Overview of emerging delivery technologies

2017 WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation

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Overview of Emerging Technologies
Transdermal microarray patches (MAPs) for pharmaceutical delivery

Description:

- Patches consist of hundreds of tiny projections that deliver solid vaccine into the skin. Some platforms require an applicator for delivery (integrated or separate).
- IPV, MR, influenza, rotavirus, tetanus toxoid, and other vaccines evaluated.
- Essential medicines research – ARVs, contraceptives, antimalarials, antibiotics.
- Potential for enhanced thermostability (CTC use) and controlled release delivery (schedule reduction).

Status

- Influenza clinical studies completed – presentation/publications (Georgia Tech, Vaxxas, CosMED).
- PATH and AMP field evaluations – programmatic suitability.
- MR TPP – future WHO WG.

Abbreviations: AMP, Agence de Médecine Préventive; ARV, antiretroviral; CTC, controlled temperature chain; IPV, inactivated poliovirus vaccine; MR, measles-rubella; TPP, target product profile; WG, working group; WHO, World Health Organization.
PATH Ghana MAP field evaluation

https://www.youtube.com/channel/UCrm8as6d1TRTyJ9kn2l9M0w
Nanopatch™ with applicator

INSTRUCTIONS FOR USE

1. Hold infant as shown to prevent movement
2. Identify a healthy application site (anterior shown)
3. Remove foil seal from applicator
4. Place applicator on skin. Press centre until a click is heard
5. Leave applicator in place for 10 seconds
6. Remove applicator perpendicular to skin
7. Dispose of the applicator into safety box

IMPORTANT: This device is single use disposable

Photos: Vaxxas
NanoPass – Hollow microneedle array

**Description:**
- Hollow microneedles on a hub attached to a syringe (Luer interface).

**Status**
- MicronJet 600™ FDA clearance and CE Mark.
- Evaluated for various seasonal and pandemic flu vaccines, Zoster vaccine, IPV, PPD, and insulin.
- Infants, adults, elderly clinical experience.
- BCG newborn immunizations in Brazil utilizing technology.

Abbreviations: BCG, bacillus Calmette-Guérin; FDA, US Food and Drug Administration; IPV, inactivated poliovirus vaccine; PPD, purified protein derivative.
Intradermal devices for fIPV delivery

**Description**
- Intradermal-capable technologies utilized for fractional-dose vaccine delivery.
- WHO SAGE recommendation for fIPV delivery (vaccine shortage).

**Status**
- WHO has purchased supplies of three devices for ID delivery of IPV.
- Clinical studies of IPV delivered intradermally with Tropis and ID adapter demonstrate noninferior immunogenicity compared to ID delivery with needle and syringe ([Cuba: Resik, 2015; Pakistan: Saleem, 2015](#)).
- Countries adopting fIPV currently utilizing autodisable syringe – other devices still under consideration for use.

<table>
<thead>
<tr>
<th>0.1 mL autodisable syringe with (BCG syringe)</th>
<th>West ID adapter with Helm autodisable syringe</th>
<th>PharmaJet Tropis jet injector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available now</td>
<td>4.1M units available in Q2 2017</td>
<td>5M syringes and 5,000 reusable injectors expected Q2/Q3 2017</td>
</tr>
</tbody>
</table>

Abbreviations: BCG, bacillus Calmette-Guérin; fIPV, fractional-dose inactivated poliovirus vaccine; ID, intradermal; IPV, inactivated poliovirus vaccine; SAGE, Strategic Advisory Group of Experts; WHO, World Health Organization.
Use method – Autodisable needle and syringe

Giving an intradermal injection

Disposable syringe jet injectors

**Description**

- DSJI needle-free method for delivery of vaccines, improving injection safety (elimination of sharps).

**Status**

- PharmaJet: Manufacturer of Stratis® SC/IM (0.5 mL) and Tropis ID® (0.1 mL).
- Regulatory clearances:
  - Stratis® SC/IM – United States, European Union, India, Pakistan, Iran, Kuwait, Saudi Arabia, United Arab Emirates, Brazil, Columbia. WHO prequalification (device).
  - Afluria® and Afluria QIV influenza vaccines are FDA approved for use with the Stratis® (adults).\(^1\)
  - Tropis® ID – European Union. WHO prequalification application under review.
- Serum Institute of India: 2017 relabeling MCVs for Stratis® delivery (PATH/Bill & Melinda Gates Foundation supported MMR clinical study\(^2\) – noninferiority demonstrated).
- Global Polio Eradication Initiative: Tropis ID® – use for fIPV delivery.

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2. [https://clinicaltrials.gov/ct2/show/NCT02253407](https://clinicaltrials.gov/ct2/show/NCT02253407)

**Abbreviations:** DSJI, disposable syringe jet injector; FDA, US Food and Drug Administration; fIPV, fractional dose poliovirus vaccine; ID, intradermal; IM, intramuscular; MCV, measles-containing vaccine; MMR, measles, mumps, and rubella; QIV, quadrivalent influenza vaccine; SC, subcutaneous; WHO, World Health Organization.
Blow-fill-seal technology

Description

• BFS technology is a method of producing liquid-filled containers that are formed, filled, and sealed in a continuous, automated system.
• Advanced aseptic process for packaging of sterile pharmaceutical products.

Status

• Evaluation of LAIV and rotavirus vaccine delivery has occurred with this technology.
• GSK ROTARIX® BFS development – MMD 5-dose conjoined strip (single VVM), 10 strips per secondary package (cold chain volume reduction).
• Global Good design – low cold chain volume ampoule.
• Parenteral injection-capable design in development (cPAD). ApiJect – rommelag collaboration.
• BFS filling feasibility (Maropack/GSK).

Abbreviations: BFS, blow-fill-seal; cPAD, compact prefilled autodisable; GSK, GlaxoSmithKline; LAIV, live attenuated influenza vaccine; MMD, multi-monodose; VVM, vaccine vial monitor.
Blow-fill-seal process
Polymer tube / preformed technology

Description

- Preformed tubes such as those produced by Lameplast and Rexam are generally made from polyethylene or polypropylene in either single units or strips.
- Tubes are left open at the end opposite the nozzle for filling. A heat-sealing step provides closure after filling.
- Used for Merck RotaTeq® and GSK ROTARIX vaccines.
- Serum Institute (rotavirus), EuBiologics (cholera), and other manufacturers adopting tube container.

Status

- Rotavirus and cholera manufacturers are adopting tube technology.
- Lameplast is currently developing lower cold chain volume design (reduced spacing between tubes).
Integrated reconstitution technology

**Description**

- Improves the ease and safety of delivering reconstituted vaccines and pharmaceuticals by physically integrating the dry product and the diluent.

**Status**

- Hilleman Laboratories – integrated reconstitution and administration device (IRAD).
  - Dual chamber, frangible seal reconstitution technology for oral delivery.
  - Heat-stable rotavirus vaccine with potential for CTC/outside cold chain use (>6 months @ 45°C).
  - Human factors evaluation of IRAD design (India).
  - Phase I/II (adults/infants).

Abbreviation: CTC, controlled temperature chain.
Glass cartridge and ampoule technology

**Description**

- Widely utilized standard primary containers.
- Low-cost, widely available technology.
- Potential for significant reduction in cold chain volume.

**Status**

- Two manufacturers are developing platforms for application in LMIC:
  - Duoject/PnuVax (application: PCV-13).
  - Stevanato Group – glass cartridge and ampoule delivery designs.

Abbreviations: LMIC, low- and middle-income countries; PCV, pneumococcal conjugate vaccine.
Electroporation

**Description**
- Electrodes targeting epidermal, dermal, and subdermal routes for DNA vaccine delivery.

**Status**
- Clinical studies: Zika, Ebola, HIV, MERS.
- Inovio acquired Bioject (needle-free jet injector).
- Adapting electroporation and needle-free jet injector into one device (single disposable cartridge, cost reduction, increased ease of use).

<table>
<thead>
<tr>
<th>CELLECTRA°-3P</th>
<th>Surface EP (SEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Minimally invasive</td>
<td>• Noninvasive</td>
</tr>
<tr>
<td>• 3 mm electrodes</td>
<td>• 4x4 electrode array</td>
</tr>
<tr>
<td>• Targets epidermal, dermal and subdermal regions</td>
<td>• Specifically targets epidermis</td>
</tr>
<tr>
<td>• In clinical use</td>
<td>• In late-stage preclinical development</td>
</tr>
</tbody>
</table>

Abbreviation: EP, electroporation; ID, intradermal; MERS, Middle East Respiratory Syndrome.
Introduction to the Vaccine Technology Impact Assessment (VTIA) Model
The Total System Effectiveness analytical framework

- **Total System Effectiveness (TSE)** is an analytical framework to evaluate tradeoffs for alternative vaccine presentations.
- It evaluates the commodity and delivery costs, as well as health impact, safety, coverage, and equity, taking into account programmatic considerations.
- TSE can be used to:
  - Inform R&D investment decisions by vaccine and technology developers and donors.
  - Inform procurement decisions by countries and donors.
  - Align global stakeholders around product priorities to reach **SDG goal 3**.

Information needed to inform vaccine / technology decision-making

Abbreviations: R&D, research and development; SDG, Sustainable Development Goal; TSE, Total System Effectiveness.
PATH’s approach to TSE evaluation

Vaccine Prioritization Framework (VPF)

Target vaccines

Technology pairing

Potential vaccine technologies

-and filtering out of nonviable pairs

Prioritization Framework: Evaluation criteria (scoring tool)

EFFICACY

EFFECTIVENESS

SAFETY

AVAILABILITY

COST

OTHER FACTORS

Vaccine Technology Impact Assessment (VTIA)

- Commodity costs
- Delivery costs
- Health impact

Further qualitative evaluation
Vaccine Technology Impact Assessment (VTIA) model

- Provides a **comparative economic evaluation** of the commodity and delivery costs and health impact for current vaccine/technology presentation(s) compared with new presentation(s).

- Excel-based model that enables scenario analyses for new presentations since technologies considered are under development.

- Helps identify the key variables influencing the estimated costs and health impact.

- Analyses to date include rotavirus, measles-rubella, inactivated polio, and ETEC vaccines.

- Enables a country-level, regional, or global analysis for LMIC.
  - Analyses to date are national level—assuming the entire country/region uses the same technology.
  - Also analyzed a mixed vaccine presentation for one country.

Abbreviations: ETEC, enterotoxigenic *Escherichia coli*; LMIC, low- and middle-income countries.

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3.8 Achieve universal health coverage, including financial risk protection, access to high-quality essential health care services and access to safe, effective, high-quality, and affordable essential medicines and vaccines for all.
Capabilities of the VTIA model

- Comparison of impact of alternative target product profiles (TPPs) on procurement and delivery costs.
- User can:
  - Change one or more TPP attribute to determine impact on the procurement and delivery costs.
  - Conduct comparisons to baseline technology:
    - Vaccine efficacy and/or safety impact – estimate # of children effectively immunized and adverse events.
    - Coverage impact – estimate # of additional children immunized.

Abbreviation: TPP, target product profile.
Vaccine Technology Impact Assessment (VTIA) model

Commodity costs
- Vaccine costs.
- Delivery technology costs.
- Safety box costs.

Delivery costs
- Cold chain costs.
- Transport costs.
- Administration costs.
- Waste disposal costs
- One-time program costs

Health impact
- Number of children effectively immunized.
- Potential for increase in coverage.
- Potential for reduction in adverse events following immunization.
VTIA model cost inputs – Selected

**Commodity costs**
- Vaccine price per dose*
- Number of doses per FIC*
- Vaccine wastage rate
- Vaccine coverage rate
- Price per syringe / adapter*
- Price per safety box

**Delivery costs**
- Volume per dose*
- Volume (per dose) needing to be stored in the cold chain*
- Average cold chain costs per cm³
- Average transport costs per cm³ per km
- Number of facilities at each level of the supply chain
- Time taken by health workers to administer each vaccine dose*
- Health worker salaries

**Health impact**
- Vaccine’s clinical efficacy (current vaccines)
- Potential of new technology to improve efficacy and percentage increase*
- Programmatic errors during vaccine administration (current presentation)
- Potential of new technology to reduce programmatic errors and percent reduction*
- Potential impact on coverage and potential percent increase in coverage

* Indicates technology-specific inputs. Note: This list is not exhaustive.

Abbreviation: FIC, fully immunized child.
Selected data sources for the VTIA model

- Product menu for vaccines supplied by UNICEF for Gavi, the Vaccine Alliance.
- World Health Organization (WHO)-preferred product characteristics documents.
- WHO vaccine-preventable diseases monitoring system.
- WHO immunization comprehensive multiyear plans.
- Cold chain equipment manager database.
- Published literature.
- Cost of goods assessments conducted by PATH.
- Expert consultations and assumptions.
Limitations of the VTIA model

- Does not include research and development costs but assumes that technology prices account for these costs.
- Does not estimate the health impacts, such as disease cases, hospitalizations, disability-adjusted life years, deaths, etc.
- Is not a cost-effectiveness analysis.
- Is not an optimization model.
VTIA model current status

- WHO December 2016 workshop.
- VTIA model continues to be modified and updated.
- Additional analyses for Version 2.0 will include:
  - Expansion of the subnational analyses to evaluate the impact of mixed vaccine presentations (different vial sizes of the same vaccine) in additional countries.
  - Modeling of vaccines used for campaigns and special strategies, such as controlled temperature chain.
  - Modeling of technologies for additional vaccines such as fIPV and yellow fever.
- Bill & Melinda Gates Foundation TSE Working Group.
  - Additional test cases (case studies) based on needs from TSE Working Group needs.

Abbreviations: fIPV, fractional dose inactivated poliovirus vaccine; TSE, Total System Effectiveness; WHO, World Health Organization.
ETEC vaccine – R&D case study

- An oral ETEC candidate vaccine has a complex presentation requiring reconstitution.

- Utilized VTIA and the qualitative prioritization framework to assess potential alternative presentations.

- Results informed selection of formulation, packaging, and delivery approaches for further technical analysis.

Abbreviation: ETEC, enterotoxigenic Escherichia coli; R&D, research and development.
Application of technology prioritization and VTIA – TSE research and development case study

Identified potential product presentations
- Met with key stakeholders to align expectations and gather background information.
- Assessed baseline presentation based on WHO programmatic suitability prequalification requirements.
- Identified eight alternative presentations with better programmatic suitability for analysis.

Collected model inputs
- Worked with developers to identify and compile necessary data inputs.
- Used the vaccine TPP and PATH formulation, packaging, and delivery device expertise to set values (or ranges) for unknown product variable.

Qualitative assessment
- Evaluated the presentations focusing on key attributes such as PTRS, cold chain volume, administration time, and risk of user error.
- Used qualitative approaches to represent key trade-offs between various presentation alternatives.
- Developed decision trees and other visualizations.

Quantitative assessment
- Evaluated the presentations using the V-TIA model.
- Focused analysis on the potential systems cost impacts of the presentations.
- Summarized outputs in tandem with the qualitative assessment findings.

Refined model inputs and shared results
- Shared preliminary results with stakeholders and gathered feedback.
- Created an ongoing, iterative process using results to refine model inputs, including incorporation of new technology designs into the analysis, and improve outputs.
- Incorporated new technology designs into analysis.

Abbreviations: PTRS, probability of technical and regulatory success; TPP, target product profile; WHO, World Health Organization.

*a Key issues identified included the use of three formulation components and onsite water, the two sequential mixing steps required, and limited product stability following preparation.
*b Included identification of potential formulation components and dose volume, preparation of rough COGS estimates, prototyping of containers/delivery devices to calculate cold chain volume estimates, and conducting in-house time-and-motion studies to estimate delivery times.
Through PATH’s ETEC vaccine assessment, a novel primary container design concept was developed.

Potential advantages:

- No separate devices required for mixing and oral delivery.
- Minimizes risk of inadvertent injection (no syringes used).
- Compatible with available fill-finish equipment (glass vials and blow-fill-seal or preformed polymer tubes).

This approach may be considered for other oral vaccines requiring reconstitution.

Abbreviations: ETEC, enterotoxigenic Escherichia coli; OPV, oral poliovirus vaccine.
ETEC prioritization output

ETEC Technology Prioritization - Six Key Scores

- Safety
- Access, usability, acceptability
- COGS
- Technical/manufacturing feasibility
- Systems cost
- Efficacy/effectiveness

Abbreviation: ETEC, enterotoxigenic Escherichia coli.
Selected ETEC programmatic suitability considerations

Are all vaccine antigens, adjuvant, and buffer stable together in a single liquid?

Non-aqueous formulation

Is the vaccine formulated as two liquid components?

Both aqueous

Is the vaccine formulated as one dry component and one liquid?

No

Is the vaccine one dry component and two liquids (bartender approach)?

Yes

Water supplied with vaccine

High probability/short timeline

Low probability/long timeline

Medium probability/timeline

Key

Probability of technical success/timeline to availability

- High probability/short timeline
- Medium probability & timeline
- Low probability/long timeline

Abbreviation: ETEC, enterotoxigenic Escherichia coli.
ETEC VTIA analysis – Cost drivers

Three components
(Bartender approach)

Two components
(Liquid and dry or two liquids)

One component
(Liquid only)

<table>
<thead>
<tr>
<th>Component</th>
<th>Commodity costs</th>
<th>Cold chain costs</th>
<th>Transport costs</th>
<th>Human resource costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartender +H2O</td>
<td>91.3%</td>
<td>2.7%</td>
<td>4.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Bartender +H2O</td>
<td>89.0%</td>
<td>2.3%</td>
<td>5.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Vial + sachet</td>
<td>93.7%</td>
<td>1.2%</td>
<td>1.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Tube + sachet</td>
<td>93.7%</td>
<td>1.4%</td>
<td>2.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>2 vials</td>
<td>92.9%</td>
<td>1.4%</td>
<td>4.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>2 tubes (non-aq)</td>
<td>94%</td>
<td>0.5%</td>
<td>2.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>2 tubes (aq)</td>
<td>93%</td>
<td>0.6%</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>1 tube (non-aq)</td>
<td>97%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>1 tube (aq)</td>
<td>96%</td>
<td>0.7%</td>
<td>0.6%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Abbreviations: aq, aqueous, ETEC, enterotoxigenic Escherichia coli; H2O, water; non-aq, non-aqueous.
ETEC VTIA analysis – Average cost per child vaccinated

<table>
<thead>
<tr>
<th>Three components (Bartender approach)</th>
<th>Two components (Liquid and dry or two liquids)</th>
<th>One component (Liquid only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartender -H2O</td>
<td>2 vials</td>
<td>1 tube (aq)</td>
</tr>
<tr>
<td>Bartender +H2O</td>
<td>2 tubes (non-aq)</td>
<td>1 tube (non-aq)</td>
</tr>
<tr>
<td>Vial + sachet</td>
<td>2 tubes (aq)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Probability of technical success / timeline to availability</th>
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<tbody>
<tr>
<td>High probability/short timeline</td>
</tr>
<tr>
<td>Medium probability &amp; timeline</td>
</tr>
<tr>
<td>Low probability/long timeline</td>
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</tbody>
</table>

Abbreviations: aq, aqueous, ETEC, enterotoxigenic Escherichia coli; H2O, water; non-aq, non-aqueous.
Thank you
Use method – West ID adapter with Helm autodisable needle and syringe

1. Unpack the West ID adapter and Helm autodisable needle and syringe separately.
2. Insert the West ID adapter into the vial.
3. Attach the Helm autodisable needle to the syringe.
4. Draw up the desired amount of vaccine into the syringe.
5. Ensure the syringe is properly sealed before use.
6. Place the syringe on the injection site.
7. Push the plunger to deliver the vaccine.
8. Discard the used syringe.

• Currently, the intradermal adapter and autodisable needle and syringe are packaged separately.
• In the future, they will be co-packaged in the same blister pack.

Image: West Pharmaceutical Services, Inc.
Use method – West intradermal adapter

West ID adapter

Use method – PharmaJet Tropis jet injector

1. Prepare injector
2. Fill syringe
3. Load injector
4. Give injection

Photos: PharmaJet
Use method – PharmaJet Tropis jet injector

Workflow of the PharmaJet Tropis vs. Mantoux Needle Injection

Use method – Stratis jet injector

1. Prepare injector
2. Fill syringe
3. Load injector
4. Give injection

Photos: PharmaJet
Use method – PharmaJet Stratis jet injector

Workflow of the PharmaJet Stratis vs. Needle Injection