Intradermal Delivery of Vaccines

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

August 27, 2009

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Authorship and purpose

This report was commissioned by PATH, the Disposable Syringe Jet Injector Project and Project Optimize (Immunization Systems and Technologies for Tomorrow), a collaborative project between PATH and the World Health Organization (WHO). The report was authored by Julian Hickling and Rebecca Jones from Working in Tandem Ltd.

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

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

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).
**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 vaccine 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).
Intradermal Delivery of Vaccines

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

If IDD improves 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. 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

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

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.
Intradermal Delivery of Vaccines

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

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID superior to IM/SC</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>ID superior to IM/SC</strong></td>
<td><strong>RD ID superior to FD IM/SC</strong></td>
</tr>
<tr>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td><strong>ID equivalent to IM/SC</strong></td>
<td><strong>RD ID equivalent to FD IM/SC</strong></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>ID inferior to IM/SC</strong></td>
<td><strong>RD ID inferior to FD IM/SC</strong></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

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 IM 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**

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID</td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

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
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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

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID superior to IM/SC</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
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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)

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID superior to IM/SC</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID superior to IM/SC</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>ID superior to IM/SC</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Trials comparing equivalent doses delivered ID vs. IM/SC</th>
<th>Trials comparing reduced-dose (RD) delivered ID vs. full-dose (FD) IM/SC</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ID superior to IM/SC</td>
<td>ID equivalent to IM/SC</td>
<td>ID inferior to IM/SC</td>
</tr>
<tr>
<td>Influenza (seasonal)</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rabies</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Polio (IPV)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Measles</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>YF&lt;sup&gt;a&lt;/sup&gt;, TBE, DTP, TT</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>6</strong></td>
<td><strong>10</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> 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. 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.

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