

## 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)
<b>Formulation requirement</b>	Liquid. <sup>b</sup>	Liquid. <sup>b</sup>	Liquid. <sup>b</sup>	Liquid. <sup>b</sup>	Dry (coated onto or formed into needles).	Liquid or dry.
<b>Vaccine type</b>						
<b>Subunit /inactivated whole organism</b>	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.
<b>Live</b>	OK.	OK, risk of	OK, risk of	OK, risk of	OK, risk of shedding <sup>32</sup>	OK, risk of shedding (stable,

<sup>32</sup> 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)
<b>attenuated<sup>a</sup></b>		shedding.	shedding.	shedding.	(stable, viable dry formulation might be difficult).	viable dry formulation might be difficult).
<b>Polysaccharide-protein conjugate</b>	OK.	Possibly OK, might require re-formulation. <sup>33</sup>	Possibly OK, might require re-formulation. <sup>33</sup>	Possibly OK, might require re-formulation. <sup>33</sup>	Possibly OK, (might be difficult to achieve a dry immunogenic formulation).	Possibly OK, (likely to need potent ID adjuvant).
<b>DNA</b>	OK.	OK.	OK.	OK.	OK.	OK.
<b>Adjuvant</b>						
<b>Alum</b>	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).
<b>Oil in water</b>	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

<sup>33</sup> 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.<sup>34</sup>
- Oil-in-water adjuvants such as MF59<sup>®</sup> (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.

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<sup>34</sup> 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 <sup>b</sup>	Vaccine type	Liq/ lyo <sup>35</sup>	Adju- vant			Predicted compatibility of vaccine with device <sup>a</sup>						
				Cost <sup>c</sup>	Limited supply <sup>d</sup>	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)
<b>Dengue (future)</b>	Live recomb virus.	Lyo.	No.									
<b>DTP-HepB-Hib</b>	Inactivated.	Liq.	Al.									
<b>ETEC</b>	Inactivated (LT toxin).	Patch.	No.									
<b>Influenza (pandemic)</b>	Inactivated split/ recomb.	Liq.	Al.									
	Inactivated split/ recomb.	Liq.	Oil in water.									
	Inactivated whole-virion.	Liq.	No.									

<sup>35</sup> Working in Tandem for Project Optimize 2008

# Intradermal Delivery of Vaccines

Vaccine <sup>b</sup>	Vaccine type	Liq/ lyo <sup>35</sup>	Adju- vant			Predicted compatibility of vaccine with device <sup>a</sup>						
				Cost <sup>c</sup>	Limited supply <sup>d</sup>	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)
<b>Influenza (seasonal)</b>	Inactivated split/ recomb.	Liq.	No.									
<b>Hepatitis B</b>	Inactivated protein subunit.	Liq.	Al.									
<b>HPV</b>	Inactivated VLP.	Liq.	Al. <sup>b</sup>									
<b>Japanese encephalitis</b>	Inactivated.	Liq.	Al.									
	Live-attenuated.	Lyo.	No.									
<b>Malaria</b>	Recomb. protein (RTS,S).	Lyo.	Oil-in- water.									
<b>Measles</b>	Live attenuated.	Lyo.	No.									
<b>Meningitis mono- valent (conjugated)</b>	Inactivated PS.	Lyo.	Al.									

# Intradermal Delivery of Vaccines

Vaccine <sup>b</sup>	Vaccine type	Liq/ lyo <sup>35</sup>	Adju- vant			Predicted compatibility of vaccine with device <sup>a</sup>						
				Cost <sup>c</sup>	Limited supply <sup>d</sup>	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)
<b>Meningitis multivalent (conjugated)<sup>e</sup></b>	Inactivated PS.	Liq.	Al.									
<b>Measles-mumps- rubella</b>	Live-attenuated.	Lyo.	No.									
<b>Pneumococcal multivalent</b>	Inactivated PS.	Liq.	Al.									
<b>Polio (IPV)</b>	Inactivated whole virion.	Liq.	No.									
<b>Rabies</b>	Inactivated whole virion.	Lyo.	No.									
<i>Salmonella typhi</i>	Inactivated PS.	Liq.	No.									
<b>TB (current, BCG)</b>	Live-attenuated myco- bacterium.	Lyo.	No.									
<b>TB (future)</b>	Live-recomb. myco- bacterium.	Lyo.	No.									

## Intradermal Delivery of Vaccines

Vaccine <sup>b</sup>	Vaccine type	Liq/ lyo <sup>35</sup>	Adju- vant	Cost <sup>c</sup>	Limited supply <sup>d</sup>	Predicted compatibility of vaccine with device <sup>a</sup>						
						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)
Tetanus	Live recomb. virus vector.	Lyo.	No.									
	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:

- 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.
- 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-adsorbed HPV vaccine is considered; an oil-in-water adjuvanted formulation (Cervarix<sup>®</sup>, 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.
- Vaccine cost: Solid circles= high cost, open circles= low cost. Data from PATH internal documents (PATH, unpublished data).
- Limited supply: solid circles= supply constraints, open circles= no supply constraints. Data from PATH vaccine development framework (PATH, unpublished data).
- 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<sup>®</sup>, Merck, a 4-valent vaccine) or AS04, an oil-in-water adjuvant also containing alum (Cervarix<sup>®</sup>, 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<sup>®</sup> adjuvant will not be compatible with devices that require a dry formulation. At least one investigator is evaluating the feasibility of coating Gardasil<sup>®</sup> onto solid microneedles.<sup>36</sup>

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

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<sup>36</sup> Mark Kendall, oral communication, March 18, 2009.

been completed (results not available)<sup>37</sup> and the first stage of the main immunogenicity study is underway.<sup>38</sup>

#### 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<sup>®</sup>), 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<sup>®</sup>, 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 Fludax<sup>®</sup> (Novartis) containing MF59<sup>®</sup> adjuvant, which is licensed for use in older people (aged  $\geq 65$  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.<sup>39</sup>

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<sup>37</sup> Professor Tony Nelson, oral communication, February 18, 2009.

<sup>38</sup> 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<sup>®</sup> (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<sup>®</sup>) 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.<sup>40</sup> 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.<sup>41</sup>

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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<sup>39</sup> Mark Kendall, oral communication, March 18, 2009; Mark Prausnitz, oral communication, February 20, 2009.

<sup>40</sup> Philippe Laurent, oral communication, March 2, 2009.

<sup>41</sup> 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.<sup>42</sup>

### 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.

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<sup>42</sup> 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.<sup>43</sup> 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.<sup>44</sup> 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.<sup>45</sup>

#### 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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<sup>43</sup> Martin Friede, oral communication, April 8, 2009.

<sup>44</sup> Global Post-eradication IPV Supply and Demand Assessment: Integrated Findings. Oliver Wyman Inc, March 2009.

<sup>45</sup> 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.<sup>45</sup> 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.<sup>46</sup>

##### 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

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<sup>46</sup> 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.<sup>47</sup>

### 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.<sup>48</sup>

### 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.

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<sup>47</sup> Dexiang Chen, oral communication, April 8, 2009.

<sup>48</sup> 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.<sup>49</sup>
- 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

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<sup>49</sup> 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.