine.

7.1.3. DNA vaccines

In theory, DNA vaccines have the advantage of being potentially compatible with most or all of the IDD device types; however, further improvements in the immunogenicity of DNA vaccines are needed before they are likely to have wide applicability. These might include the addition of adjuvants, intracellular targeting, and/or use of novel particulate formulations to enhance uptake by APCs.

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

7.1.4. Use of disposable syringe jet injectors for IM/SC delivery

From Table 16, it is apparent that continuing to use the IM/SC route but with a needle-free DSJI device has the fewest restrictions in terms of formulation and vaccine compatibility. Thus, this approach could achieve several of the benefits associated with IDD in terms of reduced sharps-use and possible dose sparing in a shorter time-frame with less expense and at less risk because extensive reformulation work would not be needed.

7.2. Drivers for switching to IDD

To warrant the investment required, a change to IDD must offer significant benefits over the status quo in terms of several key drivers. As already discussed, the main potential benefits that might follow from IDD delivery of vaccines include:

- **Reduced costs**, resulting from administration of reduced doses.
- **Improved access/supply** of vaccines for which there is limited manufacturing capacity.
- **Improved cold-chain capacity and lower transport and storage costs**, by reducing storage volume of vaccines.
- **Improved safety,** by reducing sharps usage.

Some of these benefits are not exclusive to IDD and could also be obtained if dose sparing could be shown to be possible using the IM/SC route.

7.3. Identification of vaccines for IDD

A simple analysis of which of a limited range of existing and future vaccines might be technically most feasible for the main classes of IDD device (orange circles) and their possible ranking in terms of cost and availability (red circles) has been undertaken (Table 17); IM/SC delivery with DSJI has been included for comparison with IDD by DSJI. TCI patches have also been included.

Table 17. IDD drivers and suitability of IDD devices for use with existing and future vaccines

Vaccine[b]	Vaccine type	Liq/ lyo[35]	Adju-vant	Cost[c]	Limited supply[d]	Predicted compatibility of vaccine with device[a]						
						DSJI (IM/SC)	DSJI (ID)	ID micro-injector or adaptor	Hollow MN syringe	Hollow MN patch	Solid MN (coated/ degrade-able)	Transcutan-eous patch (needle-free)
Dengue (future)	Live recomb virus.	Lyo.	No.			●	◕	◕	◕	○	◑	◔
DTP-HepB-Hib	Inactivated.	Liq.	Al.	◑	○	●	◔	◔	◔	◔	◔	○
ETEC	Inactivated (LT toxin).	Patch.	No.			○	○	○	○	○	○	◕
Influenza (pandemic)	Inactivated split/ recomb.	Liq.	Al.	◑	●	●	◑	◑	◑	◑	◔	○
	Inactivated split/ recomb.	Liq.	Oil in water.	◑	●	●	◑	◑	◑	◑	○	○
	Inactivated whole-virion.	Liq.	No.	◑	●	●	●	●	●	●	◔	○

[35] Working in Tandem for Project Optimize 2008

Vaccine[b]	Vaccine type	Liq/ lyo[35]	Adju-vant	Cost[c]	Limited supply[d]	Predicted compatibility of vaccine with device[a]						
						DSJI (IM/SC)	DSJI (ID)	ID micro-injector or adaptor	Hollow MN syringe	Hollow MN patch	Solid MN (coated/ degrade-able)	Transcutan-eous patch (needle-free)
Influenza (seasonal)	Inactivated split/ recomb.	Liq.	No.	◑	●	●	●	●	●	●	◕	○
Hepatitis B	Inactivated protein subunit.	Liq.	Al.	○	○	●	◑	◑	◑	◑	◔	○
HPV	Inactivated VLP.	Liq.	Al.[b]	●	●	●	◑	◑	◑	◑	◔	○
Japanese encephalitis	Inactivated.	Liq.	Al.	◑	◑	●	◑	◑	◑	◑	◔	○
	Live-attenuated.	Lyo.	No.			●	◕	◕	◕	○	◑	◔
Malaria	Recomb. protein (RTS,S).	Lyo.	Oil-in-water.			●	◑	◑	◑	○	○	○
Measles	Live attenuated.	Lyo.	No.	○	○	●	◕	◕	◕	○	◑	◔
Meningitis mono-valent (conjugated)	Inactivated PS.	Lyo.	Al.	○	●	●	◑	◑	◑	○	◔	○

Vaccine[b]	Vaccine type	Liq/ lyo[35]	Adju-vant	Cost[c]	Limited supply[d]	Predicted compatibility of vaccine with device[a]						
						DSJI (IM/SC)	DSJI (ID)	ID micro-injector or adaptor	Hollow MN syringe	Hollow MN patch	Solid MN (coated/ degrade-able)	Transcutan-eous patch (needle-free)
Meningitis multivalent (conjugated)[e]	Inactivated PS.	Liq.	Al.	●	●	●	◑	◑	◑	◑	◔	○
Measles-mumps-rubella	Live-attenuated.	Lyo.	No.	○	○	●	◕	◕	◕	○	◑	◔
Pneumococcal multivalent	Inactivated PS.	Liq.	Al.	◑	●	●	◑	◑	◑	◑	◔	○
Polio (IPV)	Inactivated whole virion.	Liq.	No.	◑	●	●	●	●	●	●	◔	○
Rabies	Inactivated whole virion.	Lyo.	No.	●	●	●	●	●	●	○	◔	○
Salmonella typhi	Inactivated PS.	Liq.	No.	○	○	●	◑	◑	◑	◑	◑	○
TB (current, BCG)	Live-attenuated myco-bacterium.	Lyo.	No.	○	○	○	●	●	●	○	◑	◔
TB (future)	Live-recomb. myco-bacterium.	Lyo.	No.			○	●	●	●	○	◑	◔

Vaccine[b]	Vaccine type	Liq/ lyo[35]	Adju-vant	Cost[c]	Limited supply[d]	Predicted compatibility of vaccine with device[a]						
						DSJI (IM/SC)	DSJI (ID)	ID micro-injector or adaptor	Hollow MN syringe	Hollow MN patch	Solid MN (coated/ degrade-able)	Transcutan-eous patch (needle-free)
	Live recomb. virus vector.	Lyo.	No.			●	◕	◕	◕	○	◑	◔
Tetanus	Inactivated toxoid.	Liq.	Al.	○	○	●	◑	◑	◑	◑	◔	○
Yellow fever	Live attenuated.	Lyo.	No.	○	●	●	◕	◕	◕	○	◑	◔

Abbreviations: Al, aluminum-salt adjuvant; BCG, Bacille Calmette Guérin; DSJI, disposable syringe jet injector; DTP, diphtheria-tetanus-pertussis; ETEC, enterotoxigenic *E. coli;* HPV, human papillomavirus, IM, intramuscular, IPV, inactivated polio vaccine; liq, liquid; lyo, lyophilized; LT, heat-labile toxin; MN, microneedle; PS, polysaccharide; recomb, recombinant; SC, subcutaneous; TB, tuberculosis; VLP, virus-like particle.

Notes:
a. Compatibility with device: circles represent the suitability of the existing formulation for use with the device. Solid circles: good match between device and vaccine, minimal reformulation required, and high likelihood of success. Open circles: poor match between device and vaccine, significant reformulation required, and might be small likelihood of success.
b. Vaccine formulations currently delivered or likely to be delivered orally have been excluded from this list (e.g., cholera, shigella, rotavirus, OPV, ETEC). Live attenuated influenza viruses are not considered because they are administered intra-nasally. For simplicity, only alum-adjuvanted HPV vaccine is considered; an oil-in-water adjuvanted formulation (Cervarix®, GSK) also exists, but would be less compatible with “dry” solid microneedle formats. DNA vaccines are considered as a generic vaccine type in Table 16.
c. Vaccine cost: Solid circles= high cost, open circles= low cost. Data from PATH internal documents (PATH, unpublished data).
d. Limited supply: solid circles= supply constraints, open circles= no supply constraints. Data from PATH vaccine development framework (PATH, unpublished data).
e. Men monovalent refers to any single-valent meningitis PS conjugate vaccine, e.g., menA, menC, etc.

7.3.1. Limitations of this analysis

The relatively simple analysis presented in Table 17 has several limitations, including:

- Only the costs and limitations in vaccine supply have been used as potential drivers or needs that might be addressed by dose-reduction achieved by IDD. Costs and supply constraints have not been included for "future" vaccines because these are difficult to predict. The appropriateness of each device type for the potential delivery scenarios (campaign versus routine, level of training of health worker, etc.) for each vaccine type have also not been analyzed.

- At this stage, reducing volumes in the cold chain has not been included, due to a lack of data about current and future storage volumes for many of the vaccines and devices.

- The relative benefits of improving safety by reducing sharps use and also by reducing the amount of waste for each vaccine has not been assessed at this stage.

7.3.2. Vaccines to be considered for prioritization for studies of IDD

By this simple analysis, there are six vaccines with high purchase costs and/or that are subject to periodic or continuous supply constraints (denoted with red circles in Table 17). There are, therefore, potential benefits to be gained if dose sparing could be achieved with these vaccines and so, on these grounds, IDD of these existing vaccines could be considered as a priority, along with IDD of new vaccines. The issues associated with IDD of these vaccines are discussed below and in the Conclusions section (Section 8).

7.3.2.1. Human papillomavirus

The high cost and limited supply of HPV vaccines are presumably due to the relative newness of these vaccines and the fact that currently they are produced by only two suppliers: Merck and GSK.

The key issues with HPV VLP vaccines relating to IDD are likely to be adjuvant related. The vaccines are adjuvanted with either alum (Gardasil®, Merck, a 4-valent vaccine) or AS04, an oil-in-water adjuvant also containing alum (Cervarix®, GSK, a 2-valent vaccine). It is possible that either or both of these adjuvants will be too reactogenic for ID use and might, therefore, need to be replaced if used ID. The AS04® adjuvant will not be compatible with devices that require a dry formulation. At least one investigator is evaluating the feasibility of coating Gardasil® onto solid microneedles.[36]

A clinical trial to evaluate the safety and immunogenicity of both of these vaccines when administered ID is underway at the Chinese University of Hong Kong (Prince of Wales Hospital 2008). In this trial, full and 20% doses will be administered IM and ID using both N&S and DSJI (PharmaJet). It is understood that a pilot safety and reactogenicity study has

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

been completed (results not available)[37] and the first stage of the main immunogenicity study is underway.[38]

7.3.2.2. Influenza (pandemic)

Live attenuated influenza vaccines (LAIVs) are candidates for use as one type of pandemic-specific vaccines (PSVs), i.e., vaccines produced from the pandemic-causing strain after the start of a pandemic. As is the case with the existing seasonal LAIV (FluMist®), these would be administered intra-nasally and, as such, are not included in this analysis.

Pre-pandemic vaccines (PPVs) that can be stockpiled in advance of a pandemic and administered around the start of a pandemic are likely to be based on standard inactivated whole- or split-virion influenza vaccine formulations, but incorporating an adjuvant (in the case of subunit formulations) to enhance cross-clade immunity. Currently, these vaccines are being produced by a number of manufacturers (including GSK, Baxter, Novartis, Sanofi, CSL, and Biken) predominantly for industrialized markets and for a proposed WHO stockpile.

Some of the best clinical data to date in terms of immunogenicity have been obtained with subunit PPVs in oil-in-water adjuvanted formulations, delivered IM/SC. The suitability of these adjuvants for IDD will have to be assessed, and it is possible that alternative adjuvants will be required. To date, the only known trial of IDD of a pandemic influenza vaccine used a non-adjuvanted split-virus formulation (Sanofi) and produced disappointing results (see Section 3.4).

Inactivated whole-virion influenza vaccines (e.g., Celvapan®, Baxter) do not usually require adjuvant for good immunogenicity and have also yielded encouraging data following IM/SC delivery. Such vaccines might be more suited to IDD than formulations with oil-in-water adjuvants (such as those from GSK or Novartis). It should be possible to establish "proof-of-principle" with these vaccines relatively quickly and easily.

7.3.2.3. Influenza (seasonal)

Seasonal influenza vaccines are non-adjuvanted, with the single exception of Fluad® (Novartis) containing MF59® adjuvant, which is licensed for use in older people (aged ≥ 65 years) in some European countries. As such, most seasonal flu vaccines represent good candidates for IDD. Several trials have already been completed and formulations have recently been licensed for IDD using BD's microinjector ID needle, in healthy younger adults and older people. Thus, influenza represents a good choice of vaccine for further study and development for IDD, even if just as "proof-of-principle." It should be noted that in most clinical trials, the response in all but the youngest participants will be a booster response and might not be representative or predictive of data obtained with IDD of vaccines to induce primary immune responses.

At least two investigators of solid, coated microneedles are using commercially available seasonal influenza vaccines in preclinical studies.[39]

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[37] Professor Tony Nelson, oral communication, February 18, 2009.

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

7.3.2.4. Multivalent meningitis conjugate vaccine

The generalized use of a multivalent meningitis conjugate vaccine against meningitis types A, C, Y, and W135, such as Menactra® (Sanofi), would be the ideal solution to the control of meningitis in the future (Girard et al. 2006). However, such a vaccine is likely to be too expensive for widespread LMIC use (Girard et al. 2006); the cost to the Centers for Disease Control and Prevention (CDC) of such a vaccine (Menactra®) is US$80 per dose, which is more than the cost of the 7-valent pneumococcal conjugate vaccine (CDC 2009). There are no known publicly available data on IDD of polysaccharide-protein conjugate vaccines. It has been suggested however, that certain (unspecified) formulation issues would need to be addressed in order for this to be successful.[40] At the very least, the issues associated with aluminum-salt adjuvants would need to be addressed. Of all the vaccine types, there is probably the least information on IDD of polysaccharide-protein conjugate vaccines; therefore, these represent an important class of vaccines for which data should be gathered.

7.3.2.5. Pneumococcal conjugate vaccine

The points made above for meningitis conjugate vaccines will also apply to pneumococcal polysaccharide-protein conjugate vaccines.

7.3.2.6. Inactivated poliovirus vaccine

IPV is a relatively costly vaccine with insufficient manufacturing capacity to support the goal of increasing IPV use as and when poliovirus is eradicated. Although ID has been the standard route of delivery for IPV in some countries in the past (Weniger and Papania 2008), there have been relatively few comparative trials of IDD vs. IM delivery of IPV, although WHO-sponsored studies have recently been completed or are underway.[41]

IPV represents a good candidate for dose sparing and the limited data obtained to date are moderately encouraging. Current formulations do not contain adjuvant.

7.3.2.7. Rabies

IDD of rabies vaccines is widely used and promoted by WHO; however, well-designed studies to demonstrate formally the degree of dose sparing achievable, and to determine whether or not there is a real difference between the ID and IM routes, are still lacking and would be valuable. Rabies represents a good model vaccine for evaluating novel IDD devices in naïve recipients.

7.3.3. Other vaccines

7.3.3.1. Hepatitis B vaccine

The cost and supply arguments to support dose sparing for hepatitis B vaccine are not strong; however, as a monovalent vaccine with well-established, straightforward *in vitro* and *in vivo*

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[39] Mark Kendall, oral communication, March 18, 2009; Mark Prausnitz, oral communication, February 20, 2009.

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

[41] Bruce Weniger, CDC, oral communication, February 23, 2009.

assays of potency, it can be a useful model for establishing proof of principle and/or as a test-vaccine for novel devices. It might, for example, be very useful to develop a birth-dose of hepatitis B that is very easily administered and thermostable, which could be a goal perhaps of solid, coated microneedles.

At least one investigator has plans to coat hepatitis B vaccine onto solid microneedles.[42]

7.3.3.2. Yellow fever

This was not identified as one of the top six priority vaccines for IDD in this analysis; however, consideration should be given to yellow fever vaccine due to concerns regarding limited vaccine supply. Yellow fever vaccine could also serve as a useful prototype live attenuated vaccine to assess issues such as virus shedding from ID injection sites. It could also be a good model for the Chimerivax™ family of vaccines (recombinant viruses based on YF) against flaviviruses such as dengue, Japanese encephalitis, and West Nile fever.

7.3.3.3. Combination vaccines

Vaccines such as DTP-HepB-Hib are probably a poor choice as early candidates for evaluating IDD. The presence of several vaccines means that a panel of immunological read-outs will be needed; if any reformulation is required, it is likely to be complex.

7.3.3.4. Vaccines administered by oral or respiratory routes

The question of whether IDD is preferable to other non-injected routes of delivery such as inhalation or oral delivery remains to be formally addressed. We have assumed that in cases where an effective oral vaccine exists, or is being developed, then IDD is unlikely to offer significant advantages over this route in terms of immunogenicity, ease of administration, or cost.

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

8. Conclusions

8.1. Status of the data supporting IDD and dose sparing

There have been a considerable number of clinical trials of IDD but very few studies have compared equivalent doses delivered by the ID and IM/SC routes and fewer have considered specifically targeting the epidermis. Evidence to convincingly support the concept that the dermis or epidermis are immunologically superior to the muscle or subcutaneous tissue for vaccine delivery is therefore limited.

There is, however, a considerable body of data to support the concept that for at least some vaccines, satisfactory and protective immune responses can be achieved by administering reduced doses of vaccines by the ID route. This remains an area of active research and the recent data (some of it obtained using novel IDD devices) are encouraging. The fact that, in some cases, dose reductions might also be achievable via the IM/SC route should not be overlooked.

Because of the potential benefits of IDD and novel IDD devices, this route of delivery should continue to be explored, and additional, better designed trials should be conducted to evaluate the possibility of dose sparing by IDD and also IM/SC routes.

8.2. Development of IDD devices

The different devices being developed and reviewed in this report all have different attributes. Those that are compatible with liquid formulations and that are not prefilled (including PATH's ID needle adaptor, some DSJIs, intradermal needles, and syringe-mounted hollow microneedles) should be the easiest and fastest to take to the clinic for evaluation. This is because they might not need vaccine reformulation and, for trial use, manufacturers would not need to change their fill/finish lines.

Solid, coated, or biodegradable microneedles will require extensive development work but offer several additional advantages in terms of integrating vaccine and device, requiring only a small cold-chain volume, and enhanced ease of use. There is no published clinical experience with these devices, but they have considerable promise and should continue to be supported. Even if the development of this class of device (and the necessary vaccine formulations) is successful, they will only be available for clinical use in the longer term.

It seems likely that hollow microneedle patches prefilled with vaccine will require more development work than other devices that use liquid formulations, in order to produce and test compatible devices and formulations.

The highest-risk devices appear to be needle-free transcutaneous patches. These might only be useful for one or two vaccines that have specific immunological properties. Administration is not as simple as might be expected, generally involving a skin-stripping step and lengthy application times.

There are some preclinical data but very little published clinical data on devices designed to deliver DNA intracellularly in the skin. Such devices might allow considerable dose sparing of antigen-encoding DNA vaccines, but further work on devices affordable for LMIC use will be necessary.

8.3. Vaccines to be considered for investigation of IDD

8.3.1. Inactivated polio vaccine

IPV is a relatively costly vaccine with limited manufacturing capacity. The ability to use jet injectors for IPV delivery (IM/SC or ID) in campaign settings would be useful, and the Polio Eradication Committee is supportive of IDD for IPV.[43] In addition, the existing data on IDD of IPV are moderately encouraging.

8.3.1.1. Issues to be addressed.

- The level and duration of demand for IPV pre- and post-eradication is uncertain. Estimates vary between current levels of 80 million doses per year, to 190–425 million doses per year.[44] Some countries, such as India, are believed to be moving toward the use of IPV in combination vaccines (e.g., DTaP-IPV). The combination vaccines might be more problematic for IDD because of the presence of aluminum-salt adjuvants.

- IPV is a relatively unstable vaccine and the tertiary and quaternary structure of the antigens needs to remain intact in order for antigenicity to be maintained. Producing dry formulations for use with devices such as coated solid microneedles might therefore be difficult. Because of the status of development of these devices, this would only be an issue in the long term.

Further studies of IDD of IPV are already underway or are being planned:

- Evaluation of supplemental ID or IM doses of IPV compared with monovalent OPV: to be conducted in India, sponsored by Panacea (India) and in association with WHO, PATH, the Indian Council of Medical Research, the Ministry of Health and Family Welfare of India, the Department of Health and Family Welfare of Uttar Pradesh, and CDC. This study will use DSJIs (developed by PharmaJet) and started in April 2009.

- An extension of the recent WHO study of IDD of IPV (by jet injection) is ongoing in Cuba.[45]

8.3.2. Human papillomavirus

HPV vaccines have not yet been introduced into LMICs, but are expected to be relatively high cost. The WHO Vaccine Packaging and Presentation Advisory Group (VPPAG) is currently drawing up a specification for a "second generation" HPV VLP vaccine, which could provide the opportunity to influence and introduce a new presentation and route of delivery for existing and future manufacturers.

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[43] Martin Friede, oral communication, April 8, 2009.

[44] Global Post-eradication IPV Supply and Demand Assessment: Integrated Findings. Oliver Wyman Inc, March 2009.

[45] Martin Friede, oral communication, April 8, 2009.

8.3.2.1. Issues to be addressed

- Second-generation vaccines from manufacturers other than GSK and Merck are unlikely to be available in the short- to medium-term. Current presentations include prefilled syringes and 1- and 2-dose vials (without preservative).

- Aluminum salts are included in the current VLP formulations from both GSK and Merck for stability of the vaccine rather than immunogenicity.[45] These could potentially cause unacceptable levels of reactogenicity if delivered ID. Studies to evaluate this issue have already started (Prince of Wales Hospital 2008).

- Immunological correlates of protection have not been established for HPV vaccines; therefore, efficacy trials would be required to support introduction of a novel device or route of delivery. Low-grade premalignant lesions can, however, be used as predictive biomarkers of cervical cancer.

8.3.3. Rabies

There is already considerable experience with, and data from, IDD of rabies vaccines, as well as a continuing need for dose-reduction in order to reduce the cost of vaccination. Rabies vaccines do not contain adjuvants and therefore present a useful model system for testing novel IDD devices. This could be achieved in LMICs (pre- or post-exposure) or in the first instance in "higher-risk" individuals (e.g., animal handlers and vets) in industrialized countries, with a standard dose follow-up.

8.3.3.1. Issues to be addressed

- The need for dose reduction in pre-exposure and post-exposure regimens, as well as the relative ease of conducting studies in these settings, needs to be established.

8.3.4. Yellow fever

The supply of yellow fever vaccines can be limited. This vaccine could serve as a useful prototype live attenuated vaccine to assess issues such as virus shedding from ID injection sites using various devices. It could also be a good model for the Chimerivax™ family of vaccines (recombinant viruses based on YF) against flaviviruses such as dengue and Japanese encephalitis (JE). A small preclinical study in non-human primates using a prototype version of BD's Soluvia® device with Chimerivax™-JE produced encouraging results (Dean et al. 2005). A trial of IDD of YF vaccine using DSJIs is being planned.[46]

8.3.4.1. Issues to be addressed

- The significance of the risk of shedding or aerosol generation by IDD devices needs to be assessed. It is possible that devices such as the PATH/SID ID needle adaptor might be more appropriate for YF vaccine than alternative methods that generate an aerosol or deliver the vaccine to the most superficial layers of the skin.

- The titer and therefore potency of live-attenuated vaccines falls over the duration of the vaccines' shelf-life. Dose-reduction studies will need to be conducted with

[46] Darin Zehrung, oral communication, April 8, 2009.

vaccine batches near to the end of their shelf-life to determine whether a sufficient dose to induce protection is still being delivered. This is particularly significant for dengue vaccines, where an inadequate immune response to one serotype can lead to enhancement of pathology upon subsequent infection with any of the four serotypes.[47]

8.3.5. Meningitis A conjugate vaccine

Polysaccharide (PS)-conjugate vaccines against meningitis and pneumococcus are currently expensive and/or supply-constrained. There have been no published studies of IDD of this class of vaccines so it is not known whether non-inferior responses (vs. IM) or dose sparing will be possible.

The tetanus-conjugated monovalent meningitis A vaccine being developed by the Serum Institute of India and the Meningitis Vaccine Initiative (MVI) could be a convenient model for other PS-conjugate vaccines:

- Immunological correlates of protection exist.
- The vaccine can be prepared with or without alum (the adjuvant is contained in the diluent used for reconstitution and could be replaced by injectable water).
- There is an interest in reducing cold-chain volumes for this vaccine.

8.3.5.1. Issues to be addressed

- It is likely that at least some degree of reformulation of PS-conjugate vaccines will be needed in order to make them suitable for IDD.[48]

8.3.6. Novel tuberculosis vaccines

These could be interesting candidates for IDD. Some of the vaccines are based on recombinant versions of BCG, which is currently delivered ID. Other approaches use recombinant virus vectors such as modified vaccinia Ankara (MVA) or adenovirus, which have been delivered ID in preclinical models and in some clinical trials.

8.3.6.1. Issues to be addressed

- This work is at a relatively early stage of clinical development and further discussion with experts is required to assess feasibility.

[47] Dexiang Chen, oral communication, April 8, 2009.

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

8.4. General gaps in knowledge and next steps

Many important questions remain to be answered including:

- Does IDD provide the potential for greater dose sparing than can be achieved by continuing to use the IM/SC route?
    - This can only be addressed by conducting trials that compare equivalent doses delivered by IM/SC and IDD, and by testing a range of doses via each route.
    - Whenever possible, clinical trials should include devices designed specifically for IDD in order to improve the reliability and reproducibility of this route and also to provide information on the device itself. Novel IDD devices need to at least match the published or accepted reliability of the Mantoux method, which is currently the "gold-standard" method for IDD using N&S.
- Will the dose-sparing phenomenon be applicable to a wide range of vaccine types and formulations?
    - Trials using a wider range of vaccines including protein–polysaccharide conjugate vaccines are required.
    - It will be important for trials to demonstrate that IDD of reduced doses of a vaccine nearing the end of its shelf-life, when its titer or potency will be lower than when it was first released, still induce non-inferior immune responses. This point is particularly important for live attenuated vaccines.
- Are existing adjuvants too reactogenic when delivered IDD, and will they need to be removed from, or at least reduced in content, in vaccine formulations?
    - Well-designed studies to assess the reactogenicity of different doses of aluminum-salt adjuvants are required. Ideally a standardized reporting format for vaccination-related adverse events would be used, as proposed by groups such as the Brighton Collaboration (2009). It might be possible to conduct some of this work using *ex vivo* human skin explants.[49]
- Will novel, rationally-designed adjuvants be required for vaccines delivered to the dermis or epidermis to be sufficiently immunogenic?
    - Additional data from trials with a wider range of vaccines are required before the need for and benefits of further adjuvants can be determined; however, because of the time involved in adjuvant development, they are unlikely to be available for vaccines in the short term.
- Due to the paucity of data, the analysis in this report has had to rely on largely subjective assessments of the benefits of IDD. Devices were prioritized in terms of potential dose sparing and cold-chain volume. Issues such as cost-savings from

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

reducing sharps usage have not been considered in detail. If IDD is to be investigated further in the clinic, then a more formal analysis of the potential benefits of IDD will be required for each application and setting.

- Accurate, quantitative information is required on novel IDD devices in terms of device cost and storage requirements (in and out of the cold chain), potential savings and benefits from reducing sharps usage, and the realistic potential cost savings achievable from dose-sparing.

9. Information sources

9.1. Interviews

Telephone interviews were held with the following experts and key opinion leaders.

Name	Affiliation
James Birchall	Cardiff University, Wales, UK
Dexiang Chen	PATH, WA, USA
Martin Friede	World Health Organization (WHO), Geneva, Switzerland
Mark Kendall	University of Queensland, Australia
Philippe Laurent	Becton Dickinson (BD), France
Yotam Levin	NanoPass Technologies Ltd., Israel
Mark Prausnitz	Georgia Institute of Technology, GA, USA
Steven Reed	Infectious Disease Research Institute (IDRI), WA, USA
Michael Royals	PharmaJet, Inc., CO, USA
Rick Stout	Bioject Medical Technologies, Inc., OR, USA
Bruce Weniger	Centers for Disease Control (CDC), GA, USA
Darin Zehrung	PATH, WA, USA

9.2. Figures

Images of IDD devices were provided by PATH unless otherwise indicated and are used with permission.

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Appendix 1: Summary of ongoing/planned clinical trials of intradermal delivery

Clinical trials evaluating intradermal (ID) delivery of vaccines—ongoing and planned

The summaries of clinical trials have been classified as shown below.

Table	Page	Trial status	Vaccines	Subjects
A	A-2	Ongoing/planned.	Licensed.	Immunocompetent.
B	A-8	Ongoing/planned.	Licensed.	Immunocompromised or non-responders.
C	A-11	Ongoing/planned.	Unlicensed or novel.	All subjects.

Notes
Licensed signifies a currently licensed vaccine, but the ongoing/planned trials might involve use of an unlicensed or "off-label" route or device.

Inclusion criteria:

1. Clinical trial targeted at active immunization for infectious disease.
2. Includes intradermal delivery by needle/syringe or other device.
3. Vaccines for which ID delivery is not the current gold standard or routine route of administration; some trials comparing different devices/routes for Bacille Calmette Guerin (BCG) (routinely delivered ID) have also been included.

Notes and abbreviations:
Ab: antibody; AE: adverse event; Ag: antigen; Al: aluminium; BCG: Bacille Calmette Guerin; BD: Becton Dickinson; CDC: Centers for Disease Control; CSSS: cyanoacrylate skin surface stripping; CHMP: Committee for Medicinal Products for Human Use; CPRV: chromatography purified Vero cell rabies vaccine; concn.: concentration; d: day; DTH: delayed-type hypersensitivity; DTP: diphtheria, tetanus, pertussis; EPI: expanded programme on immunization; ETEC: enterotoxigenic *E. coli*; GM-CSF: granulocyte-macrophage colony-stimulating factor; GMT: geometric mean titer; GSK: GlaxoSmithKline; h: hour; HA: haemagglutinin; HAI: haemagglutinin inhibition; HAV: hepatitis A; HBsAg: hepatitis B surface antigen; HBV: hepatitis B vaccination; HCV: hepatitis C; HCW: healthcare worker; HDCV: human diploid cell inactivated virus; HepB: hepatitis B; HI: hemagglutination inhibition; HIV: human immunodeficiency virus; HPA: Health Protection Agency; IC: intracutaneous; ID: intradermal; IFN-γ: interferon gamma; IAVI: International AIDS Vaccine Initiative; IM: intramuscular; IU: international units; LTT: lymphocyte transformation test; m: months; M&F: males and females; MF59: type of adjuvant; mOPV1: monovalent oral polio vaccine type 1; MPL: mono phosphoryl lipid A; MN: microneedle(s); mo: months old; MSD: Merck Sharp Dohme; MVA: modified vaccinia Ankara; N: number of participants in trial group; N&S: needle and syringe; NIAID: National Institute of Allergy and Infectious Diseases; NIBSC: National Institute for Biological Standards and Control; OPV: oral polio vaccine; PAHO: Pan American Health Organization; PEP: post-exposure prophylaxis; PCECV: purified chick embryo cell vaccine; PFU: plaque-forming units; PREP: pre-exposure prophylaxis; Prof.: professor; PVCV: Purified Vero cell vaccine; RCT: randomized controlled trial; SAE: serious adverse events; SC: subcutaneous; SK: SmithKline; SKB: SmithKline Beecham; TB: tuberculosis; tba: to be announced; TC: transcutaneous; tOPV: trivalent oral polio vaccine; TIV: trivalent inactivated vaccine; vs.: versus; US HHS: United States Department of Health and Human Services; VLP: virus-like particle; VZV: varicella zoster virus; yo: year old; wo: weeks old; WHO: World Health Organization; WRAIR: Walter Reed Army Institute of Research.

Appendix 1: Continued

Summary table A: Ongoing/planned trials—licensed vaccines—immunocompetent subjects

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Hepatitis A						
Sponsors include: PharmaJet.	At logistical planning stage.	**Vaccine:** probably Epaxal (Berna/Crucell). **Vaccine type:** if Epaxel, inactivated virus adsorbed onto virosomes. **Device:** ID: will include jet injector (PharmaJet).	**Country:** Brazil.			Michael Royals, PharmaJet, personal communication.
Human papillomavirus (HPV)						
Pilot efficacy bridging study of two human HPV vaccines administered ID and IM. **Sponsors, collaborators include:** Self-funded, The Chinese University of Hong Kong; PharmaJet, USA. **Principal investigator:** Prof. E Anthony S Nelson, The Chinese University of Hong Kong.	Pilot completed. Main trial on one age group (44 women) underway.	**Vaccine:** Cervarix™ (GSK), Gardasil™ (Merck) for each group. **Vaccine type:** Virus-like particles ± alum (Merck vaccine) or AS04™ (GSK vaccine). **Devices:** ID: jet injector (PharmaJet) or N&S; IM: N&S.	**Sample size:** 10 (for pilot); 120 (main study). **Study population:** pilot study: (male adults) with 20% dose ID of Cervarix or Gardasil to test reactogenicity by ID N&S. Main study: Females (10–15 yo, 18–26 yo, 36–45 yo), pre-screened for Ab, HPV DNA, history of Pap smear. **Countries:** Hong Kong, China.	**Type:** main study randomized with three age strata; not double-blind. **Schedule for main study:** 3 doses (at 0, 2, 6 m) full-dose IM vs. 20% dose IM, vs. 20% dose ID by jet injector, vs. 20% dose ID N&S. **Endpoints for main study:** safety and reactogenicity at 1, 3, 7 m; immunogenicity: dose comparison of Ab response at 7 m; seroconversion at 7 m.	Comprehensive trial design comparing; 20% dose IM and ID, two IDD methods and two vaccines. Trial is also of interest because Gardisil™ contains alum and Cervarix™ contains AS04™ (MPL + alum) as an oil-in-water emulsion. Main study also included a pilot study to evaluate safety and reactogenicity.	**Trial ID:** ACTRN12608000339358 **Links:** http://www.anzctr.org.au/trial_view.aspx?ID=82825

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Influenza - seasonal						
Safety, tolerability, and immunogenicity of different combinations of trivalent influenza vaccine varying influenza antigen dose, adjuvant dose, and route of administration in healthy elderly individuals aged 65 years and older. **Sponsors:** Novartis.	Recruiting.	No details of flu vaccine or ID device.	**Sample size:** 700. **Study population:** healthy older subjects aged > 65 years), without history of seasonal flu vaccine in past 6 months or adjuvanted seasonal flu vaccine in past 2 years. **Countries:** Belgium.	**Type:** Phase Ib, randomized, single-blind. **Schedule:** 10 groups including two with ID (one with high A/H3N2, but neither with MF59). **Endpoints:** immunogenicity 21 days. AEs collected to 21 days.	Assessing seasonal flu vaccine with addition of high A/H3N2 ± full or 25% dose MF59 adjuvant. No details of dose/volume.	**Trial ID:** NCT00848848 October 2008 to February 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00848848
Needle-free Jet Injection of Reduced-Dose, Intradermal, Influenza Vaccine in ≥ 6 to < 24-Month-old Children. **Sponsors, collaborators include:** CDC, WHO, PAHO, PATH, Sanofi, Bioject. **Principal investigator:** Bruce Weniger, CDC.	Ongoing. Efficacy not assessed in first phase. Safety data still blinded.	**Vaccine:** Vaxigrip®, (Sanofi). **Vaccine type:** trivalent inactivated, liquid, no adjuvant. **Devices:** ID: Biojector 2000 with ID spacer; IM: N&S.	**Sample size:** 48 for Phase I plus 402 for Phase II. **Study population:** children aged 6–24 mo, no history of influenza vaccine. **Countries:** Dominican Republic.	**Type:** randomized, blinded, Phase I and then Phase II. **Schedule:** 2 doses, 4 weeks apart: 0.1 ml ID by Biojector vs. 0.1 ml IM by N&S, vs. 0.25 ml IM by N&S. **Endpoints:** safety, seroconversion (4 weeks after second dose), GMTs, seroprotection (HI assay); samples to day 56.	Study still blinded. Local AEs were mild. Most systemic AEs are likely unrelated to vaccination dose and route, but can only be determined after unblinding of Phases I and II.	**Trial ID:** NCT00386542 October 2006 to December 2009. **Trial ID:** NCT00386542 October 2006 to December 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00386542 Abstract 11th Annual Conference on Vaccine Research. Available at: http://www.nfid.org/pdf/conferences/vaccine08abstracts.pdf

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
						More information at: http://www.cdc.gov/vaccinesafety/vaxtech/nfit/flu.htm
Immune response in adults and elderly subjects vaccinated with inactivated influenza vaccines. **Sponsors:** Sanofi-Aventis.	Ongoing, not recruiting.	**Vaccine type:** inactivated, split-virion. **Devices:** presume IM: N&S; ID could be their ID delivery system?	**Sample size:** 160. **Study population:** adults 18–40 yo and 60–85 yo. **Countries:** France.	**Schedule:** 0.1 ml ID vs. 0.5 ml IM. **Endpoints:** safety and immunogenicity.	Comparing immune response to ID and IM in elderly and healthy adult populations.	**Trial ID:** NCT00776438 September 2007 to July 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00776438
Polio - IPV						
Immunogenicity and safety of a fractional booster dose of IPV ID vs. IM. **Sponsors, collaborators include:** Panacea Biotech, Sanofi Pasteur.	Recruiting.	**Vaccine:** Imovax IPV (Sanofi). **Vaccine type:** trivalent inactivated virus. **Devices:** ID via N&S (Mantoux).	**Sample size:** 228. **Study population:** healthy infants (15–18 mo) previously recruited for IPV25 study. **Countries:** Philippines.	**Type:** Phase II, not randomized, open label. **Schedule:** full-dose IM vs. 20% dose ID. **Endpoints:** immunogenicity and safety.	Fourth booster dose IPV fractionally as ID one month after IPV25 study.	**Trial ID:** NCT00885157 (IPV26) April 2009 to January 2010. **Links:** http://clinicaltrials.gov/ct2/show/NCT00885157
Evaluation of humoral immune response induced by a supplemental dose of IPV administered ID or IM vs. a dose of mOPV1. **Sponsors, collaborators include:** Funded by WHO, also Primary sponsor: Panacea	Ongoing.	**Vaccine:** IPV (GSK, licensed in some countries but not India for SC/IM); IPV (Panacea, license submitted in India for IM use). mOPV1 (Panacea, licensed in India), mOPV1 (Sanofi, about 4.4-fold higher potency than	**Sample size:** pilot: 30. **Study population:** pilot: children from Moradabad, India (2–4 yo, 5–6 yo, 7–9 yo) 0.1 ml ID by jet injector (older children first), vaccine as "supplemental dose." Main study: healthy infants aged 6–9 mo who have had "a few doses"	**Type:** randomized controlled trial (not blinded) to 5 groups. **Schedule:** 1 dose of: group a: 20% (0.1 ml) GSK IPV ID; group b: 100% GSK IPV IM; group c: 100% Panacea IPV IM; group d: Panacea mOPV1; group e: Sanofi mOPV1. All at 1–3 w after mOPV1	IPV has been used ID by jet injector but with a different device (Cuba/Oman studies). If 20% GSK IPV is equivalent to 100% Panacea IPV, then further studies are planned with fractional dosing of Panacea IPV.	**Trial ID:** ISRCTN90744784 Pilot study started April 2009. **Links:** http://apps.who.int/trialsearch/Trial.aspx?TrialID=ISRCTN90744784

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Biotech, India. Also funded by WHO. **Principal investigator:** Dr. Jacob John.		Panacea, not licensed for use in India but used in other countries e.g., Egypt) **Vaccine type:** trivalent inactivated virus or monovalent live attenuated. **Devices:** ID: jet injector (PharmaJet; submitted for licensing in India); IM by N&S; mOPV: oral drops.	of tOPV. **Countries:** India (Moradabad, Western Uttar Pradesh).	round. GSK IPV via IM and ID, Panacea IPV via IM. **Endpoints:** seroconversion (≥ 4-fold rise at day 28); Ab titers (IgA vs. IgM at day 28) to all three PV types. Booster effect of IPV vs. mOPV1 0074o type 1 PV. Compare full vs. 20% doses for GSK IPV; Panacea IPV vs. GSK IPV; Sanofi mOPV1 vs. Panacea mOPV1. **Sampling:** three blood samples at day 0, 7 days after vaccine, day 28.	Pilot study first to evaluate potential side effects of ID jet injection with IPV: monitor for 30 mins and then visit 24–48 hr.	
Rabies						
Sponsors, collaborators include: PATH, PharmaJet, Indian Immunologicals	At planning stage – aiming to start late 2009	**Vaccine:** Rabies vaccine (Indian Immunologicals). **Vaccine type:** inactivated virus. **Devices:** ID: by jet injection (to include PharmaJet) and/or ID needle adaptors (PATH), or microneedles (manufacturer tba).	**Sample size:** not yet established. **Study population:** probably healthy adults. **Countries:** India.	**Schedule:** probably will include 0.1 ml by ID jet.		Darin Zehrung, PATH, personal communication. Michael Royals, PharmaJet, personal communication.

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Tuberculosis (TB)						
BCG vaccine oral intradermal **Sponsors, collaborators include**: NIAID.	Trial has been suspended.	**Vaccine:** SSI BCG™ (Staten Serum Institute) or BCG (Connaught strain). **Vaccine type:** live attenuated mycobacterium. **Devices:** presume by N&S.	**Sample size:** 70. **Study population:** adults (18–40 yo), prescreened. **Countries:** United States.	**Type:** Phase I. **Schedule:** 2 doses 60 ml oral vs. 0.1 ml ID both at 0, 1 years. **Endpoints:** safety and immunogenicity.		**Trial ID:** NCT00396370 December 2008 to December 2010. **Links:** http://clinicaltrials.gov/ct2/show/NCT00396370
Yellow fever (YF)						
Dose-sparing via ID jets **Sponsors, collaborators include**: PATH, PharmaJet.	At planning stage.	**Vaccine:** YF vaccine. **Vaccine type:** live attenuated. **Devices:** ID by jet injector (PharmaJet).	**Sample size:** not yet established. **Study population:** not yet established. **Countries:** Brazil.	Not yet established.		Darin Zehrung, PATH, personal communication.
Varicella zoster virus (VZV)						
Dose-sparing by ID including by jet injector **Sponsors include:** Brazil's National Immunization Programme (University of Sao Paulo); Sao Paulo State Centers for Disease Control, PharmaJet.	Aims to start in June 2009.	**Vaccine:** imported into Brazil ("2 or 3 choices"). **Vaccine type:** live attenuated. **Device:** ID: jet injector (PharmaJet) and/or N&S.	**Sample size:** 600. **Study population:** infants, 1–2 yo. **Countries:** Brazil.	**Schedule:** 0.1 ml ID of conventional concn. Vaccine (i.e,. 20% of dose); vs. 0.1 ml ID at double concn. (i.e., 40% dose); vs. 0.1 ml ID conventional concn. by N&S (i.e., 20%); vs. 1 ml SC by N&S (100% dose).	Aims to reduce cost of "expensive vaccine" implementation into the EPI in Brazil. Interesting, because no known clinical experience of VZV by ID route.	Michael Royals, PharmaJet, personal communication.

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population (including sample size), geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Principal investigator: Dr. Glacus de Souza Brito.						

Appendix 1: Continued

Summary table B: Ongoing/planned trials—licensed vaccines—immunocompromised/non-responder subject groups

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Hepatitis B						
Hepatitis B Vaccination (HBV) in HIV Infected Children. **Sponsors, collaborators include:** The HIV Netherlands Australia Thailand Research Collaboration, ART AIDS Charity Fund. **Principal investigator:** Torsak Bunupuradah.	Recruiting.	**Vaccine:** Not known. **Vaccine type:** likely to be recombinant HBsAg with Al-based adjuvant. **Devices:** presume N&S.	**Sample size:** 80. **Study population:** anti-HBsAb-negative HIV-infected children (12 m–18 yo) treated with highly active antiretroviral therapy (HAART). **Countries:** Thailand.	**Type:** Phase II: randomized, open label. **Schedule:** course of 2 µg (0.1 ml) HBV vaccine ID vs. 2 µg (0.1 ml) IM. **Endpoints:** immunogenicity at 4, 8 weeks after vaccination. AEs at 7 months.	To evaluate prevalence of protective anti-HBV antibody, comparing ID vs. IM.	**Trial ID;** NCT00886964 From April 2009 to October 2011. **Links:** http://clinicaltrials.gov/ct2/show/NCT00886964
Three strategies of vaccination against HBV in HIV-infected patients. **Sponsors, collaborators include:** Sanofi Pasteur, French National Agency for Research on AIDS and Viral Hepatitis. **Principal investigator:** Odile Launay.	Recruiting.	**Vaccine:** GenHevac B Pasteur (Sanofi). **Vaccine type:** recombinant antigen with Al hydroxide adjuvant. **Devices:** presume N&S.	**Sample size:** 420. **Study population:** HIV^+ adults (≥ 18 yo) with $CD4^+$ T-cell counts > 200/mm^3; have to be anti-HBV-negative (and no history of HBV vaccination). **Countries:** France.	**Type:** Phase III; randomized open label. **Schedule:** 3 or 4 doses, at 0, 1, (2) and 6 m, either 20 or 40 µg IM or 4 µg ID (4 doses for ID). **Endpoints:** anti-HBV seroconversion up to 42 m after vaccination.		**Trial ID:** NCT00480792 June 2007 to December 2008. **Links:** http://clinicaltrials.gov/ct2/show/NCT00480792

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Response to hepatitis B vaccine in celiac disease patients **Sponsors, collaborators include:** Shaare Zedek Medical Center, Israel. **Principal investigator:** Maskit Bar Meir	Not yet recruiting.	**Vaccine:** EngerixB™ (GSK). **Vaccine type:** recombinant protein, alum adsorbed. **Devices:** presume N&S.	**Sample size:** 210. **Study population:** celiac patients (> 1 yo) who didn't respond to initial IM HBV vaccine in infancy. **Countries:** Israel.	**Type:** RCT. **Schedule:** non responders to initial (IM) priming receive booster 3-dose schedule (same dose in 0.5 ml) via IM or ID at 0, 1 and 6 months. **Endpoints:** immunogenicity (GMTs) over 2 years.		**Trial ID:** Clinical trial database: NCT00739128 October 2008 to October 2010. **Links:** http://clinicaltrials.gov/ct2/show/NCT00739128
Influenza - seasonal						
ID vs. IM trivalent influenza vaccine in adult lung transplant recipients **Sponsors, collaborators include:** University of Alberta, University of Lausanne Hospitals **Principal investigator:** Deepali Kumar	Ongoing.	**Vaccine:** Vaxigrip™ (Aventis-Pasteur Canada). **Vaccine type:** trivalent inactivated. **Devices:** presume N&S.	**Sample size:** 90. **Study population:** lung transplant patients (18–75 yo). **Countries:** Canada, Switzerland.	**Type:** randomized, single blind. **Schedule:** 2 doses 0.1 ml ID vs. 1 dose 0.5 ml IM. **Endpoints:** seroconversion (4 weeks), safety (up to 7 days).		**Trial ID:** NCT00760175 October 2008 to April 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00760175
Influenza vaccine revaccination in ambulatory elderly subjects **Sponsors, collaborators include:** Sanofi-Aventis	Enrolling.	**Vaccine:** Fluzone™ (Sanofi). **Vaccine type:** trivalent inactivated. **Devices:**	**Sample size:** 1200. **Study population:** elderly (> 65 yo) who had been in previous trial (FID29). **Countries:** United	**Type:** Phase II. **Schedule:** 3 Fluzone formulations by 0.1 ml ID vs. 0.5 ml IM. **Endpoints:** safety, immunogenicity.		**Trial ID:** NCT00775450 October 2008 to September 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00775450

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	**Status**	**Vaccine(s), vaccine types, devices used**	**Total study population, geographical**	**Trial design, schedule, endpoints**	**Notes**	**Trial ID, start/end date, links**
		presume N&S but could be Soluvia® ID microinjector.	States.			
Influenza vaccination at a reduced dose using mesotherapy in HIV/AIDS patients at the Hadassah AIDS Center, Jerusalem **Sponsors, collaborators include:** Hadassah Medical Organization **Principal investigator:** Shlomo Maayan	Ongoing.	**Vaccine:** Vaxigrip™ (Sanofi). **Vaccine type:** trivalent inactivated. **Devices:** mesotherapy device (multiple ID injections).	**Sample size:** ~100. **Study population:** HIV^+ adults (18–70 yo). **Countries:** Israel.	**Schedule:** dilution of vaccine in saline to 10%; deliver via mesotherapy (ID). **Endpoints:** immunogenicity and acceptability.	Mesotherapy**:** multiple ID vaccinations on torso, axillae, and back. Aims to avoid rise in HIV viral load after IM flu vaccinations.	**Trial ID:** NCT00758212 To January 2009. **Links:** http://clinicaltrials.gov/ct2/show/NCT00758212

Appendix 1: Continued

Summary table C: Ongoing/planned trials—unlicensed vaccines, all subject groups

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Dengue						
Sponsors include: PharmaJet, Inviragen Inc.	Very early planning stage.	**Vaccine:** Inviragen **Vaccine type:** Recombinant live attenuated virus **Device:** to include jet injector (PharmaJet).	**Sample size:** To be determined. **Study population:** adult volunteers, 18–45 yo. **Countries:** to be determined.	**Type:** Phase I.		Michael Royals, PharmaJet, personal communication.
HIV						
Phase I study of vaccination schedule of experimental HIV vaccines **Sponsors, collaborators include:** NIAID, National Institutes of Health Clinical Center	Ongoing.	**Vaccine:** VRC-HIVDNA016-00-VP (DNA) and VRC-HIVADV014-00-VP (adenovirus). **Vaccine type:** DNA vaccine (prime) and live recombinant adenovirus (boost). **Devices:** N&S.	**Sample size:** 60. **Study population:** adults 18–50 yo (with or without pre-existing antibodies to rAd). **Countries:** United States.	**Type:** Phase I. **Schedule:** ID vs. IM vs. SC as prime in prime boost. **Endpoints:** mostly safety, some immunogenicity.		**Trial ID:** NCT00321061 From April 2006. **Links:** http://clinicaltrials.gov/ct2/show/NCT00321061
Safety of and immune response to a modified vaccinia Ankara (MVA) HIV vaccine in HIV-	Recruiting.	**Vaccine:** MVA-CMDR (HIV-1 CM235)	**Sample size:** 48. **Study population:** HIV⁻ adults (18–40	**Type:** Phase I. **Schedule:** ID vs. IM.		**Trial ID:** NCT00376090 From September 2006.

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
uninfected adults **Sponsors, collaborators include:** US Department of Defense, WRAIR **Principal investigator:** Mary Marovich		**Vaccine type:** live recombinant vaccinia virus. **Devices:** probably N&S.	yo). **Countries:** United States.	**Endpoints:** safety, immunogenicity.		**Links:** http://clinicaltrials.gov/ct2/show/NCT00376090
HIV candidate vaccine, ALVAC-HIV-1, administration in HIV-negative adults **Sponsors, collaborators include:** Aventis Pasteur **Principal investigator:** Mary Marovich	No longer recruiting.	**Vaccine:** ALVAC-HIV™. **Vaccine type:** live recombinant canarypox virus. **Devices:** probably N&S.	**Sample size:** 36. **Study population:** adults (18–55 yo). **Countries:** United States.	**Type:** Phase I. **Schedule:** transfusion of ex vivo transfected, autologous dendritic cells then ID vs. IM. **Endpoints:** unclear.		**Trial ID:** NCT00013572 From March 2001 **Links:** http://clinicaltrials.gov/ct2/show/NCT00013572
Sponsors, collaborators include: Bioject, IAVI, St. Stephen's AIDS Trust at the Chelsea & Westminster Hospital, London, UK	No results available.	**Vaccine:** ADVAX DNA™ (Aaron Diamond) + TBC-M4 (MVA). **Vaccine type:** DNA vaccine (prime) and live recombinant vaccinia (boost). **Devices:** ID: jet injector Biojector®	**Sample size:** no details. **Study population:** probably healthy adult volunteers. **Countries:** UK.	**Type:** heterologous prime boost. **Schedule:** **Endpoints:** probably safety, some immunogenicity.		**Links:** Trial "initiated." Bioject press release 24 February 2009: http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20090224005392&newsLang=en

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
		2000.				
Influenza – avian/pandemic						
Sponsors, collaborators include: Intercell, US HHS	No results available.	**Vaccine:** Pre-pandemic vaccine H5N1 strain (Solvay). **Vaccine type:** inactivated (cell-derived) virus, liquid, no adjuvant. **Devices:** Intercell IS patch™ for trans-cutaneous delivery of IS-adjuvant only.	**Sample size:**~500. **Study population:** adults. **Countries:** United States.	**Type:** Phase II. **Schedule:** **Endpoints:** safety, immunogenicity.	Phase I trial: 1 dose 45 µg HA (IM) then covered with IS patch resulted in 73% seroprotection. H5N1 strain vaccine is injected (presumed to be IM).	**Links:** Press release on Intercell website 10 December 2008: http://www.intercell.com/main/forbeginners/news/not-in-menu/news-full/browse/1/back_to/news/article/usd-125-m-funding-for-the-development-of-intercells-vaccine-patch-system-for-pandemic-influenza-fr/
Safety and immunogenicity of influenza H9 vaccine in humans **Sponsors, collaborators include:** University of Leicester, Crucell, NIBSC, HPA **Principal investigator:** Karl G Nicholson	Recruiting.	**Vaccine:** Pre-pandemic vaccines (Crucell). **Vaccine type:** whole virus + virosomal H9N2 strain ± adjuvant. **Devices:** probably N&S.	**Sample size:** 360. **Study population:** adults (> 18 yo). **Countries:** UK.	**Type:** Phase I. **Schedule:** group a: whole virus by IM at 1.5, 5, 15, 45 µg HA/dose +/- alum; group b: whole virus by ID at 5, 15 µg; group c: virosomal vaccine by IM at 1.5, 5, 15, 45 µg. **Endpoints:** safety, immunogenicity.	Whole virus (no adjuvant) 5 and 15 µg/dose will be tested both IM and ID.	**Trial ID:** NCT00814229 From August 2007 to January 2009. **Links:** http://clinicaltrials-lhc.nlm.nih.gov/ct2/show/NCT00814229
Phase I open-label study of recombinant DNA plasmid vaccine, VRC-AVIDNA036-00-	Recruiting.	**Vaccine:** VRC-AVIDNA036-00-VP.	**Sample size:** 44. **Study population:** adults (18–60 yo).	**Type:** Phase I. **Schedule:** 500 µg ID by N&S vs. 1 mg by Biojector		**Trial ID:** NCT00489931 From July 2007.

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
VP, encoding for influenza virus H5 hemagglutinin protein given ID **Sponsors, collaborators include:** NIH		**Vaccine type:** DNA vaccine. **Devices:** Biojector 2000™ or traditional N&S.	**Countries:** United States.	(two injections in same/different arms). **Endpoints:** safety, immunogenicity.		**Links:** http://clinicaltrials.gov/ct2/show/NCT00489931
TB						
Dose-escalation study on safety and immunogenicity of VPM1002 in comparison with BCG in healthy male volunteers **Sponsors, collaborators include:** Vakzine Projekt Management GmbH **Principal investigator:** Yveline Conrad	Recruiting.	**Vaccine:** VPM1002 **Vaccine type:** live, recombinant urease C-deficient listeriolysin-expressing BCG vaccine strain. **Devices:** probably N&S.	**Sample size:** 80. **Study population:** healthy males (18–55 yo) ± history of BCG vaccination. **Countries:** Germany.	**Type:** Phase I, randomized. **Schedule:** BCG vs. novel vaccine, 4 doses ID. **Endpoints:** safety and immunogenicity to 6 months.		**Trial ID:** NCT00749034 September 2008 to December 2010. **Links:** http://clinicaltrials.gov/ct2/show/NCT00749034
Study of MVA85A, in asymptomatic volunteers infected with TB, HIV, or both **Sponsors, collaborators include:** University of Oxford, University of Cape Town	Recruiting.	**Vaccine:** MVA 85A. **Vaccine type:** recombinant live attenuated mycobacterium. **Devices:** probably N&S.	**Sample size:** 36. **Study population:** adults aged 21–50 yo TB^{+} ± HIV ± HIV treatment. **Countries:** South Africa.	**Type:** Phase I, non-randomized. **Schedule:** 1 dose ID to each of 4 patient groups. **Endpoints:** immunogenicity (1 year).		**Trial ID:** NCT00480558 June 2007 to June 2008. **Links:** http://clinicaltrials.gov/ct2/show/NCT00480558

Appendix 1: Continued

Trial name, sponsor(s), collaborators, principal investigators	Status	Vaccine(s), vaccine types, devices used	Total study population, geographical	Trial design, schedule, endpoints	Notes	Trial ID, start/end date, links
Principal investigator: Helen McShane						
Safety and immunogenicity of a TB vaccine; MVA85A, in healthy HIV-infected volunteers **Sponsors, collaborators include:** University of Oxford	Recruiting.	**Vaccine:** MVA85A. **Vaccine type:** recombinant live attenuated mycobacterium. **Devices:** probably N&S.	**Sample size:** 20. **Study population:** HIV^+ adults (18–50 yo), BCG vaccinated. **Countries:** UK.	**Type:** Phase I. **Schedule:** presume 1 dose ID at two 10-fold different dose levels. **Endpoint:** safety and immunogenicity over 12 months.		**Trial ID:** NCT00395720 October 2006 to October 2008. **Links:** http://www.clinicaltrial.gov/ct2/show/NCT00395720
Safety, immunogenicity, and impact of MVA85A, on the immunogenicity of the EPI vaccines **Sponsors, collaborators include:** University of Oxford; Medical Research Council **Principal investigator:** Helen McShane	Recruiting.	**Vaccine:** MVA85A. **Vaccine type:** recombinant live attenuated mycobacterium. **Devices:** probably N&S.	**Sample size:** 471. **Study population:** babies (2–3 mo) with history of BCG vaccination in first 2 weeks of life. **Countries:** Gambia.	**Type:** Phase I, randomized. **Schedule:** all doses ID, alongside DTwP-Hib (3 doses) and tOPV (4 doses) and HepB (3 doses). **Endpoints:** dose selection, safety and immunogenicity over 12 months.		**Trial ID:** NCT00480454 October 2006 to July 2008 **Links:** http://clinicaltrials.gov/ct2/show/NCT00480454