Microarray patches: Opportunities for global health impact and health equity
Technology overview and development resources

Workshop for Developing Countries Vaccine Manufacturers
Network International

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https://www.path.org/programs/mdht/mapresources/
Outline

• Background
• Microarray patch (MAP) technology overview
• MAP target product profiles (TPPs)
• Addressing MAP challenges
• Vaccine Innovation Prioritisation Strategy (VIPS)
What do you see as the biggest barrier(s) currently limiting access to routine immunizations?

A. Inadequate infrastructure for cold chain leading to vaccine wastage due to temperature exposure.
B. Inadequate delivery service points (e.g., remote populations).
C. Inadequate availability of appropriately trained health care workers.
D. Missed opportunities due to reluctance to open multidose vials.
E. Vaccine hesitancy or fear of injections and needles.
F. Other (put in the chat).
Background

MAP technology overview
MAP Target Product Profiles
Addressing MAP challenges
Vaccine Innovation Prioritisation Strategy
PATH is a global team of innovators working to eliminate health inequities so people, communities, and economies can thrive.
PATH'S MISSION

Advance health equity through innovation and partnerships.
One PATH, one mission, many experts

More than 1,500 strong, our global team includes experts and thought leaders from dozens of specialties including:

- **Product development**—contraceptives, rapid diagnostics, and other devices.
- **Primary health care**—people-centered health systems strengthening.
- **Vaccines and essential medicines**—development, formulation, manufacturing, and rollout.
- **Digital transformation**—electronic immunization registries and other real-time systems.
- **Epidemic preparedness and response**—disease surveillance, responder training, and coordination.
- **Advocacy and communications**—elevating community priorities, influencing local and global stakeholders.
We offer end-to-end product development services, from technology ideation to impact.

We are a multidisciplinary group of public health researchers, clinicians, scientists, engineers, designers, health economists, project managers, and business strategists in the following portfolios:

- Formulation Technologies
- Health Technologies for Women and Children
- Living Labs Initiative
- Supply Systems & Equipment
- Packaging & Delivery Technologies

Device staff also work closely with and support the PATH Center for Vaccine Innovation and Access.

The Packaging & Delivery Technologies Portfolio works to identify, assess, and advance innovative primary packaging and delivery devices for vaccines and pharmaceuticals that maximize efficacy, increase access, and reduce cost.

Various packaging and delivery technologies.
Innovative delivery strategies are needed to eliminate health inequities.
Global health need: Vaccines that can travel to the people who need them

Progress on global vaccine coverage significantly stalled during the pandemic.

In 2021, there were 18.2 million zero-dose children, primarily in the most disadvantaged communities.

New tools, such as microarray patches, can fill the gap if they have the right attributes.

To achieve impact, microarray patches must be paired with innovative delivery strategies.


Abbreviation: DTP3, diphtheria tetanus toxoid and pertussis.
How familiar are you with the microarray patch platform?

A. Not at all familiar
B. Slightly familiar
C. Somewhat familiar
D. Moderately familiar
E. Extremely familiar
MAP technology overview
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Microarray patch (MAP) technology overview

- A patch may have **hundreds or thousands of tiny projections**.
- The projections can be **coated with or composed of a vaccine** (dry formulation).
- **The patch is applied to the skin and pressed down** so that the projections penetrate the top of the skin. The vaccine dissolves in the skin, and the patch can be removed.
- The projections only **penetrate the top layers of the skin** to deliver the vaccine.
- It is typically perceived as **less painful than an injection**.
- Some platforms require an **applicator** for delivery (integrated or separate).
- Vaccine microarray patches (MAPs) are in **early-stage development**; it may be a decade or more before a vaccine MAP product could be introduced.
Vaccine MAPs could transform immunization delivery

- **Single-dose form**: Less pain during administration
- **Higher acceptability**: Compact and lightweight
- **Reduced wastage and missed opportunities**: Reach zero-dose and hard-to-reach populations
- **Lower cold chain requirements and costs**: Enable faster rollout in a pandemic
- **Enhanced thermostability**: Create platform delivery for adult vaccination
- **Administered by minimally trained health care worker**: Enhanced safety and less dependency on ancillary supplies
- **Ease of use**: Needle-free device
- **Key**
  - Attribute
  - Benefit
  - Value to immunization
Types of microneedles

**Step one:** Microprojections are applied.

**Step two:** Pharmaceutical is released.

Microarray patches (MAPs)

Liquid delivery via microneedles
Manufacturing methods for coated MAPs

**Dip coating**

A

B

C

**Spraying**

A

B

C
Manufacturing methods for dissolving or hydrogel MAPs

Micromolding: Solvent casting

Surface drawing: Droplet-born air blowing

Formulation source

A

B

C

Formulation
The clinical evidence base for vaccine MAPs is expanding

Results are published or anticipated for the measles-rubella (MR) vaccine, inactivated rotavirus vaccine (IRV), and the vaccines for influenza, COVID-19 virus (SARS-CoV-2), hepatitis B (Hep B), and Japanese encephalitis (JE) in Phase 1, as well as Phase 2 for MR and SARS-CoV-2.
First clinical proof of concept of vaccine MAPs in infants

- First completed Phase 1 & 2 clinical trial in unprimed 9-month-olds with a microarray patch (MAP) for measles-rubella (MR) vaccine in The Gambia, a country where measles is endemic.

- High and similar seroprotection and seroconversion rates for MR in all cohorts for both the MAP and subcutaneous (SC) injection.

- Vaccination by MAP was safe and well tolerated, with no allergic reactions or related serious adverse events.

- Over 90% of the parents of toddlers and infants enrolled in the trial, who took part in an acceptability survey, said the MAP technology would be better than SC injection.
Why PATH formed the MAP Center of Excellence

Global health need
Improve presentations of vaccines and pharmaceuticals in low- and middle-income countries (LMICs).

Ease of use
Coverage and equity
Thermostability
Sharps waste

Opportunities
- Increase coverage by enabling alternative delivery scenarios (e.g., delivery by minimally trained personnel).
- Expand access in harder-to-reach populations.
- Deliver vaccines beyond the cold chain.
- Improve adherence to drug regimens.
- Reduce the burden on health systems.

Challenges
- Product-specific focus, which limits the opportunity for platform-wide efficiencies.
- Siloed information.
- Unclear pathway to manufacturing scale-up and regulatory approval.
- Uncertain market potential in LMICs and return on investment for vaccine/pharmaceutical manufacturers.
PATH's role and impact: Microarray patch field

PATH advises on regulatory and licensure requirements

PATH's data inform target product profiles and prioritization

PATH develops strategic approaches

Funders

PATH’s input informs investments

Product developers

PATH’s support generates data and informs value propositions

Manufacturers

PATH advises on regulatory and licensure requirements

Global initiatives (VIPS, PADO)

Evaluation frameworks, economic analyses, technical input on innovations

Dialogue and technical assistance

Input on product attributes; implementation of research

Development of quality attributes and test methods

Informing of standards and guidance documents

Countries

Needs assessments, user evaluations

PATH’s work accelerates product licensure and introduction

Regulators/standards

Abbreviations: BARDA, Biomedical Advanced Research and Development Authority; CEPI, Coalition for Epidemic Preparedness Innovations; DCVMN, Developing Countries Vaccine Manufacturers Network; FDA, US Food and Drug Administration; Gavi, Gavi, the Vaccine Alliance; PADO, Paediatric Antiretroviral Drug Optimization; USP, United States Pharmacopeia; UNICEF, United Nations Children’s Fund; VIPS, Vaccine Innovation Prioritisation Strategy.
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PATH’s approach to developing target product profiles

Goals
- Develop and disseminate target product profiles (TPPs) describing minimally acceptable and optimal attributes of microarray patch (MAP) products with a focus on low- and middle-income country (LMIC) contexts and use cases.
- Guide and inform development efforts of MAP products for high-priority global health applications.

Key product attributes
Intended use case, target population, safety, efficacy, dosage, dosing regimen, stability, and disposal.

Status
TPPs developed for vaccines against human papillomavirus (HPV), rabies, and COVID-19 are available on PATH’s resource page. TPPs developed for measles-rubella (MR) vaccine MAPs are available on WHO’s website.

Unique TPP characteristics
- TPPs are intended to be broad for a specific indication and are not manufacturer specific.
- Highlight the needs of users and immunization program priorities in LMICs.
- Describe product attributes that will facilitate reaching previously unvaccinated populations and improving health equity.
- Serve as a tool to signal which MAP applications are considered high priorities for global health.
Target product profile development process

- Review literature
- Conduct interviews with global and in-country stakeholders
- Solicit feedback from MAP developers and vaccine manufacturers
- Post online

Revise as comments are received and/or new data are generated

MR vaccine MAP
- Measles-rubella microarray patch (MR-MAP) target product profile
- Draft June 2019

Rabies vaccine MAP
- Rabies vaccine microarray patch
- Target product profile
- Draft June 2020

HPV vaccine MAP
- Prophylactic HPV vaccine microarray patch target product profile
- Draft August 2023

COVID-19 vaccine MAP
- COVID-19 vaccine microarray patch target product profile
### Key attributes of a vaccine MAP: Usability considerations

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Insights</th>
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</table>
| Wear time                     | • Ideally, wear time should be under one minute.  
• Wear time of several minutes may be acceptable in certain use cases but could create additional burden on the healthcare worker or reduce compliance. |
| Indicator or applicator       | • An indicator or applicator alerts the user that the MAP has been appropriately administered and can only be activated once per MAP.  
• The device can be used by a lesser trained person (e.g., a community health worker) with minimal training.  
• The device should be integrated with the MAP and not require the user to put it together. |
# Key attributes of a vaccine MAP: Thermostability considerations

<table>
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</tr>
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</table>
| **Cold chain volume** | • The cold chain volume, including all packaging, should be minimized as much as possible.  
  • Current MAP prototypes are roughly three to five times larger than multidose vial presentations, ranging from 12 to 25 cm³.                                                                                                                                               |
| **Heat stability**   | • Controlled temperature chain (CTC) allowing a single excursion of the MAP at the end of its shelf life is beneficial for outreach or delivery outside of a health facility but may not be possible for all vaccines.  
  • MAPs could allow for higher temperature vaccine vial monitors (VVMs) than vaccine vials. MAP packaging should include appropriate VVMs.                                                                                                           |
### Key attributes of a vaccine MAP: Manufacturing considerations

<table>
<thead>
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</thead>
</table>
| **Manufacturability** | • Prior to MAP manufacturing, bulk antigen will require reformulation and possibly concentration.  
                            • Dose limitations are based on the type of MAP and manufacturing process.                                                                                                           |
| **COGS/Price**  | • Incremental increases in the cost of goods sold (COGS) and price may be acceptable.  
                                • Many low- and middle-income countries (LMICs) are price sensitive and may not be willing to pay large price premiums for MAPs despite recognizing their programmatic benefits.  
                                • MAPs have the potential to be cost-effective even at higher procurement prices.                                                                                                  |
### Vaccine antigen qualities for microarray patches

<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Is the antigen stable when dried?</strong></td>
<td>Antigens that can be dried or lyophilized with minimal excipients are best suited to the MAP manufacturing process.</td>
</tr>
<tr>
<td><strong>Is the antigen robust to withstand manufacturing?</strong></td>
<td>During the manufacturing process, the antigen may be exposed to elevated pressures, velocities, or temperatures. Labile antigens may still be used in MAPs but may require longer processing times or require more complex manufacturing.</td>
</tr>
<tr>
<td><strong>Is the antigen able to be concentrated?</strong></td>
<td>The bulk antigen should be concentrated such that a full dose is present in approximately 10 µl or less.</td>
</tr>
<tr>
<td><strong>Is there a robust assay for the antigen?</strong></td>
<td>A robust potency assay is needed during formulation screening and process development.</td>
</tr>
<tr>
<td><strong>What is the route of delivery of the antigen?</strong></td>
<td>Data demonstrating intradermal vaccination is immunogenic increase the chance of success for a MAP. Oral vaccines may not be suitable for MAP delivery.</td>
</tr>
<tr>
<td><strong>Does the antigen require an adjuvant?</strong></td>
<td>Adjuvants may increase the local reactogenicity following MAP vaccination, and adjuvants commonly used in liquid vaccines can be difficult to formulate in a MAP. Novel adjuvants may be necessary if an adjuvant is indicated.</td>
</tr>
<tr>
<td><strong>Is the antigen approved by a regulatory authority?</strong></td>
<td>Both a novel antigen and novel delivery method may increase complexity to achieve regulatory approval.</td>
</tr>
<tr>
<td><strong>Does the antigen have a correlate of protection?</strong></td>
<td>Correlates of protection or other immunological end points may accelerate clinical development.</td>
</tr>
</tbody>
</table>

**Abbreviations:** MAP, microarray patch; mfg, manufacturing.
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Impact of five years of the MAP Center of Excellence: Addressing key challenges for MAPs

Project goal: Advance MAPs as a technology platform for high-priority needs in low- and middle-income countries (LMICs).
Engagement and dissemination

Activities

- Published MAP resources website and newsletter.
- Advanced global initiatives with partner organizations (WHO, Gavi, UNICEF, BARDA, CEPI, Bill & Melinda Gates Foundation, etc.):
  - Vaccine Innovation Prioritisation Strategy (VIPS)
  - MR MAP Product Development Working Group
  - BARDA MAP vaccine alliance
  - Global Accelerator for Paediatric formulations (GAP-f)
  - Paediatric Antiretroviral Drug Optimization (PADO)
- Organized and cohosted the Microneedles Conference in May 2023.

Learnings: Working together, MAPs are being accelerated faster than individual or siloed efforts would allow.

Abbreviations: BARDA, Biomedical Advanced Research and Development Authority; CEPI, Coalition for Epidemic Preparedness Innovations; Gavi, Gavi, the Vaccine Alliance; MR, measles-rubella; UNICEF, United Nations Children’s Fund; WHO, World Health Organization.
User needs

Activities

• **Global and country stakeholder needs assessments:**
  – HPV vaccine
  – Rabies vaccine
  – Typhoid conjugate vaccine
  – Pediatric HIV treatment
  – Pandemic/outbreak response

• **Human factors evaluations:**
  – HIV prevention
  – Multipurpose prevention (HIV and contraception)
  – Measles-rubella (MR) vaccine

Learnings: In-country studies have identified user needs for training, instructions, and intuitive design of MAP products—demonstration and practice are key.

Gaps identified: Implementation research is a critical next step to plan how the unique characteristics of MAPs will fit into programmatic delivery.
Technical development

Activities

• Created expert and country-informed target product profiles (TPPs) for microarray patch (MAP) delivery of measles-rubella (MR), human papillomavirus (HPV), rabies, and COVID-19 vaccines, as well as HIV drugs.

• Developed a packaging report with technical, usability, and design considerations.

• Developed and tested a large-area MAP feedback indicator.

• Conducted a thermostability study of MR MAPs.

• Planned and developed protocol for MR MAP Phase 2 clinical trials.

Key questions: To what extent should product design be optimized before entering the clinic? What trade-offs should be made?
Manufacturing

Activities

- Cohosted a three-day manufacturing workshop with Harro Höfliger (Germany) with 75 participants across the industry.
- Conducted an industry survey and interviews to understand the state of the industry and challenges by both developer and MAP type.
- Evaluated manufacturing scale-up processes, costs, and timelines.
- Published a manuscript calling for pilot manufacturing capabilities to be funded in parallel to proof-of-concept clinical trials.

Learnings: Design of pilot plants for automated vaccine MAP production.

Gaps identified: Manufacturing scale-up through production for Phase 3 clinical research is a critical next step to future licensure.
Activities

- Formed MAP Regulatory Working Group:
  - Twenty-three organizations have contributed to date.
  - Six working group meetings were held.
- Defined dosage form and potential critical quality attributes.
- Published sterility risk assessment.
- Evaluated and developed test method.

Goal: To inform publication of a regulatory document to guide MAP development and review (e.g., United States Pharmacopeia chapter on microneedles).
Activities

- **Measles-rubella (MR) and contraceptive** MAP business cases.
- Cost of goods analyses.
- Estimating the **dose demand** for MR MAPs.
- Cost of delivery for MR MAPs based on PATH’s *Vaccine Technology Impact Assessment (VTIA) model*.
- Cost-effectiveness analyses (hepatitis B vaccine, typhoid conjugate vaccine, HIV prevention, contraception).
- Investment strategies.

Learnings: For MAP products focused on the markets of low- and middle-income countries (LMICs), market-shaping strategies will be needed. Dual market potential may increase commercial viability.

Gaps identified: Understanding procurers’ willingness to pay for MAPs’ programmatic advantages will be critical to understanding potential uptake.
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Vaccine Innovation Prioritisation Strategy
The Vaccine Innovation Prioritisation Strategy (VIPS) is a global partnership between the Gavi Secretariat, World Health Organization (WHO), United Nations Children’s Fund (UNICEF), Bill & Melinda Gates Foundation, and PATH—known as the VIPS Alliance—to prioritise and drive vaccine product innovation to increase equitable vaccine coverage in low- and middle-income countries and contribute to global health security.
VIPS has prioritised 3 innovations with the broadest public health benefits, that can help better meet country needs & contribute to coverage and equity goals.
VIPS Alliance Action Plan

End-to-end, five-year MAP action plan that achieves the following:

- Identifies activities needed to accelerate the development and future uptake of vaccine MAP products for LMIC use.
- Aspires to advocate for vaccine MAPs in general and attract the interest of other global health partners and funders.

Recent and/or planned VIPS activities include the following:

- Antigen prioritization.
- Cost of goods sold analysis.
- Business models and potential financing mechanisms.
- MAP full vaccine value assessment and country consultations.
- Implementation and policy preparations.
Proposed priority list of vaccine targets for use with MAPs

<table>
<thead>
<tr>
<th>Priority 1 group</th>
<th>Priority 2 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>Group B <em>Streptococcus</em> (GBS), <em>S. agalactiae</em></td>
</tr>
<tr>
<td>Measles-rubella (MR)/measles, mumps, and rubella (MMR) viruses</td>
<td><em>Neisseria meningitidis</em> A,C,W,Y,(X)</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td><em>Salmonella Typhi</em></td>
</tr>
<tr>
<td>Rabies virus</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Yellow fever</td>
<td></td>
</tr>
<tr>
<td>Influenza virus, seasonal and pandemic</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td></td>
</tr>
</tbody>
</table>
Question for audience

What other resources would help facilitate the development of vaccine MAPs with your antigens?
Engagement opportunities

**Newsletter**: Please contact MAPs@path.org to be adding to the mailing list.

**MAP Resources page**: For more information on PATH’s work on microarray patches, go to https://www.path.org/programs/mdht/mapresources/.

**VIPS site**: For more information on the VIPS Alliance and the technologies, go to https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy

**Target product profiles**: To review and provide input on MAP target product profiles, go to https://www.path.org/resources/microarray-patch-target-product-profiles-tpp/.

For more information contact:

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maps@path.org
Formulation and delivery capabilities at PATH

Technical design documentation
- Target product profiles
- Product requirement specifications
- User requirements
- Programmatic fit requirements
- Hazard/risk analyses
- Value proposition analyses

Discovery and research
- Container/delivery device design
- Adjuvant down-selection
- Preclinical support
- Toxicology and immunogenicity

Drug substance
- Bioanalytical and potency assay development and qualification
- Due diligence and selection of USP/cGMP-grade excipient suppliers/vendors
- Development and qualification of reagents and growth and maintenance cell lines

Drug product
- Liquid and lyophilized formulation development
- Process scale-up and optimization
- Fill/finish equipment and cost of goods sold (COGS)
- Preservative selection and testing for multidose formulations

Delivery technologies
- Verification testing
- Delivery performance characterization
- Heuristic evaluation
- Human factors evaluation
- Rapid design and prototyping
- WHO-prequalification support
- COGS and total cost of delivery analyses

Packaging and labeling
- Secondary packaging configurations
- Cold chain volume analyses
- Primary container label
- Vaccine vial monitors (VVMs)
- Instructions for Use (IFU) development

Stability evaluation
- Real-time and accelerated stability studies
- Stability studies for supporting VVM and controlled temperature chain (CTC) selection

Clinical studies
- Protocol development and dose verification for clinical study preparations
- Bedside mixing protocol
- Device evaluation
- Acceptability analyses

General industry support
- Technical guidance specification development
- Market and supply chain landscaping/analyses
- Human-centered design optimization
- Rapid testing and feedback from stakeholders

Abbreviations: cGMP, current good manufacturing practices; USP, United States Pharmacopeia; WHO, World Health Organization.
Engagement and dissemination: Resource examples

VIPS Alliance Action Plan

MAP Resources web page

MR MAP: Recent progress, remaining challenges
User needs:
Resource examples

Assessment of the acceptability and programmatic suitability of an HPV vaccine microarray patch in Ethiopia

HPV MAP assessment

Rabies vaccine report

A rabies vaccine MAP Understanding user and program needs

User and program-needs brief
Technical development: Resource examples
Manufacturing: Resource examples

Manufacturing readiness assessment for evaluation of the microneedle array patch industry: an exploration of barriers to full-scale manufacturing

Abstract
Microneedle array patch (MAP) technology is a promising new delivery technology for vaccines and pharmaceuticals, yet barriers to full-scale manufacturing exist. PATH conducted a manu- to identify both the current manufacturing readiness of the industry...
Regulatory: Resource examples

Risk assessment article

Regulatory Working Group website
Business strategy: Resource examples

Cost-effectiveness evaluation

PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE
Evaluating the potential cost-effectiveness of microarray patches to expand access to hepatitis B birth dose vaccination in low-and middle-income countries: A modelling study

Christopher P. Seaman,1,2,3 Mercy Mwandawiro,4 Collette Friend,5 Christopher Morgan,6,7 Courtney Jarreham,1,8 Jessa Howell,3,9,10 Margaret Heiland11,12 Nick Scott13

MR MAP future-demand evaluation

Estimating the future global dose demand for measles–rubella microarray patches
Melissa Ko1, Stefano Malvotti2, Thomas Cherian1, Carston Mantel1, Robin Biellik1, Courtney Jarreham1, Marion Meminetti-Arnould2, Jean-Pierre Amorij2, Hans Christiansen3, Mark J. Papain2, Martin I. Meltzer2, Balchir Girma Marensha5, Desiree Pastoor1, David K. Durnheim4, Birgitte Grenning1 and Malteusz Hasso-Agopowicz7,8

MR MAP business case

Measles-Rubella Microarray Patch Vaccines: A Business Case Analysis

Hormonal Contraceptive Microarray Patch: A Business Case Analysis

Contraceptive MAP business case