Landscape Analysis

Trends in vaccine availability and novel vaccine delivery technologies: 2008–2025

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OPTIMIZE Immunization systems and technologies for tomorrow

PATH World Health Organization

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Acronyms and abbreviations

BCG	Bacille Calmette Guerin (for tuberculosis)
bioneedle	biodegradable implants
CDC	US Centers for Disease Control and Prevention
CMD	Classical Mexican Device
CMV	cytomegalovirus
conj.	conjugated (usually polysaccharide conjugated to protein)
D	diphtheria toxoid (d: low-dose; D: high-dose)
DCJI	disposable cartridge jet injectors
DPI	dry powder inhaler
DTP	diphtheria, tetanus, pertussis
EPI	Expanded Programme on Immunization
ETEC	enterotoxigenic *Escherichia coli* (*E. coli*)
Flu	influenza
HepA	hepatitis A
HepB	hepatitis B
HepE	hepatitis E
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
ID	intradermal
IM	intramuscular
IN	intranasal
IPV	inactivated polio vaccine
JE	Japanese encephalitis
LMICs	low- and middle-income countries
LT	heat-labile toxin of *E. coli*
Men	meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X)
MIT	Massachusetts Institute of Technology
MMR	measles, mumps, and rubella
MR	measles, rubella
MUNJI	multi-use-nozzle jet injector
N-S	needle and syringe
mOPV	monovalent oral polio vaccine (types 1, 2, or 3)
OPV	oral polio vaccine
P	pertussis
PATH	Program for Appropriate Technology in Health
PCV	pneumococcal conjugate vaccine
pMDI	pressurized metered-dose inhalers
Pneumo	pneumococcus (from *Streptococcus pneumoniae*)
PS	polysaccharide
RSV	respiratory syncytial virus
Sabin-IPV	inactivated polio vaccine made from Sabin attenuated strains
SC	subcutaneous
T (or TT)	tetanus toxoid
TB	tuberculosis
TCI	transcutaneous immunization
TIV	trivalent influenza vaccine
unconj.	polysaccharide unconjugated to protein
VZV	varicella zoster virus
WHO	World Health Organization
YF	yellow fever

Executive summary

A landscape analysis has been undertaken to identify trends in the availability of vaccines and novel vaccine delivery technologies that are and will be of relevance to low- and middle-income countries (LMICs) between now and 2025.

The key findings are:

- The number of vaccines potentially available for use in LMICs will increase during the period 2008–2025.
- Vaccine manufacturers are conservative, and the majority of existing and new vaccines will continue to be delivered by needle and syringe unless incentives and or data are generated to support alternative delivery methods.
- A wide range of novel vaccine technologies, many of which are needle-free and/or employ alternative immunization routes, are being developed. Overall, the goals of these technologies are to:
    - Reduce needle and syringe use.
    - Reduce the dose of vaccine required and/or reduce wastage.
    - Deliver the vaccine by a route that will stimulate an appropriate immune response.
- Some of the approaches will require significant effort to be spent developing appropriate vaccine formulations that are compatible with the delivery technology, in addition to developing the device/technology itself. Consequently, these approaches will not be available until the medium to long term (after 2015).
- Short-term activities are possible based on increasing use of existing technologies that would improve vaccination safety, such as increasing use of syringes with auto-disable and anti-stick mechanisms.
- Suitable combinations of delivery technology and “available” vaccine need to be identified for use in “demonstration” projects to evaluate new delivery technologies.
- Ultimately, introduction of novel vaccine delivery technologies will require their incorporation early in the development path of novel vaccines.

TRENDS IN VACCINE AVAILABILITY: 2008–2025

Choice of vaccine types to be surveyed

This landscape analysis surveys both the current and future availability of vaccines for use in low- and middle-income countries (LMICs) and the status of vaccine delivery technologies.

For the first part, 32 single and combination vaccine types/disease applications were selected on the basis that:

- They are considered high priority for use in LMICs.
- It was probable that one or more vaccines are likely to be licensed by 2025 (i.e., at least one vaccine is in phase I clinical trials).

A full list of the vaccines surveyed, including developers, formulations, and target populations is presented in References.

The survey used publicly available information, supplemented with documentation provided by PATH and other key stakeholders and transcripts of interviews of experts (see Annex 1 for details).

Vaccine availability and use: 2008–2025

Vaccine availability

From the survey (see Table 1), 18 vaccine applications/types currently have prequalified vaccines, 11 have licensed but no prequalified vaccines (yet), ~17 are likely to have new or "replacement" vaccines by 2015, and an additional ~4 are likely to have new or replacement vaccines by 2025.

These predictions are based on the following criteria:

- For a novel vaccine to be available in 2015, it was required to be in phase II or III trials in 2008. A few exceptions have been made:
    - Where the technology for a vaccine has been transferred to another manufacturer and is in production but likely to accelerate through clinical trials rapidly.
    - Where the vaccines have been used before singly but not in combination and are therefore likely to accelerate through trials more quickly than others.
- Vaccines predicted to be available by 2025 were required to be in phase I clinical trials in 2008.

However, it should be noted that:

- Overall, probabilities of success for vaccines in phase I trials have been estimated to be only 10–51% for most vaccines, and even lower for some disease applications (e.g., < 1% for malaria) (GAVI Alliance Vaccine Investment Strategy Project: http://www.gavialliance.org/vision/strategy/vaccine_investment/index.php).
- Different vaccines require different numbers of phase II/III clinical trials before licensing, and the trials are of varying duration.
- For most vaccine types surveyed, there will be a long list of promising candidates in preclinical development, some of which might be accelerated and reach the market before those listed in this analysis. It is also possible that these early-stage vaccines might benefit more from the applications of vaccine delivery technology than the more advanced vaccines.

Table 1. Summary of projected vaccine availability.

Prequalified vaccines available in 2008[a]	Approved, but not prequalified vaccines available in 2008	New vaccines possibly available by 2015	New vaccines possibly available by 2025
▪ BCG. ▪ Cholera. ▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ HepB. ▪ IPV. ▪ Measles. ▪ MenAC-unconj. ▪ MenACW135-unconj. ▪ mOPV1. ▪ OPV. ▪ MMR. ▪ MR. ▪ Rabies. ▪ Rotavirus. ▪ Tetanus. ▪ YF.	▪ DTP-HepB-Hib-IPV. ▪ Flu-pandemic[b]. ▪ Flu-seasonal. ▪ HepA. ▪ HPV. ▪ JE. ▪ mOPV3. ▪ PCV. ▪ Pneumo-unconj. ▪ Typhoid. ▪ VZV.	▪ Dengue. ▪ DTP-HepB-Hib-IPV. ▪ ETEC. ▪ Flu-pandemic[b]. ▪ Flu-seasonal. ▪ HepE. ▪ HPV (2nd generation and/or low cost). ▪ Malaria. ▪ Measles (dry powder). ▪ MenA-conj. ▪ MenACW135Y-TT. ▪ MR (dry powder). ▪ PCV. ▪ Rotavirus (low cost). ▪ Sabin-IPV. ▪ Shigella. ▪ TB.	▪ CMV. ▪ Flu-pandemic. ▪ Malaria (2nd generation). ▪ RSV.

a. United Nations/World Health Organization (WHO) prequalification information from WHO website, June 2008.
b. Includes "mock-dossier" and pre-pandemic vaccines.
Other information and predictions were derived from publicly available information (mainly from company websites).

Abbreviations used: BCG: Bacille Calmette Guerin, for tuberculosis; **CMV:** cytomegalovirus; **conj.:** conjugated, usually polysaccharide conjugated to protein; **D:** diphtheria toxoid (**d:** low-dose; **D:** high-dose); **ETEC:** enterotoxigenic *E. coli*; **Flu:** influenza; **HepA:** hepatitis A; **HepB:** hepatitis B; **HepE:** hepatitis E; **Hib:** *Haemophilus influenzae* type b; **HPV:** human papillomavirus; **IPV:** inactivated polio vaccine; **JE:** Japanese encephalitis; **Men:** meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X); **MMR:** measles, mumps, and rubella; **MR:** measles, rubella; **mOPV:** monovalent oral polio vaccine (types 1, 2, or 3); **OPV:** trivalent oral polio vaccine; **P:** pertussis; **PCV:** pneumococcal conjugate vaccine; **Pneumo:** pneumococcus, from *Streptococcus pneumoniae*; **RSV:** respiratory syncytial virus; **Sabin-IPV:** IPV made from Sabin attenuated strains; **T:** tetanus toxoid (or **TT**); **TB:** tuberculosis; **unconj.:** polysaccharide unconjugated to protein; **VZV:** varicella zoster virus; **YF:** yellow fever.

Delivery strategies

The delivery strategies used now and in the future (Table 2) impact the types of delivery technology (and logistics) that will be most appropriate.

For example, for routine use:

- Many vaccines will continue to be delivered in routine settings. Delivery technologies that are difficult to use or require lengthy preparation will be problematic in routine settings, as will the use of many disparate delivery technologies.

For campaign use or outbreak response:

- Novel delivery technologies or logistical procedures that are not the norm may be better suited for use in campaigns or outbreak response. For example, the use of aerosol measles vaccine would be easier to implement in a campaign setting, with focused training on the new delivery method.

The nature of the vaccine will impact the strategy, too; for example, a vaccine that can and should be given as a birth dose (contrasting with one used in older babies) might particularly benefit from a device that can be used easily by a birth attendant and a format that is unit dose.

From this survey, the number of vaccine types likely to be given as "routine" is likely to increase from 20 to ~32; as campaign, from 13 to ~16; and as outbreak response, from 8 to ~10. Some are given by more than one type of delivery strategy.

Table 2. Possible delivery strategies for current and future vaccines.

Routine		Campaign		Outbreak response	
2008	**Future**	**2008**	**Future**	**2008**	**Future**
▪ BCG. ▪ Cholera[a]. ▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ DTP-HepB-Hib-IPV. ▪ Flu-seasonal. ▪ HepA. ▪ HepB. ▪ HPV[b]. ▪ JE. ▪ Measles. ▪ MenAC-unconj. ▪ MMR. ▪ MR. ▪ OPV. ▪ PCV. ▪ Rotavirus[b]. ▪ Tetanus. ▪ YF.	▪ Cholera. ▪ CMV. ▪ Dengue. ▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ DTP-HepB-Hib-IPV. ▪ ETEC. ▪ HepA. ▪ HepB. ▪ HepE. ▪ HPV. ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ IPV. ▪ JE. ▪ Malaria. ▪ Measles. ▪ Men A-conj. ▪ Men AC-conj. ▪ MenACW135Y-TT. ▪ MMR. ▪ MR.	▪ DT/dT. ▪ DTP-HepB-Hib. ▪ HepA. ▪ HepB. ▪ HPV. ▪ JE. ▪ Measles. ▪ MenAC-unconj. ▪ MMR. ▪ MR. ▪ Tetanus. ▪ Typhoid. ▪ YF.	▪ CMV. ▪ DT/dT. ▪ Flu-pandemic. ▪ HepB. ▪ HPV. ▪ JE. ▪ Malaria. ▪ Measles. ▪ MenA-conj. ▪ MenACW 135Y-TT. ▪ MMR. ▪ MR. ▪ RSV. ▪ Shigella. ▪ TB (new). ▪ Tetanus.	▪ Cholera. ▪ DT/dT. ▪ HepA. ▪ MenAC-unconj. ▪ MenACW135. ▪ mOPV. ▪ Typhoid. ▪ YF.	▪ DT/dT. ▪ HepE. ▪ Flu-pandemic. ▪ Men A-conj. ▪ Men AC-conj. ▪ MenACW 135Y-TT. ▪ mOPV. ▪ Shigella. ▪ TB (new). ▪ Typhoid.

Routine		Campaign		Outbreak response	
2008	**Future**	**2008**	**Future**	**2008**	**Future**
	▪ OPV. ▪ PCV. ▪ Rotavirus. ▪ RSV. ▪ TB. ▪ Tetanus. ▪ Typhoid. ▪ VZV. ▪ YF.				

a. Has been used for routine vaccination in some countries.
b. Routine use expected soon.
Source: WHO position papers for vaccine applications supplemented with expert opinion from recent interviews by PATH staff.

Abbreviations used: BCG: Bacille Calmette Guerin, for tuberculosis; **CMV:** cytomegalovirus; **conj.:** conjugated, usually polysaccharide conjugated to protein; **D:** diphtheria toxoid (**d:** low-dose; **D:** high-dose); **ETEC:** enterotoxigenic *E-coli*; **Flu:** influenza; **HepA:** hepatitis A; **HepB:** hepatitis B; **HepE:** hepatitis E; **Hib:** *Haemophilus influenzae* type B; **HPV:** human papillomavirus; **IPV:** inactivated polio vaccine; **JE:** Japanese encephalitis; **Men:** meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X); **MMR:** measles, mumps, and rubella; **MR:** measles, rubella; **mOPV:** monovalent oral polio vaccine (types 1, 2, or 3); **OPV:** trivalent oral polio vaccine; **P:** pertussis; **PCV:** pneumococcal conjugate vaccine; **RSV:** respiratory syncytial virus; **T:** tetanus toxoid (or **TT**); **TB:** tuberculosis; **unconj.:** polysaccharide unconjugated to protein; **VZV:** varicella zoster virus; **YF:** yellow fever.

Extensions to target populations

For a few of the vaccine types surveyed, there are likely to be desired or actual extensions to the current target populations, which might affect the formulations and delivery technologies used (Table 3). For example:

- Extensions to a birth dose might require easier-to-use delivery technologies, for birth attendants to use outside a clinical setting, and/or technologies that can be administered safely and reliably to a neonate (e.g., intranasal [IN] dosing can be more difficult in babies).
- Extensions to younger or older age groups can require more-immunogenic formulations. Examples of this (though not necessarily relevant for LMICs) include:
    - Using novel adjuvants (e.g., MF59™ in Fluad™ seasonal influenza vaccine), which might not be compatible with some of the novel delivery technologies, for example, those that involve intradermal (ID) delivery.
    - Increasing the amount of antigen (e.g., Zostavax™ compared with Varivax™), which can increase the manufacturing costs and affect supply.

Table 3. Possible extensions in target groups by 2025.

Extend to birth dose	Extend to babies or younger children	Extend to boys[a]	Extend to elderly
▪ HPV. ▪ Rotavirus.	▪ Cholera. ▪ Flu-seasonal. ▪ HepA. ▪ HPV. ▪ Measles. ▪ Men. ▪ Pneumo. ▪ Typhoid.	▪ HPV (possibly).	▪ VZV.

a. This is an example of an extension within the same age group that is less likely to affect the delivery technology used.
Source: Survey of vaccines, using publicly available information.

Abbreviations used: Flu: influenza; **HepA:** hepatitis A; **HPV:** human papillomavirus; **Men:** meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X); **Pneumo:** pneumococcus, from *Streptococcus pneumoniae*; **VZV:** varicella zoster virus.

Trends in vaccine development

From this survey, some general points can be made regarding development of novel vaccines and their effect on identification of optimal delivery technology.

Combination vaccines vs. "single" vaccines

Combination vaccines, such as MR, MMR, DTP-HepB-Hib, and DTP-HepB-Hib-IPV, offer advantages in terms of:

- Reducing the number of injections required, which increases compliance and acceptability (and potentially reduces needlestick accidents/sharps waste).
- Usually reducing space required in the cold chain.
- Potentially reducing the direct costs of the vaccine and also its logistics (e.g., time spent reconstituting vaccines and administering them).

Disadvantages can include:

- Some combinations are as expensive as the single vaccines combined.
- Development costs can be high: they can require the formulation of diverse chemical entities with different stabilities, and non-inferiority trials will need to be performed.
- Sometimes they can make the schedules more complicated and reduce flexibility; additional doses of some antigens in the combination might be given to ensure other antigens have sufficient dosing.
- Combining antigens can reduce the immune response to some components; this is thought to be due to immunological interference. For example, Hexavac™ (DTP-HepB-Hib-IPV, Aventis Pasteur) was withdrawn in 2005 due to lower and varying immunogenicity to the HepB and Hib components,[1] although a similar vaccine (Infanrix Hexa™, GlaxoSmithKline) is still marketed. For this reason, some consider it unlikely that such combinations can be extended much beyond five or six components.

Many of the antigens used in combination vaccines are also sometimes needed as single vaccines:

- For birth doses, often just one antigen is required (e.g., HepB), meaning that countries utilizing the combination vaccine (e.g., DTP-HepB-Hib) might also need to purchase the single antigen HepB.
- Single antigens (or smaller combinations) are often required for booster doses (e.g., dT in older children and adults).
- The particular country purchasing the vaccine might prioritize one vaccine-type antigen higher than the others in the combinations, e.g., tetanus vs. diphtheria, or measles vs. mumps.

In conclusion, many of the existing vaccine types and new entrants will need to be available as singles, small combinations, and larger combinations for Expanded Programme on Immunization (EPI) use.

Polysaccharide and polysaccharide conjugate vaccines

Some vaccine types (e.g., Neiserria meningitis [Men] and pneumococcus [Pneumo]) aim to generate an immune response to polysaccharide epitopes, to which a long-lasting immune response is inherently difficult to generate. If the polysaccharide is linked (conjugated) to a protein, this usually increases its immunogenicity, giving a longer-lasting response that can be boosted in future years.

In general:

- There are likely to be further developments of conjugate vaccines, aiming for more-immunogenic vaccines (e.g., for Men and Pneumo).

A second issue is that some vaccine types (especially Men and Pneumo) stimulate serotype-specific immunity, but there are many circulating serotypes that vary geographically across LMICs. To protect against all serotypes requires more than one antigen source to be formulated in the vaccine.

In general:

- There are likely to be vaccines with increasing valencies (more serotypes included) aiming to increase the breadth of protection; however, some serotypes are much more difficult to formulate and especially conjugate.
- It should not be assumed that the perfect vaccine would include all serotypes. Epidemiology is very important in selection; for LMICs, meningitis A and C are the serogroups of most relevance because they are most associated with epidemics.
- In the future, there are likely to be alternative strategies that could change the landscape of these vaccines—for example, using protein subunit antigens that give a more broad-spectrum protection and circumvent some of the conjugation problems.

Enteric vaccines

The enteric vaccines are important for routine, campaign, and outbreak use in LMICs. There are prequalified rotavirus vaccines about to be used routinely in LMICs and also against cholera, and licensed but underused vaccines for typhoid. There are no licensed vaccines against either Shigella or enterotoxigenic *E. coli* (ETEC) but several in clinical and preclinical development.

In general:

- Live attenuated enteric vaccines are either already effective or show promise as oral vaccines, but inactivated, killed vaccines are also useful or under development.

- There can be some level of cross-reactivity and cross-protection; e.g., Dukoral™ provides some cross-protection against ETEC due to the cholera toxin B content of the vaccine.
- Some of the candidate vaccines in early or preclinical development are based on live attenuated strains (e.g., Shigella and Salmonella) expressing other antigens (e.g., ETEC); these have potential, therefore, to protect against more than one enteric pathogen.
- Combination vaccines against enteric pathogens tend to be developed/marketed in industrialized countries as "travelers' diarrhea" vaccines; these might also be appropriate for use in LMICs, provided they are suitable for use in the required target population and the costs are acceptable.

Polio

There are three existing vaccines for polio:

- Trivalent oral polio vaccine (OPV), which gives good protection against all three types, and is very easy to administer as an EPI vaccine.
- Monovalent oral polio vaccines (for types 1, 2, or 3), which have recently been licensed to help with outbreaks of a particular type because they are more immunogenic than the trivalent vaccine.
- Inactivated polio vaccine (IPV), which is probably less immunogenic and has to be given by injection, but is safer in the long term because there is no live virus shedding.

The choice of vaccine depends on the epidemiology in the country in question and the timing of polio eradication.

For routine use in LMICs, with eradication, there will be a move from OPV to IPV, and some countries might phase out routine polio vaccination completely. Work is underway to manufacture IPVs from attenuated Sabin strains to reduce the risk of escape of live poliovirus during manufacture.

Malaria

Malaria is the first parasite target for vaccines and inherently difficult for vaccine development (and implementation).

- Mosquirix™ (also known as RTS,S, GlaxoSmithKline) is the lead malaria vaccine candidate (in phase III trials) and could be in use by 2015. It is hoped that a second-generation vaccine (or combination with Mosquirix™) will increase the likely efficacy from the ~30% protection (against clinical disease) provided by Mosquirix™ to > 80%, which would make it more attractive to LMICs.
- There are several candidates in clinical development using a range of antigens (from various stages of the parasite), technologies (peptide, proteins, live vectors, attenuated parasites, or DNA), and approaches (including heterologous prime-boost), and with different targets (e.g., anti-infection, anti-disease, or anti-transmission). Most are likely to require injection, and some use novel adjuvants that might make them difficult to combine with other vaccines. At this stage, it is very difficult to predict which of the candidates in clinical/preclinical development are most likely to achieve license.

Tuberculosis

Tuberculosis (TB) is another inherently difficult vaccine development challenge. The existing live attenuated prequalified Bacille Calmette Guerin (BCG) (by ID vaccination) will most likely continue to be used routinely in EPI in LMICs until it can be replaced by one or more new-generation TB vaccines that both protect against severe disease in infants/children and give long-lasting protection to older age groups and preferably prevent latency and reactivation.

- Several vaccines are in clinical development, and there is a long preclinical pipeline. Some are modified BCG or live viral vectors, and some use proteins with novel adjuvants. They are more likely to be injected, but some in preclinical development could be administered orally or intranasally.

Immunization routes used for vaccine delivery

Immunization routes for current and expected vaccines

From this survey (Table 4), the majority of vaccines, live and killed, are currently delivered by either subcutaneous (SC) or intramuscular (IM) injection, and this situation is unlikely to change significantly by 2025. The obvious exceptions are vaccines (live or killed) against enteric pathogens, the majority of which are or will be delivered orally.

Immunization using routes other than SC/IM injection by needle and syringe (N-S) could yield potential benefits in terms of immunogenicity, acceptability, and ease of administration, as well as reducing the use of sharps (and associated hazards).

Table 4. Route of immunization used according to type of vaccine: live vs. inactivated.

	Live vaccines (attenuated organisms / live vectors)			**Inactivated vaccines** (proteins, PS, killed organisms)		
Route	**2008**	**2015**	**2025**	**2008**	**2015**	**2025**
SC/IM	▪ HepA. ▪ JE. ▪ Measles. ▪ MMR. ▪ MR. ▪ VZV. ▪ YF.	▪ CMV. ▪ Dengue. ▪ HepA. ▪ JE. ▪ Measles. ▪ MMR. ▪ MR. ▪ TB. ▪ VZV. ▪ YF.	▪ CMV. ▪ Dengue. ▪ HepA. ▪ JE. ▪ Malaria. ▪ Measles. ▪ MMR. ▪ MR. ▪ TB. ▪ VZV. ▪ YF.	▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ DTP-HepB-Hib-IPV. ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ HepA. ▪ HepB. ▪ HPV. ▪ IPV. ▪ JE. ▪ Men-unconj. ▪ Pneumo-conj. and unconj. ▪ Rabies. ▪ Tetanus. ▪ Typhoid.	▪ CMV. ▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ DTP-HepB-Hib-IPV. ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ HepA. ▪ HepB. ▪ HepE. ▪ HPV. ▪ JE. ▪ Malaria. ▪ Men-conj. ▪ MenACW 135Y-TT. ▪ PCV. ▪ Rabies. ▪ RSV. ▪ Sabin-IPV. ▪ Shigella.	▪ CMV. ▪ DT/dT. ▪ DTP-HepB. ▪ DTP-HepB-Hib. ▪ DTP-HepB-Hib-IPV. ▪ HepA. ▪ HepB. ▪ HepE. ▪ HPV. ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ JE. ▪ Malaria. ▪ Men-conj. ▪ MenACW135 Y-TT. ▪ PCV. ▪ Rabies. ▪ RSV. ▪ Sabin-IPV. ▪ Shigella.

	Live vaccines (attenuated organisms / live vectors)			Inactivated vaccines (proteins, PS, killed organisms)		
Route	**2008**	**2015**	**2025**	**2008**	**2015**	**2025**
					▪ TB. ▪ Tetanus. ▪ Typhoid.	▪ TB. ▪ Tetanus. ▪ Typhoid.
ID	▪ BCG.	▪ BCG.	▪ BCG.	▪ Rabies.	▪ ETEC (TCI). ▪ Flu-seasonal. ▪ Rabies. ▪ TB.	▪ CMV (DNA vaccine). ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ Rabies. ▪ TB (DNA vaccine).
Oral	▪ Cholera. ▪ OPV. ▪ Rotavirus. ▪ Typhoid.	▪ Cholera. ▪ OPV. ▪ Rotavirus. ▪ Shigella. ▪ Typhoid.	▪ Cholera. ▪ ETEC. ▪ Rotavirus. ▪ Shigella. ▪ TB (Shigella-vector). ▪ Typhoid.	▪ Cholera.	▪ Cholera.	▪ Cholera. ▪ Shigella. ▪ TB.
Respiratory (including IN)	▪ Flu-seasonal. ▪ Measles.	▪ Flu-pandemic. ▪ Flu-seasonal. ▪ MR (dry powder). ▪ Measles (dry powder).	▪ Flu-pandemic. ▪ Flu-seasonal. ▪ MR (dry powder). ▪ RSV. ▪ Measles (dry powder).		▪ RSV.	▪ HepB. ▪ RSV. ▪ Shigella. ▪ TB.

The estimates for when particular vaccines might become available use the same information sources and criteria described above. For expected or predicted vaccines, the best estimate of the likely route of delivery has been made based on the formulation of the candidate vaccine and the route of immunization being used in clinical trials. Overestimates might arise from the assumption that a vaccine licensed in 2008 (or 2015) will still be available in 2015 (and 2025). For vaccines, where a range of potential vaccine candidates are in relatively early stages of development (e.g., TB), it is not possible to predict which formulation (and therefore which route of immunization) will be successful. In these cases, several possibilities are included in the table. Some of the vaccines might also be used in novel combinations or as genetically engineered vaccines against two or more pathogens (see below).

Abbreviations used: BCG: Bacille Calmette Guerin, for tuberculosis; **CMV:** cytomegalovirus; **conj.:** conjugated, usually polysaccharide conjugated to protein; **D:** diphtheria toxoid (**d:** low-dose; **D:** high-dose); **ETEC:** enterotoxigenic *E. coli*; **Flu:** influenza; **HepA:** hepatitis A; **HepB:** hepatitis B; **HepE:** hepatitis E; **Hib:** *Haemophilus influenzae* type b; **HPV:** human papillomavirus; **ID:** intradermal; **IM:** intramuscular; **IN:** intranasal; **IPV:** inactivated polio vaccine; **JE:** Japanese encephalitis; **Men:** meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X); **MMR:** measles, mumps, and rubella; **MR:** measles, rubella; **OPV:** trivalent oral polio vaccine; **P:** pertussis; **PCV:** pneumococcal conjugate vaccine; **Pneumo:** pneumococcus, from *Streptococcus pneumoniae*; **PS:** polysaccharide; **RSV:** respiratory syncytial virus; **Sabin-IPV:** IPV made from Sabin attenuated strains; **SC:** subcutaneous; **T:** tetanus toxoid (or **TT**); **TB:** tuberculosis; **TCI:** transcutaneous immunization; **unconj.:** polysaccharide unconjugated to protein; **VZV:** varicella zoster virus; **YF:** yellow fever.

NOVEL VACCINE DELIVERY TECHNOLOGIES

Introduction

The role of route of immunization

Different vaccine delivery devices deliver vaccines to the body via different routes, which in turn has a significant effect on the nature of the immune response induced (Table 5).

Table 5. Advantages and disadvantages of available routes for vaccine delivery.

Vaccination route	Advantages	Disadvantages	Possible delivery technologies
Cutaneous (including SC, IM, ID)	▪ SC and IM are the established routes for the majority of vaccines. ▪ An efficient route of immunization, once the skin has been penetrated. ▪ Immunological correlates are established for many vaccines.	▪ Skin is a difficult barrier for large molecules (proteins) and inactivated micro-organisms to cross without use of needles.	▪ Needle-syringe. ▪ Prefilled reconstitution devices. ▪ Biodegradable implants. ▪ Jet injectors. ▪ Microneedles. ▪ Transdermal patches. ▪ ID needles. ▪ Prefilled syringes.
Respiratory (IN and pulmonary)	▪ Mimics the route of infection for many pathogens, so vaccine should induce appropriate immune response. ▪ Needle-free administration.	▪ Need to ensure delivery to the appropriate region of the respiratory tract. ▪ Effective vaccination is likely to require live vaccines, or the use of mucosal adjuvants or adhesives with inactivated vaccines. ▪ Controlling the dose of vaccine delivered can be difficult. ▪ Safety concerns, as the route offers direct access to the central nervous system. ▪ Administration can be difficult to congested infants.	▪ Inhalation devices. ▪ IN delivery.
Oral	▪ Ease of administration. ▪ Needle-free administration. ▪ Mimics the natural route of infection for enteric pathogens, so should induce appropriate immune response. ▪ Shedding of live attenuated vaccine can contribute to herd immunity.	▪ An inefficient route for immunization in terms of magnitude and duration of response.[2] ▪ Effective vaccination is likely to require live vaccines or large doses of inactivated vaccine. ▪ Delivery to the gastrointestinal tract might be less effective in some people in LMICs. ▪ Oral vaccines (e.g., Rotashield™) have been associated with rare but serious adverse events. ▪ Shedding of live attenuated vaccines can have safety issues.	▪ Prefilled reconstitution devices. ▪ Sublingual/buccal delivery. Buffered formulations or capsules for oral delivery (not reviewed).

Abbreviations used: ID: intradermal; **IM:** intramuscular; **IN:** intranasal; **LMICs:** low- and middle-income countries; **SC:** subcutaneous.

Vaccine delivery technologies surveyed

Eleven broad categories of delivery technologies were included in the survey (Table 6), ranging from ways to deliver vaccines more safely and/or more easily, to ease those that simplify the reconstitution process. Other technologies engage a different type of immune response using lower doses of antigen.

Each technology has been assigned a unique identifier (T001–T130), which is used to refer to technologies in the text. A full summary of the technologies reviewed is presented in Annex 2.

The output of the survey includes many more technologies that are not currently used for delivery of vaccines and/or may not be appropriate for vaccine delivery in LMICs because of cost or complexity. However, information has been recorded for these devices, because if they have potential to be developed into technologies appropriate for use in low-resource settings, the expertise and intellectual property is most likely to reside with the developers of these expensive and complex devices.

The survey of vaccine delivery technologies relied primarily on publicly available information, supplemented with documentation provided by experts, including PATH and WHO staff members, and an independent consultant (see References for details).

Table 6. Categorization of vaccine delivery technologies and associated benefits.

Category	Technology	Primary potential benefits
1	**Injection safety devices**	▪ Safer administration; reuse prevention and needlestick prevention. ▪ Can be used with any liquid vaccine. ▪ Readily available.
1.1	Auto-disable syringes.	
1.2	Anti-stick syringes.	
2	**Prefilled reconstitution devices**	▪ Prevents reconstitution errors. ▪ Available in unit doses. ▪ Integrated vaccine and device.
2.1	Prefilled reconstitution syringes.	
2.2	Prefilled reconstitution vials/pouches.	
3	**Implants**	▪ Integrated vaccine and device. ▪ Safer administration; no sharps for disposal. ▪ Unit dose. ▪ Potential for schedule reduction, dose-sparing (i.e., delivery of a reduced dose intradermally), and thermostability (no evidence yet).
3.1	Biodegradable implants.	
4	**Jet injectors**	▪ No sharps. ▪ Available in unit doses. ▪ Integrated vaccine and device (4.3). ▪ Dose-sparing possible.
4.1	Disposable cartridge jet injectors with prefilled unit dose cartridges.	
4.2	Disposable cartridge jet injectors: end-user filling.	
4.3	Single-use disposable jet injectors.	
4.4	Solid particle jet injectors.	
5	**Sublingual/buccal delivery**	▪ No sharps. ▪ Available in unit doses. ▪ Integrated vaccine and device. ▪ Ease of administration. ▪ Reduced pain.
5.1	Dissolvable tablets/wafers.	
5.2	Buccal/oral sprays.	
5.3	Oral patches.	

Category	Technology	Primary potential benefits
		▪ Reduced waste.
6	**Microneedles**	▪ Reduction in sharps. ▪ Available in unit doses. ▪ Integrated vaccine and device (6.2, 6.3, 6.4). ▪ Dose-sparing. ▪ Reduced pain. ▪ Reduced waste.
6.1 **6.2** **6.3** **6.4**	Hollow microneedles. Solid microneedles. Vaccine-coated microneedles. Dissolvable/biodegradable microneedles.	
7	**Inhalation/pulmonary delivery**	▪ No sharps. ▪ Available in unit doses. ▪ Potential for integrated vaccine and device. ▪ Reduced pain.
7.1 **7.2**	Liquid inhalation. Powder inhalation.	
8	**Intranasal delivery**	▪ No sharps. ▪ Available in unit doses. ▪ Integrated vaccine and device. ▪ Ease of administration. ▪ Reduced pain.
8.1 **8.2**	Nasal spray (powder). Nasal spray (liquid).	
9	**Transdermal delivery**	▪ Reduced sharps. ▪ Unit dose. ▪ Integrated vaccine and device. ▪ Reduced pain. ▪ Reduced waste.
9.1 **9.2**	Transdermal patches (microneedle-free). Transdermal patches with micro-electrodes.	
10	**Intradermal needle delivery**	▪ Available in unit doses. ▪ Potential for integrated vaccine and device. ▪ Dose-sparing.
10.1	Needle depth limiters.	
11	**Prefilled containers**	▪ Prevents dosing errors. ▪ Unit dose. ▪ Reuse prevention. ▪ Integrated vaccine and device. ▪ Ease of administration.
11.1 **11.2**	Prefilled syringes. Prefilled cartridges.	

Out of scope of the survey

Novel adjuvants and stabilization developments were excluded from this survey, but they are discussed briefly where they are relevant to potential use of the other delivery technologies. Information on the potential costs of the various devices was not included, as many are still in early research and development phases and a thorough analysis of offsetting factors for each vaccine and delivery technology pairing would be essential in order to take into account cost-saving factors such as reductions in vaccine wastage due to unit dose formats.

Key features of vaccine delivery technologies reviewed

1. Vaccine safety devices

Safety devices for N-S generally consist of mechanisms to prevent deliberate or accidental reuse of the syringe, or mechanisms for needle retraction to prevent needlestick injuries.

Auto-disable syringes
Auto-disable syringes are widely used in LMICs. Reuse is typically prevented by a mechanism that breaks the plunger if it is withdrawn after the injection has been delivered. The Star Syringe™ (T072) and BD Soloshot™ (T074) are examples that are used extensively. The BD Soloshot™ has also been designed with reduced dead space to minimize vaccine wastage.

Anti-stick syringes
Anti-stick devices usually consist of a cover or sleeve that extends over the needle following injection and locks in place. These devices are not currently used or widely used in LMICs. Examples of this type of mechanism are: BD K3™ Safety Cap (T073), BD Safetyglide™ needle (T120), BD Safety-Lok™ syringe (T121), and BD Preventis™ automatic needle shielding system (T122).

Combined auto-disable and anti-stick syringes
A number of syringes feature mechanisms whereby the needle is manually or automatically retracted into the syringe barrel after injection, thereby preventing accidental needlestick injury and preventing reuse of the syringe. Examples include:

- BakSnap® retractable safety syringe (DuoProSS, T077). In this device, the needle is retracted into the barrel and the plunger can be snapped off to disable the syringe.
- Vanishpoint™ syringe (T080), Unitract™ safe syringe (T081), and InviroSNAP safety syringe (T103). All have mechanisms for retracting the needle into the barrel, sometimes with additional features to ensure that it remains locked in place.
- Ultrasafe Passive™ delivery system (T119). This device has a more sophisticated, spring-powered auto-retraction mechanism. It is used with the Gardisil and Vaqta vaccines (both from Merck).

Table 7. Potential opportunities from use of vaccine safety devices.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Auto-disable technologies are currently available and in use. ▪ Combined auto-disable and anti-stick syringes provide opportunity to protect health care workers as well as patients. ▪ Increased uptake and use should be possible, as reformulation of vaccines and device development is not necessary. ▪ Potential for further reduction in needlestick injuries and transmission of bloodborne pathogens.	▪ No additional advantages beyond increasing uptake and use.	▪ Needles remain involved in vaccine delivery.

2. Prefilled reconstitution devices

The aim of reconstitution devices is to allow the processes of reconstitution and vaccine delivery to take place in a smooth, automatic, and error-free manner. Ideally, the acts of drawing up the correct and appropriate volume of diluent, adding it to the vaccine, ensuring complete mixing, drawing up the correct dose of reconstituted vaccine, and delivering the vaccine to the recipient are "automated" as far as possible.[3]

Prefilled reconstitution devices will have a significant role if and when dry-powder thermostable formulations of vaccine become available. Introducing a reconstitution step for a vaccine that is currently in a liquid formulation is considered to be unacceptable, unless the process is automatic and seamless and eliminates the errors that are known to occur at present with reconstitution (mismatched supply of diluent and vaccine, use of incorrect quantities, misdosing of diluent, use of a second needle, and contamination of multi-dose diluent or reconstitution vials).[4]

There appear to be few reconstitution devices available or in development for vaccine use.

- Several of the devices available are likely to be too expensive for use in LMICs. However, several promising, potentially low-cost technologies are:
  - Immunoject™ (T042), which has an integrated needle.
  - Creare's Single Vial System™ (T038) (development of this system may have stopped).
  - Frangible Seal Pouch™ (T039).
    The three systems above are likely to be compatible with a range of injection or delivery devices.
  - One of the most promising devices, Act-O-Vial™ (T040), has been used as a presentation for hydrocortisone (SOLU-CORTEF™). It is believed to be manufactured in low volumes only.[5]

Table 8. Potential opportunities from use of prefilled reconstitution devices.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ No immediate benefits because suitable devices are not currently available and/or not manufactured in large volumes. ▪ Introduction of novel reconstitution devices is possible by 2015 for use with existing lyophilized vaccine formulations. ▪ They improve speed and accuracy of reconstitution and dosing.	▪ Novel dry-powder formulations (e.g., thermostable spray-dried powders) could be introduced in prefilled reconstitution packaging.	▪ Devices tend to be suited for use with N-S or oral vaccines. ▪ Switching the packaging of an existing vaccine to a new reconstitution device is likely to require modification of the filling process by the manufacturer, stability testing, and regulatory approval of the changed container.

Abbreviation used: N-S: needle and syringe.

3. Biodegradable implants

Biodegradable implants (or bioneedles) consist of solid doses of vaccine delivered to the deep tissues or subcutaneous space. Subsequent controlled or slow-release of vaccine from the implant could potentially reduce the number of booster doses required for a vaccine. However, data to support this concept have not been generated to date. Bioneedles incorporating tetanus toxoid and trehalose have been shown in preclinical studies to have equal immunogenicity to and greater thermostability than standard, liquid tetanus toxoid.[6]

Use of bioneedles will require reformulation of existing vaccines. Delivery of the implants could be needle-free and might involve reduced pain compared with N-S (due to the high velocity of injection),[7] but will require specialized devices with compressed air or spring-powered mechanisms.[8,9]

- The Bioneedle Group™ (T024) and Solid Dose Injector™ (Glide Pharma, T026) are probably the leaders in this field regarding formulation and delivery of vaccines.

Table 9. Potential opportunities from use of biodegradable implants.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ The introduction of a biodegradable implant vaccine by 2015 is unlikely.	▪ They might be compatible with thermostable vaccine formulations. ▪ Controlled release of vaccine might reduce the number of booster doses required, but this concept has not yet been proven.	▪ Delivery devices might be complex and costly. ▪ Will require reformulation of existing vaccines.

4. Jet injectors

Jet injectors propel liquid at high pressure to deliver medications through the skin without needles. They have been used to deliver hundreds of millions of doses of vaccines over the past 50 years.[10]

- The vast majority of these were delivered using multi-use-nozzle jet injectors (MUNJIs). However, concerns that MUNJIs could be responsible for transmission of bloodborne pathogens between consecutive vaccine recipients led to the discontinuation of their use.[10] Attempts to circumvent these problems by incorporating disposable caps have not been successful.[10]
- Therefore, devices currently being developed and considered in this analysis are either disposable cartridge jet injectors (DCJIs—see below), or single-use disposable jet injectors where the whole device is discarded after a single use.
- Jet injectors for delivery of DNA vaccines are also being developed (PowderMed, T126).

Jet injectors offer the benefits of needle-free vaccine delivery and the potential for dose-sparing by virtue of the fact that delivery can be targeted to the intradermal layer. Currently, DCJIs have regulatory approval only for SC or IM delivery of vaccines. Local adverse effects following jet injection are generally comparable to or slightly higher than those associated with N-S, particularly with vaccines containing alum adjuvants. Surveys of usage of the Biojector® 2000 (T069) in the United States have found its usage characteristics to be acceptable for adult and pediatric vaccinees. Injection-site bleeding and ecchymosis are rare, but occur more often than with N-S.[10] However, jet injectors could, in theory, be suitable for all inactivated, subunit, or conjugate vaccines currently delivered by N-S. One outstanding concern is the potential reactogenicity of alum-adjuvanted vaccines, particularly when delivered intradermally. This will be evaluated as part of the DCJI evaluation project being undertaken by PATH, WHO, and the US Centers for Disease Control and Prevention (CDC).

Single-use disposable jet injectors are likely to be too expensive for widespread use in LMICs and are not considered further. PowderMed's jet injectors are also fully disposable and are being developed specifically for DNA vaccines coated onto gold particles and so would likely not be affordable for LMICs.

DCJI design features

DCJIs consist of an "injector device" or "handpiece" that contains the propellant mechanism or power source (such as a spring) into which disposable single-use cartridges are inserted. Each cartridge (or needle-free syringe) has its own sterile orifice and nozzle.

- The majority of DCJIs are used for self-administration of insulin and other hormones, and this has driven their design. The notable exception is the Biojector® 2000 (T069), which is used to administer approximately 1 million vaccine doses per year at private, public, and US Navy and Coast Guard immunization clinics.[10]
- DCJIs that have been developed for delivery of vaccines can generally be adapted to deliver vaccines SC, IM, or ID by incorporating spacers that alter the distance between the nozzle and the skin. The Biojector® 2000 (T069) has been used in ID dose reduction studies in Cuba (6-, 10-, and 14-week-old infants), Oman (2-, 4-, and 6-month-old infants), and the Dominican Republic (6- to 24-month-old infants).
- No currently available DCJI has a design appropriate for vaccine delivery in LMICs. Draft design specifications for DCJIs have, however, been produced by WHO.[11]

DCJI evaluation

A number of prototype or development DCJI devices meet the majority of the proposed WHO design requirements, including:

- Zetajet™ (Bioject, T070).
- E-Jet500™ (Euroject, T060).
- Pharmajet™ (PharmaJet, Inc., T064).
- Lectrajet® M3RA (D'Antonio Consultants International, T068).

Some or all of these will be evaluated as part of a four-year collaborative project led by PATH, involving the CDC, WHO, and others, to demonstrate the feasibility of using DCJIs to deliver routine EPI vaccines at the current dose via the existing route, whether ID, SC, or IM. The program will also explore the potential for dose-sparing by delivery of reduced doses by the ID route.

Table 10. Potential opportunities from use of jet injectors.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ The aim of the PATH DCJI evaluation project is to have a fully validated, WHO prequalified, production-ready technology ready for adoption by LMICs no later than 2011.	▪ Reduction of sharps, sharps waste, and needlestick injuries and associated costs. ▪ Simplified SC, IM, and ID delivery. ▪ Reformulation of existing vaccines is not needed. ▪ Cartridges might have lower transportation costs than prefilled syringes.[11] ▪ Potential for dose-sparing via ID delivery, leading to improved accessibility for high-cost vaccines and vaccines for which manufacturing capacity is limited.	▪ Ideally require prefilling of cartridges by vaccine manufacturers. ▪ Use of prefilled cartridges requires regulatory approval of the device and vaccine combination product, rather than approval of the device only. ▪ Use of prefilled cartridges could also be dependent on adoption of industry-standard designs for cartridges, which would need strong links between vaccine and DCJI manufacturers.

Abbreviations used: DCJI: disposable cartridge jet injectors; **ID:** intradermal; **IM:** intramuscular; **SC:** subcutaneous; **LMICs:** low- and middle-income countries; **WHO:** World Health Organization.

5. Sublingual/buccal delivery

Oral delivery of drugs via the sublingual or buccal routes has attracted considerable interest because it offers a needle-free route of administration and avoids the degradation of active moieties (especially proteins) by enzymes and low pH in the gastrointestinal tract. For some vaccines, this route has the additional advantage of stimulating local mucosal immune responses. Furthermore, unlike IN immunization, sublingual delivery does not pose the risk of redirection of antigen or adjuvant to the central nervous system.[12] Recently published preclinical studies in mice suggested that the sublingual route is an effective route for delivery of inactivated influenza vaccine and a model protein antigen (ovalbumin)[13,14]; however, these studies used powerful mucosal adjuvants to induce an immune response. Delivery of a DNA vaccine has also been demonstrated using a buccal patch.[15]

- Aridis Pharma is developing a heat-stable, thin-film formulation of a live attenuated rotavirus vaccine (Rotavax™, T032). This is probably the most advanced application of this technology for vaccine delivery.

Table 11. Potential opportunities from use of sublingual/buccal delivery.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Unlikely to be available for vaccine delivery by 2015.	▪ Simple, needle-free delivery. ▪ Suitable for self-administration. ▪ Induction of local mucosal immune responses.	▪ Reformulation of existing vaccines will be required. ▪ Might be applicable only to live attenuated vaccines against enteric pathogens; alternatively, potent, novel mucosal adjuvants might be required, which could lengthen development timelines.

6. Microneedles

Use of microneedle patches for minimally invasive delivery of vaccines across the skin is an area of active research. Microneedle devices can be grouped into five categories:

- Transdermal patches (see Section 9).
- Uncoated microneedles.
- Solid vaccine-coated microneedles.
- Biodegradable microneedles.
- Hollow microneedles.

Uncoated microneedles

- The Onvax™ system (Becton Dickinson, T020) employs a "microenhancer array" of silicon or plastic microprojections on a hand-held applicator. This is used to abrade the skin before or after topical application of liquid vaccine. Preclinical experiments have demonstrated immune responses as good as those seen with IM injection, but not as good as those obtained with ID injection using a syringe-based microneedle (T019).[16]
- 3M's Microstructured Transdermal System™ (T002) can also be used in a similar configuration. Control of the dose of vaccine delivered might be difficult using this approach, and there might be safety concerns with live attenuated vaccines.

Solid vaccine-coated microneedles
Vaccine (protein or DNA) is coated onto solid microneedles on a patch or array prior to application to the skin. Early preclinical and clinical results are encouraging, although few details are available. This approach will require development of suitable formulations. A major concern is whether a sufficient payload of vaccine can be loaded onto the microneedles using this approach.

- The leading devices are probably the Macroflux™ system (Zosano Pharma, T001) and the Microstructured Transdermal System™ (3M, T002).

Biodegradable microneedles
Microneedles are fabricated from the active vaccine plus generally recognized as safe excipients. The feasibility of manufacturing biodegradable microneedles has been demonstrated,[17] but the technology is at a very early stage and data showing successful delivery of a vaccine are not yet available.

Hollow microneedles
Hollow microneedle arrays can be applied to patches or, in some cases, can be fitted to the end of a syringe. Engineering hollow microneedles that do not break, block, or require high pressure in order to deliver the vaccine is technically demanding.[18]

- Combining the microneedles with syringes (e.g., Nanoject™ [Debiotech, T011] and Micronjet™ [Nanopass Technologies, T012]) overcomes some of these problems and has the advantage of employing existing technology to ensure the full dose of vaccine is delivered. These devices are being evaluated at PATH for the ID delivery of rabies vaccine.
- Becton Dickinson's Soluvia™ (T019) device consists of a single microneedle fitted to a prefilled syringe. The system was licensed to Sanofi Pasteur in 2005. In February 2008, Sanofi filed an application with the European Medicines Agency to use Soluvia™ for the delivery of trivalent influenza vaccine, following trials in > 7,000 subjects. Preclinical studies with a prototype device resulted in better immune responses than SC, IM, and topical delivery of anthrax vaccine.[19]

Microneedles: general features
Once the skin has been penetrated, delivery of vaccines to the epidermal or dermal layers is a very efficient route of immunization, which also offers the potential of dose-sparing. Furthermore, the microneedles employed in these devices are designed to be too short to trigger pain receptors.

In theory, microneedle delivery could be feasible for all vaccines that are currently delivered by N-S, particularly inactivated, subunit, or conjugated vaccines; however, it is by no means certain that dose-sparing will result in an equivalent immune response for all (or any) vaccines. It is possible, even likely, that novel formulations of vaccines will be needed. Vaccines might need to be concentrated so that the same amount of antigen can be delivered in a smaller volume. Adjuvants based on aluminum salts might have unacceptable safety profiles when delivered ID and will need to be replaced with novel adjuvants that have different mechanisms of action and better reactogenicity profiles in the skin.

Table 12. Potential opportunities from use of microneedles.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Hollow microneedle delivery of existing formulations of liquid vaccines could have dose-sparing benefits, assuming reactogenicity profiles are acceptable. ▪ The delivery of novel vaccines with liquid formulations, especially if they are developed specifically for ID delivery. ▪ Coated and/or biodegradable microneedle delivery is unlikely to be available by 2015.	▪ Increased uptake of hollow microneedle technology for novel and existing liquid vaccines with potential dose-sparing benefits. ▪ Development of formulations compatible with biodegradable or coated microneedles, offering dose-sparing, thermostability, and ease of administration.	▪ Microneedles might still have the potential to transmit bloodborne pathogens and so need to be treated as "sharps;" however, any risks are likely to be far less than for N-S. ▪ Extensive vaccine formulation development will be needed for some formats. ▪ Patches might be required to be in place for minutes–hours; confirming delivery of the full dose might be difficult.

Abbreviations used: ID: intradermal; **N-S:** needle and syringe.

7. Inhalation/pulmonary delivery

The optimal target tissue within the respiratory tract for vaccine delivery has not yet been identified. For the purposes of this survey, devices for respiratory delivery of vaccines have been divided into those for aerosol delivery to the lungs (but they might also deliver a proportion of the dose to the nasal tissues) and those designed specifically for IN delivery (see Section 8).

- Large-scale pulmonary vaccination has been achieved with measles vaccine, using the custom-made "Classical Mexican Device (CMD)," which incorporates a jet nebulizer. Seroconversion rates compared favorably with SC immunization, although many children received much higher doses of vaccine than was necessary (reviewed in Section 1).
- The CMD had several design limitations, and WHO has identified three nebulization devices manufactured by Omron, Trudell, and Aerogen that meet the desired performance criteria. Examples of each of these technologies are provided in Annex 2 (T086, T097, T125. NB: the devices listed may not be exactly the same as those identified by WHO). The current WHO Measles Aerosol Project aims to license at least one method for aerosol delivery of measles vaccine.

Inhalers can be classified into three major categories:

- Nebulizers.
- Pressurized metered-dose inhalers (pMDI).
- Dry powder inhalers (DPI).

Inhalers can further be classified into:

- Active (aerosol generated by an external energy source) devices.
- Passive (aerosol generated by patient's inspiratory effort) devices.

Nebulizers
Nebulizers can deliver larger doses than pMDIs and DPIs, with very little patient involvement or skill required; however, delivery is time-consuming and relatively wasteful of active ingredients.[20]

- Breath-activated nebulizers (e.g., AeroEclipse™, T125) aim to reduce waste by ensuring the aerosol is delivered during inspiration only.

The high shear forces involved in nebulization have been reported to degrade large molecules: a 71% loss in measles vaccine potency was reported after the CMD was run continuously for 20 minutes.[21]

pMDIs
The majority of pharmaceutical aerosol products are pMDIs; however, they have several drawbacks for vaccine delivery. First, only a small amount of the emitted dose (10–20%) is delivered to the lungs. Second, most devices require hydrophobic propellants, which are incompatible with vaccine formulations. Finally, breath-actuated devices are required to overcome problems arising from poor hand-to-mouth coordination.[22]

DPIs
DPIs avoid the use of propellants; aerosols are created by directing air through loose powders of active substance plus inert carrier. Active DPIs reduce the inspiratory effort required by the patient, and are, therefore, more suitable for use with infants. Notable devices in this category include:

- Spiros™ Inhalers (T099), originally developed by Dura Pharmaceuticals (subsequently acquired by Elan). These are breath-activated, battery-powered devices originally developed for measles vaccine delivery.[23]
- Pulmonary DPIs (Nektar, T089), which were designed to be compatible for use with Nektar's thermostable, spray-dried, sugar-glass powders. Delivery is independent of patient inspiratory effort.
- Aspirair™ (Vectura, T094), a high-efficiency device, claimed to be more economical than most DPIs.
- Newborn inhaler device (Massachusetts Institute of Technology [MIT], T106), a prototype, low-cost device designed for delivery of particulate bacterial vaccines to infants.[24]

A coordinated program is being funded by the Bill & Melinda Gates Foundation Grand Challenges in Global Health program to develop a thermostable, dry-powder formulation of measles vaccine. Formulations are being developed by Aktiv-Dry, and one part of the program involves developing, in association with Becton Dickinson, an inexpensive, single-dose dispenser that delivers the vaccine to the respiratory tract.

Aerosol delivery: concerns and drawbacks
Some of the main concerns regarding pulmonary vaccine delivery include the following:

- Aerosol has the potential to exacerbate respiratory diseases such as asthma, and excipients in aerosol formulations can be allergenic, particularly for vaccines manufactured in eggs.
- Inactivated vaccines can be poorly immunogenic when delivered by the respiratory route unless potent adjuvants are used; however, use of *E. coli* heat-labile toxin (LT) in an IN influenza vaccine was associated with an increased risk of Bell's palsy in vaccinees, and the vaccine was withdrawn from the market in 2001.[10]
- Passive devices that require the patient's inspiration to generate the aerosol might be unsuitable for vaccination of infants who might not have the respiratory power required.
- In general, dosing might be unreliable if a single inhalation is used to deliver the vaccine. In contrast, active devices are likely to be more dependable in terms of dose delivered, but treatment may require 30–60 seconds per recipient.

Finally, it should be noted that several of the inhaler devices were being developed for the delivery of inhaled insulin. The lead product, Exubera™, was recently withdrawn from the market due to concerns of increased risk of lung cancer in former smokers (news article in *Nature Biotechnology*. 2008;26(5):479). This has led to the cancellation of several other similar programs. While these devices were not necessarily suitable for vaccine delivery in LMICs, it is possible that these events will have an impact on development of inhaler technology overall.

Table 13. Potential opportunities from use of inhalation/pulmonary devices.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Introduction is likely of an aerosol formulation of measles (or measles-rubella) for campaign use.	▪ Needle-free delivery of thermostable, dry-powder formulations is likely.	▪ Risk of exacerbation of respiratory diseases. ▪ Problems controlling the destination and the amount of dose delivered. ▪ Might be suitable only for live attenuated vaccines.

8. Intranasal delivery

IN delivery shares many of the advantages and also disadvantages associated with pulmonary aerosol delivery: it should stimulate beneficial, local, mucosal responses, and vaccination is needle-free; however, in the absence of suitable mucosal adjuvants, the IN route is likely to be suitable only for the delivery of live attenuated vaccines.

Liquid nasal sprays

- The Accuspray™ (Becton Dickinson, T056), used to deliver the live attenuated influenza vaccine. FluMist™ is currently licensed for IN vaccine delivery in the United States. It consists of a prefilled spray syringe that is simple to use, inexpensive, and disposable.[10] The Accuspray™ was also used to deliver an experimental adjuvanted hepatitis B vaccine (NASVAC™); however, 5 doses of 100µg per dose were required for good seroconversion,[25] illustrating the relative inefficiency of the IN route for non-live vaccines.
- The VP3 pump™ (Valois, T049) has been used in phase I trials of influenza[26] and Shigella[27] vaccines.
- The OptiMist™ device (OptiNose AS, T057) has also been evaluated for inactivated influenza vaccine delivery, either with or without mucosal adhesive and adjuvant. The device is activated by exhalation, which closes the connection between the nose and throat, ensuring the dose is deposited in the nose and not the lungs. The device can also be used with dry-powder formulations.

Dry powder delivery
Becton Dickinson is developing an investigational DPI (T107), which has been evaluated in preclinical studies. Considerable effort is also being directed to the development of novel adjuvants, delivery vectors, and formulations that enhance IN delivery; however, these approaches lie outside the scope of this report.

Table 14. Potential opportunities from use of IN delivery devices.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Likelihood of an increased uptake of live attenuated influenza vaccines delivered by IN route.	▪ Likely IN delivery of novel vaccines (live or with suitable adjuvant) against respiratory pathogens (e.g., RSV).	▪ Risk of exacerbation of respiratory disease. ▪ Problems controlling the destination and amount of the dose delivered, particularly in infants with active nasal infections and/or secretions. ▪ Might be suitable only for live attenuated vaccines.

Abbreviations used: IN: intranasal; **RSV:** respiratory syncytial virus.

9. Transdermal delivery

Many systems have been developed for transdermal delivery of small-molecule drugs, most of which are not applicable to the large molecules or whole organisms used in vaccines and so have not been included in Annex 2.

For transdermal delivery of vaccines, some means of disrupting the stratum corneum is required to allow large molecules to reach the dermal or epidermal layers. Use of microneedles to abrade the skin has already been discussed (Section 6). Other approaches to breach the stratum corneum are being evaluated, such as electromagnetic energy; however, it is questionable whether these sophisticated approaches will be appropriate for use in LMICs.

- The most advanced technology for needle-free transdermal delivery is Iomai's transcutaneous immunization (TCI) (T016). The LT of ETEC and the B subunit of cholera toxin are powerful adjuvants and are able to induce strong immune responses against themselves. These molecules may be able to pass through the stratum corneum more readily than other proteins, or, more likely, the minute amounts of LT and the B subunit of cholera toxin that reach the epidermis are able to induce a potent immune response. These molecules appear to be the only proteins for which passive TCI might be appropriate. Recent data from a phase II clinical trial of a travelers' diarrhea vaccine based on TCI delivery of LT showed that the vaccine provided significant protection against severe disease.[28] However, pretreatment with a mild abrasive is still required, and the LT patches need to be worn for 5–8 hours to ensure delivery of vaccine,[29] which raises issues regarding time taken for vaccination and how to ensure full patient compliance.

Table 15. Potential opportunities from use of transdermal technology.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Likely development of needle-free TCI ETEC vaccine, based on LT.	▪ Likely development of TCI-based cholera vaccine.	▪ LT is expressed by only 53% of ETEC isolates[30]; vaccination takes approximately 6 hours. ▪ The approach might be applicable only to a very small subset of proteins.

Abbreviations used: ETEC: enterotoxigenic *E. coli*; **LT:** heat-labile toxin of *E. coli*; **TCI:** transcutaneous immunization.

10. Intradermal needle delivery

ID delivery using N-S can be performed using the Mantoux technique; however, this is considered to be slow and technically difficult. Modification of N-S so that they can be easily used for ID delivery might provide some of the benefits associated with dose-sparing.

- The Soluvia™ device (Becton Dickinson, T019) represents one approach to achieve this end, by developing a syringe with a single microneedle.
- Another approach actively being pursued in a collaboration between PATH and SID Technologies (T018) is the development of an adapter that can be used with standard needles. The approach should be low cost and simple to develop.

Table 16. Potential opportunities from use of ID needle delivery.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Delivery of existing (or concentrated) formulations of liquid vaccines could have potential dose-sparing benefits, assuming reactogenicity profiles are acceptable. ▪ Likely to be delivery of novel vaccines with liquid formulation, especially if developed for ID delivery.	▪ Likely to be increased evaluation and uptake of hollow microneedle technology for delivery of novel and existing liquid vaccines.	▪ Continued use of sharps. ▪ Possible reactogenicity of adjuvants.

Abbreviation used: ID: intradermal.

11. Prefilled syringes

Prefilled syringes are already used for some vaccines, e.g., HepB, tetanus, DTP-HepB (Ecovac4™, Panacea) (all in Uniject™ devices); HepA, dT, HepB, HPV, MenC, MenACW135Y, rabies, typhoid, and VZV. Prefilled syringes reduce vaccine wastage, avoid the need for preservatives, simplify delivery, and reduce vaccine administration errors.

Table 17. Potential opportunities from use of prefilled syringes.

Opportunities 2008–2015	Opportunities 2015–2025	Barriers to use
▪ Likely increased use of prefilled syringes for existing and novel vaccines.	▪ Likely increased use of prefilled syringes for novel vaccines.	▪ Continued use of sharps. ▪ Unit dose format takes up more cold chain space.

Additional technologies that are relevant to the future development of vaccine delivery

This landscape analysis has focused on vaccine delivery ***devices***; therefore, several areas of active research relevant to enhancing the efficacy of vaccines were not covered, including:

Vaccine platform technologies
New platform technologies for the active components of vaccines have been considered only on a vaccine-specific basis. Some technologies have the potential of altering the composition, and therefore, the delivery and storage of a wide range of vaccines.

- *DNA vaccines*
  DNA vaccines offer many potential advantages for vaccine design and delivery, including ease of manufacture and stability at room temperature; however, despite being the focus of active research for nearly two decades and some encouraging results in small-rodent models, clinical trials have yet to demonstrate efficacy in humans. In order for DNA vaccines to achieve a radical impact on vaccination, step changes both in their delivery and immunogenicity will be required.
- *Heterologous prime-boost regimens*
  Heterologous prime-boost regimens (in which the antigen is delivered in more than one format in the prime and boost immunizations) have received much attention because of their ability to stimulate broad immune responses, and cell-mediated immune responses in particular. Typically, preclinical regimens consist of a DNA vaccine prime, followed by a boost with a live attenuated viral vector expressing the same antigen. Use of these potentially complex regimens, possibly involving live, genetically modified virus vectors, will have a significant impact on storage and delivery technologies required.

Adjuvants
The majority of inactivated (killed organism, protein, or protein-polysaccharide conjugate) vaccines need to be formulated with an adjuvant in order to be immunogenic. This is particularly true if vaccines are delivered via mucosal routes. Many of the vaccine delivery technologies discussed in this analysis would benefit from the development of novel adjuvants, such as:

- Adjuvants that promote antigen presentation in the dermis but that are non-reactogenic, or
- Adjuvants that enhance mucosal responses.

Adjuvants are regarded as an active component of a vaccine formulation, and as such, have not been included in this analysis.

Delivery vehicles
Micro- and nano-particulate formulations are essentially “delivery vehicles” for vaccines. They can provide many beneficial properties, including:

- Slow or controlled release.

- Enhanced immunogenicity.
- Improved delivery to the lungs or nasal passages.

Use of different particulate formulations will have an impact on which delivery technology will be most appropriate for a vaccine; however, because the delivery vehicle is an aspect of the vaccine formulation, analysis of the relative merits of the various particle and emulsion formulations was not within the scope of this report.

Factors to be considered when evaluating new vaccine delivery technologies

Implications of changes to approved vaccines

Regulatory implications

Changing the delivery device and/or formulation of an existing, approved vaccine requires the generation of new data to support the changes and regulatory approval for the changed product before it can be used. The degree of testing and level of scrutiny will depend upon the relevant national regulatory authority and the type and extent of change. The exact nature of testing and regulatory approval will be case-specific. An ***indication*** of the regulatory implications of changes relevant to use of new delivery devices is shown in Table 18.

All the changes will require approval from the relevant national regulatory authority, ranging from a notification of the change to a full new biologics license application, e.g., for the Food and Drug Administration in the United States.

Clinical trials to support changes to formulation or mode of delivery are more straightforward for vaccines that have defined immunological correlates. In the absence of a defined immunological correlate of protection, it might be possible to conduct a "non-inferiority clinical trial" using an immunological endpoint; however, if the route of vaccination is changed significantly (e.g., SC/IM injection to ID delivery by a patch), it is possible that a qualitatively different immune response would be induced, so trials based on immunological correlates or non-inferiority of immune response (e.g., serum immunoglobulin G titers) would not be based on valid comparisons.

Table 18. Examples of changes in vaccine formulation or delivery device and the likely level of retesting required to support the new product (by the US Food and Drug Administration).

	Data required to support changes to approved vaccine			
Type of change	**Analytical testing (incl. stability)**	**GLP[a] animal studies (toxicity or efficacy)**	**Clinical trials, adult**	**Clinical trials, pediatric**
Product presentation (no reformulation)				
Change in container.	**Stability**	**No**	**No**	**No**
Liquid-powder or powder-liquid.	**Yes**	**Probably**	**Probably**	**No**
Change in inactive components				
Removing preservatives.	**Yes**	**No**	**No**	**No**
Adding approved excipient.	**Yes**	**Probably**	**Probably**	**Probably**
Adding novel excipient.	**Yes**	**Yes**	**Probably**	**Yes**
New delivery method (no reformulation)				
New route.	**No**	**Yes**	**Yes**	**Yes**
Dose reduction/increase.	**No**	**Maybe**	**Yes**	**Yes**
New device				
New device and route.	**Yes**	**Yes**	**Yes**	**Yes**
New device and formulation.	**Yes**	**Yes**	**Yes**	**Yes**
Change in active components				
Adding an adjuvant (approved or novel).	**Yes**	**Yes**	**Yes**	**Yes**

Adapted from *Vaccine Development and Reformulation Challenges*, PATH internal document; 2008.
a. GLP: Good Laboratory Practice.

Commercial implications

In addition to the requirements and costs of further testing of a changed approved product, simply changing the container of the vaccine could require significant investment on behalf of the manufacturer, to change filling lines. The investment and time involved in making significant changes to the presentation or route of delivery of existing vaccines might not be worthwhile or cost-effective, especially for inexpensive, yet effective vaccines such as DTP, MMR, etc.

Existing data supporting use of novel immunization routes

ID immunization

There is currently considerable interest in use of ID vaccination because of the potential dose-sparing effect. This has been heightened by the realization that global manufacturing capacity is insufficient for vaccines against potential threats such as pandemic influenza.

Many live and inactivated vaccines have been delivered by the ID route over the past seven decades, generating substantial literature (reviewed in Section 6). Overall, the data are mixed; whether or not ID delivery results in dose-sparing varies between different studies and between different vaccines. This is perhaps best illustrated with influenza vaccine:

- One of the first studies to reignite interest in ID delivery reported equivalent immune responses with a 6µg/dose ID, compared with the standard 15µg/dose IM (i.e., a 60% dose reduction[31]); however, a subsequent study comparing equivalent reduced doses delivered by the two routes showed no difference in immune response following ID or IM vaccination,[32] although ID immunization did induce more local inflammation.

The data to suggest ID vaccination as a means of dose-sparing are, therefore, equivocal at best, and further studies to evaluate ID delivery with different types of vaccine are warranted.

Aerosol immunization

Encouraging data have been obtained on delivering vaccines to the respiratory tract in experimental models; however, the size and anatomy of the respiratory tract in these models differs greatly from humans, and in most cases, vaccine is delivered to the entire respiratory tract, which would not be the case in humans.[10] Furthermore, non-live vaccines delivered by respiratory routes are poorly immunogenic unless adjuvants or muco-adhesives are used. Incorporating such components into vaccines would be a significant change, requiring lengthy characterization.

Current or near-term availability of vaccine delivery technologies (2008)

The only currently available vaccine delivery technologies that could be immediately employed for use with existing vaccines are auto-disable and safety syringes. Because auto-disable syringes are already widely used in LMICs, new auto-disable syringes with needlestick prevention features would offer an additional degree of safety.

The near-term technologies include prefilled syringes and reconstitution devices. Their application to existing vaccines represents a change to the container, and as such, accompanying stability testing and regulatory approvals are required. The application of these technologies to vaccines in development, however, would be quite straightforward to implement. A number of efforts are underway to provide vaccines in prefilled syringes. Vaccines that are currently available or soon to be available in prefilled syringes are listed in Table 19.

At present, there are no reconstitution devices suitable for use in LMICs that are manufactured in sufficient quantities. However, PATH is evaluating potential technologies for this purpose, and incorporating these technologies into the development of spray-dried, thermostable formulations of new vaccines should be relatively straightforward and could have a significant impact on the potential acceptability and uptake of dry-powder thermostable vaccines such as hepatitis B, meningitis A (conjugate), and measles vaccine.

Table 19. Current usage of prefilled syringes or reconstitution devices.

Vaccines available in Uniject™ devices		Vaccines available in other prefilled syringes		Injected vaccines not available in prefilled syringes
2008	**Future**	**2008**	**Future**	**2008**
▪ DTP-HepB. ▪ HepB. ▪ Tetanus.	▪ None known.	▪ dT. ▪ DTP-HebB-Hib-IPV[b]. ▪ Flu-pandemic. ▪ Flu-seasonal. ▪ HepA. ▪ HepB. ▪ HPV. ▪ IPV. ▪ MenACW135Y. ▪ MenC. ▪ MMR[c,d]. ▪ Pneumo. ▪ Rabies. ▪ Typhoid. ▪ VZV.	▪ JE (killed). ▪ MenACW135Y-TT (possibly).	▪ BCG[a]. ▪ DT. ▪ DTP-HepB-Hib. ▪ Measles[c]. ▪ MenA-conj[c]. ▪ MenAC. ▪ MenACW135. ▪ MR. ▪ YF.

a. Delivered ID.
b. Available in Bioset™ reconstitution device.
c. Lyophilized vaccine.
d. Diluent only.

Abbreviations used: BCG: Bacille Calmette Guerin, for tuberculosis; **conj.:** conjugated, usually polysaccharide conjugated to protein; **D:** diphtheria toxoid (**d:** low-dose; **D:** high-dose); **Flu:** influenza; **HepA:** hepatitis A; **HepB:** hepatitis B; **Hib:** *Haemophilus influenzae* type b; **HPV:** human papillomavirus; **IPV:** inactivated polio vaccine; **JE:** Japanese encephalitis; **Men:** meningitis, from *Neisseria meningitidis* (serotypes A, C, W135, Y, or X); **MMR:** measles, mumps, and rubella; **MR:** measles, rubella; **P:** pertussis; **Pneumo:** pneumococcus, from *Streptococcus pneumoniae*; **T:** tetanus toxoid (or **TT**); **VZV:** varicella zoster virus; **YF:** yellow fever.

Promising applications of novel vaccine delivery technologies for existing and new vaccines

Novel vaccine technologies and existing vaccines

In the medium term, some potentially beneficial changes in the delivery of existing approved vaccines might be possible that require no or only minor reformulation. These are listed in Table 20.

Table 20. Existing approved vaccines that might be appropriate for possible application of novel vaccine technologies.

Vaccine	Change	Rationale	Programs
Trivalent influenza vaccine.	ID delivery via hollow microneedles or DCJIs.	▪ No adjuvant–therefore avoids reactogenicity issues. ▪ Existing liquid formulation (or possible concentrated formulation).	Evaluated by Sanofi Pasteur using Soluvia™ ID microneedles.
EPI vaccines, various.	DCJI delivery including ID reduction evaluation.	▪ Evaluate dose-sparing potential for relatively expensive vaccines. ▪ Evaluate acceptability of alternative delivery technology.	To be included in PATH, CDC, WHO DCJI evaluation project.
Rabies.	ID delivery via hollow microneedles or DCJIs.	▪ No adjuvant–therefore avoids reactogenicity issues. ▪ Rabies vaccine delivery is unreliable.	Part of PATH ID delivery evaluation.
Measles.	Aerosol delivery.	▪ Vast clinical experience with existing formulation.	WHO Measles Aerosol Project underway (with CDC, Gates Foundation, Serum Institute of India, Sabin Vaccine Institute).
BCG.	Particulate formulations for aerosol delivery.	▪ Heat-stable formulations. ▪ Aerosol delivery should induce appropriate immune response.	D. Edwards, MIT (Gates Foundation Grand Challenge funding).
Lyophilized vaccines.	Presentation in prefilled reconstitution device with/without needle.	▪ Simple administration. ▪ Improved accuracy.	PATH evaluation and co-development of devices ongoing.

Abbreviations used: BCG: Bacille Calmette Guerin; **CDC:** US Centers for Disease Control and Prevention; **EPI:** Expanded Programme on Immunization; **DCJI:** disposable cartridge jet injector; **ID:** intradermal; **WHO:** World Health Organization.

Novel vaccine delivery technologies and new vaccines

The introduction of novel vaccine delivery technologies is likely to be more straightforward (and possibly cost-effective) with new vaccines because evaluation of the desired device and formulation can be incorporated into the clinical testing program. Examples are listed in Table 21.

Table 21. Vaccines/vaccine types in development that might be appropriate for exploration of novel vaccine technologies.

Vaccine	Change/development	Rationale	Programs
Rotavax™.	Development of heat-stable buccal wafers.	▪ Oral delivery. ▪ Heat-stable formulation–remove from cold chain.	Ongoing at Aridis Pharma.
Rotavax™.	Development of heat-stable liquid and dry formulations for use with reconstitution devices.	▪ Remove from cold chain. ▪ Simplify and improve reconstitution.	Ongoing at PATH in collaboration with Aridis Pharma.
Influenza (pandemic).	Use of hollow microneedles or microneedle patch for delivery.	▪ Dose-sparing and rapid, simple delivery would be advantageous in pandemic.	Iomai is developing TCI delivery of influenza vaccine.
ETEC / Holovax™.	Heat-stable powder in reconstitution device, or heat-stable buccal wafer.	▪ Oral delivery. ▪ Heat-stable formulation.	Ongoing as part of PATH Enteric Vaccines Initiative.
JE or dengue or YF (live formulations).	ID delivery by microneedle patch or hollow microneedle syringe.	▪ ID delivery should promote virus replication in epidermis. ▪ Might allow reduced dose to be used. ▪ Possible safety concerns with live virus replication on the skin.	No known programs.

Abbreviations used: ETEC: enterotoxigenic *E. coli*; **ID:** intradermal; **JE:** Japanese encephalitis; **TCI:** transcutaneous immunization; **YF:** yellow fever.

Conclusions

The development of novel vaccines is a lengthy and uncertain process; consequently, it is difficult to make accurate predictions regarding which vaccines currently in development will be efficacious and when they will be approved for use. It is clear, however, that the number of vaccines relevant for use in LMICs will increase between now and 2025.

Current trends also suggest that the vast majority of novel vaccines or vaccine combinations in the pipeline are likely to be delivered using standard methods, i.e., SC or IM injection using needles and syringes, unless clinical data are obtained and/or incentives to support alternative delivery strategies suitable for LMICs are developed.

The potential safety benefits that would result from reducing use of needles and syringes are well known. Use of novel vaccination delivery strategies could potentially have other benefits, such as ease and speed of administration, reduced dependence on trained health care workers, and reduced waste. A wide range of possible novel vaccine delivery technologies are in development, ranging from modifications to existing needles and syringes to devices that require development of new, thermostable vaccine formulations. In general, the novel approaches being considered aim to:

- Reduce N-S use.
- Reduce the dose of vaccine required and/or reduce wastage.
- Deliver the vaccine by a route that will stimulate an appropriate immune response.

These are clearly worthwhile goals. There are, however, a number of obstacles facing the development of novel vaccine delivery technologies.

- The level of investment required to support alternative vaccine delivery technologies is significant. Any changes made to an existing approved vaccine to make it suitable for a novel delivery method will require considerable preclinical and clinical testing of the new vaccine-device combination as well as substantial investment by the manufacturer in production and filling lines.
- The data to support the use of new routes or devices are not always clear-cut. For example, the data supporting dose-sparing by ID vaccination are equivocal, and to date, suggest that ID immunization might be feasible and beneficial for some vaccines but not others.
- Many of the devices currently in development are too complex and/or costly for widespread use in LMICs. Demonstration programs could help to identify promising technologies worthy of further development or adaptation for use in LMICs.
- Some of the approaches (e.g., biodegradable implants and solid vaccine-coated microneedles) will require significant effort to be spent in developing appropriate vaccine formulations that are compatible with the delivery technology, in addition to developing the device/technology itself. Consequently, these approaches will not be available until the medium to long term (after 2015). In addition, they might require a greater level of collaboration between the vaccine manufacturers and the delivery device manufacturers than has been the case until now.

Evaluation and implementation of new vaccine delivery technologies can therefore be considered over different time frames.

In the short term, activities using devices and vaccines that are available and/or easy to develop should be pursued, including:

- Increasing the use of auto-disable syringes and anti-needlestick devices. Particularly, syringes that combine both properties would improve safety.

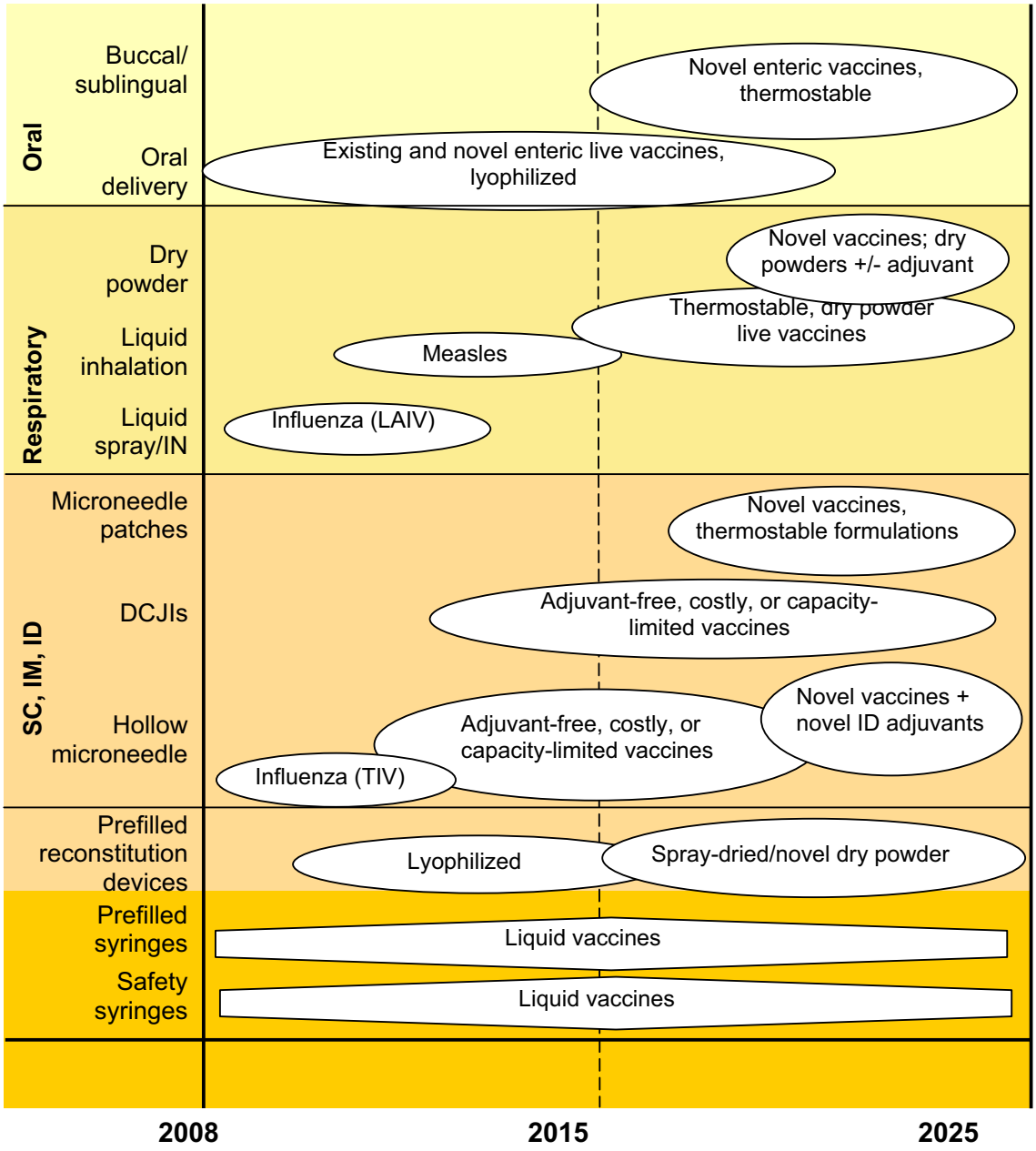
- Development and evaluation of reconstitution devices that can be used with existing vaccines and new thermostable powders when they become available.

It should also be possible, however, to undertake demonstration programs to evaluate novel delivery technologies with existing vaccines that could then yield benefits in the medium term. These projects would generate data more quickly if they focus on delivery technologies that are compatible with existing vaccine formulations. Examples include ID injection by microneedles attached to syringes, DCJIs, and evaluation of new integrated reconstitution devices. Positive data from these studies should:

- Identify which vaccines are likely to be most suitable for different delivery approaches.
- Lead to the initial introduction of the "first generation" of alternative delivery devices (either needle-free or employing microneedles).
- Generate data to support the concept of using methods other than N-S for vaccine delivery.

Ultimately, because of the costs involved, the most efficient way to incorporate new vaccine delivery methods and formulations will be to encourage their use with novel vaccines while the candidate vaccines are in late preclinical or early clinical development. A sequential adoption of novel, increasingly sophisticated vaccine delivery methods can be envisaged, as represented in the speculative figure on the following page.

Figure 1. Potential evolution of vaccine delivery methods—for discussion.



Abbreviations used: DCJI: disposable cartridge jet injector; **ID:** intradermal; **IM:** intramuscular; **IN:** intranasal; **LAIV:** live attenuated influenza vaccine; **SC:** subcutaneous; **TIV:** trivalent influenza vaccine.

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