MATEUSZ

World Health Organization

Update from Vaccine Innovation Prioritization Strategy (VIPS) on Microarray patches (MAPs)

Marion Menozzi-Arnaud, Darin Zehrung, Mateusz Hasso-Agopsowicz, Courtney Jarrahian

PDVAC

9 December 2024

Overview

1. Overview of the VIPS initiative (Marion)
2. Considerations for the design of a phase III trial and data anticipated to inform policy decision for MR-MAPs (Darin)
3. Implementation research needs for MR-MAPs (Mateusz)
4. Pipeline of MR-MAPs and other priority vaccine MAPs (Courtney)

Questions to PDVAC:

- Are there other key activities that WHO and/or VIPS partners should be leading to accelerate the product development of MR-MAP, or to diversify the pipeline?
- Are there additional activities that WHO or VIPS partners could / should do to strengthen the investment case for vaccine-MAPs more broadly?

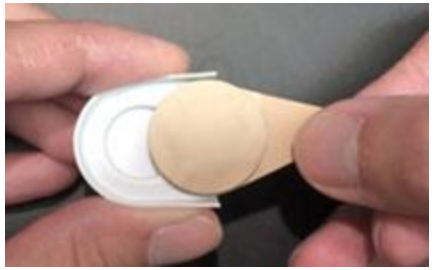
MARION

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

High-level update of the VIPS initiative

Prioritised Innovation #1

Microarray patches



- VIPS partners continue to work closely to **advance MR-MAPs – focus in 2024**:
  - Demand and public health impact modeling based on targeted use
  - Manufacturing
  - Human factor and thermostability studies
  - Regulatory
  - Implementation research questions
- **TCV-MAP FVVA** has been finalised and will be published.
- Deprioritisation of MR-MAPs in Gavi 6.0 strategy due to: uncertainty around availability late 6.0 vs 7.0, current constrained fiscal environment and need for trade-offs – **However**:
  - Several **donors recognized importance of MR-MAPs**
  - **Gavi will continue to work on MR-MAPs in 6.0** to prepare for country introduction, i.e., demand, MR market shaping roadmap, co-financing mechanism, etc.
  - If a market mechanism or pilots are needed in 6.0, alternative pathways will be explored.

High-level update of the VIPS initiative

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Prioritised Innovation #2

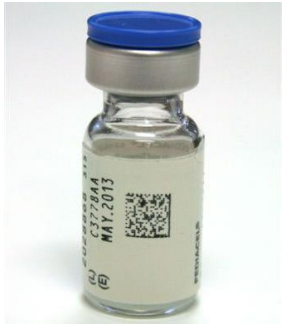
Heat stable and Controlled Temperature Chain (CTC) qualified vaccines

- **Controlled Temperature Chain (CTC)** strategy enabling removal of vaccines from the standard cold chain during final days prior to administration**:**
  - **CTC impact study for HPV in Cote d'Ivoire** is ongoing – expected to be completed by end 2025
  - Potential opportunity for a **CTC impact study for OCV in Zambia** is being explored – to be completed by end 2025
  - **Data collection from CTC implementation for OCV in Bangladesh** – planned for January 2025
  - **Integration of CTC into Hep B BD learning agenda,** to evaluate the role/importance of CTC qualification in out-of-facility vaccination – by 2027
  - **Additional CTC products qualified** or seeking qualification include 5-valent meningitis, cholera vaccine, hepB birth dose, and additional HPV products.
- **Heat stability:** Based on country consultations results - by end 2025:
  - A **'call for action'** on the need for improved thermostability of vaccine products to improve equitable access in LMICs
  - A **white paper** on challenges and needs around improved vaccine thermostability.

High-level update of the VIPS initiative

Prioritised Innovation #3

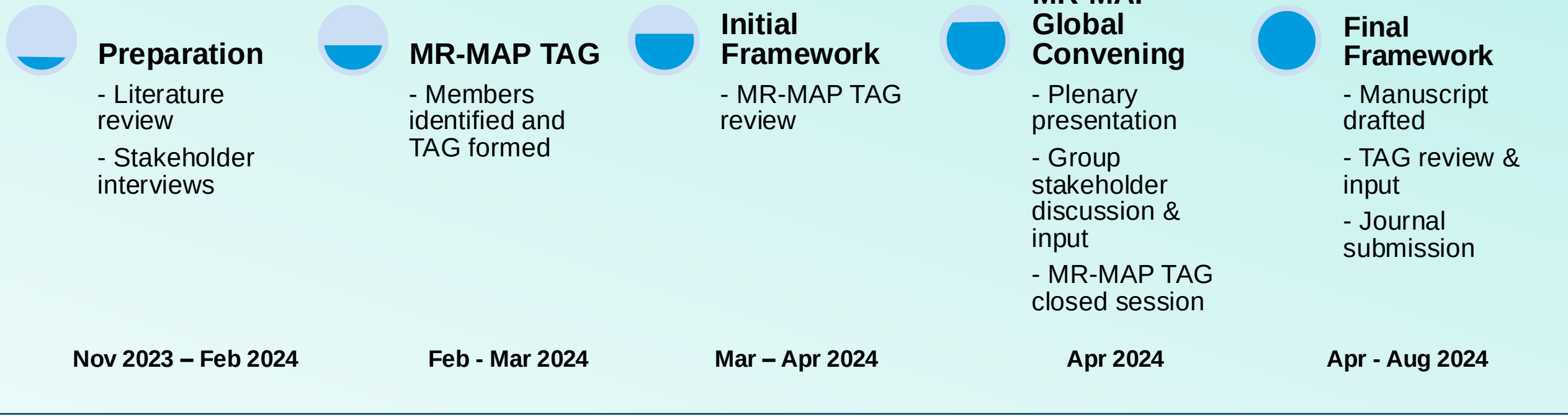
Barcodes



- A **barcodes roadmap** has been developed and **published**.
- **Short-medium term,** the roadmap objectives focus on:
  1. **Creating the enabling environment** needed for broader scale up long-term:
     - **Supply of barcoded vaccine products is currently available for most Gavi-UNICEF vaccines**
       - ✓ GS1-barcodes available on secondary packs for Gavi-funded vaccines (mandatory requirement by Gavi-UNICEF)
       - ✓ Serial number on secondary packs in good progress (preferential requirement by UNICEF since 2023)
     - **UNICEF with partners is advancing the TRVST global data repository** / data sharing
     - **WHO/MHP*** is focusing on **global policy and country guidance** for traceability and barcodes (Lisa Hedman and Anita Sands)
  2. **Demonstrating impact** to incentivize investments
     - Gavi has included barcoding into its HSS strategy for 6.0 (**targeted support to mature countries**)
     - Gavi may conduct **country pilots** on secondary packs

Methodology: MR-MAP Phase III Framework

Rationale: need to align on data needs anticipated to inform regulatory and policy decisions to prepare for future trials and research, while manufacturing sites are being built



Phase III trial for MR-MAPs – Design Considerations

World Health Organization

Clinical trial design: immunize 9–10 months of age MR naïve infants to assess non-inferiority of immunogenicity and safety (primary dose)

Non-inferiority margin: 5% NI margin could enhance country confidence for MR-MAP uptake, though a 10% margin could allow broader population diversity and higher chance of success

Additional populations: consider the incidence of HIV and malnutrition, NI margin, and operational challenges when deciding whether to include HIV and malnourished children in a trial.

Other vaccines: data showing concomitant delivery of live vaccines such as YF, JE, or polio are likely to be required due to potential for interference.

Immune assays: ELISA should be used to measure the levels of antibodies, while serum neutralizing antibody assays (SNAs) could be used to measure their functionality. Assessment of cellular immunity could be exploratory.

vaccines

MDPI

Article

Measles–Rubella Microarray Patches Phase III Clinical Trial Framework: Proposal and Considerations

Darin Zehrung [1], Bruce L. Innis [2], Auliya A. Suwantika [3], Mahmoud Ameri [4], Robin Biellik [5], James C. Birchall [6], Alejandro Cravioto [7], Courtney Jarrahian [8], Lee Fairlie [9], James L. Goodson [10], Sonali Kochhar [11], Katrina Kretsinger [12], Christopher Morgan [13], Mercy Mvunduza [8], Niraj Rathi [14], Edward Clarke [15], Jessica Joyce Mistilis [8], Marie-Chantal Uwamwezi [16], Birgitte Giersing [1] and Mateusz Hasso-Agopsowicz [1,*]

[1] World Health Organization, 1211 Geneva, Switzerland
[2] Independent Researcher, Haverford, PA 19041, USA
[3] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung 45363, Indonesia
[4] Independent Researcher, Fremont, CA 9453, USA
[5] Independent Researcher, 1278 La Rippe, Switzerland
[6] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff CF10 3NT, UK
[7] Departamento de Salud Pública, Facultad de Medicina, National Autonomous University of Mexico, Mexico City 04510, Mexico
[8] PATH, Seattle, WA 98121, USA
[9] Wits RHI, University of Witwatersrand, Johannesburg 2001, South Africa
[10] Centers for Disease Control and Prevention, Atlanta, GA 30333, USA
[11] Department of Global Health, University of Washington, Seattle, WA 98105, USA
[12] Independent Researcher, Decatur, GA 30033, USA
[13] JHPIEGO, Baltimore, MD 21231, USA
[14] PATH, New Delhi 110001, India
[15] Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine, Banjul P.O. Box 273, The Gambia
[16] PATH, 1040 Brussels, Belgium
* Correspondence: hassoagopsowiczm@who.int

check for updates

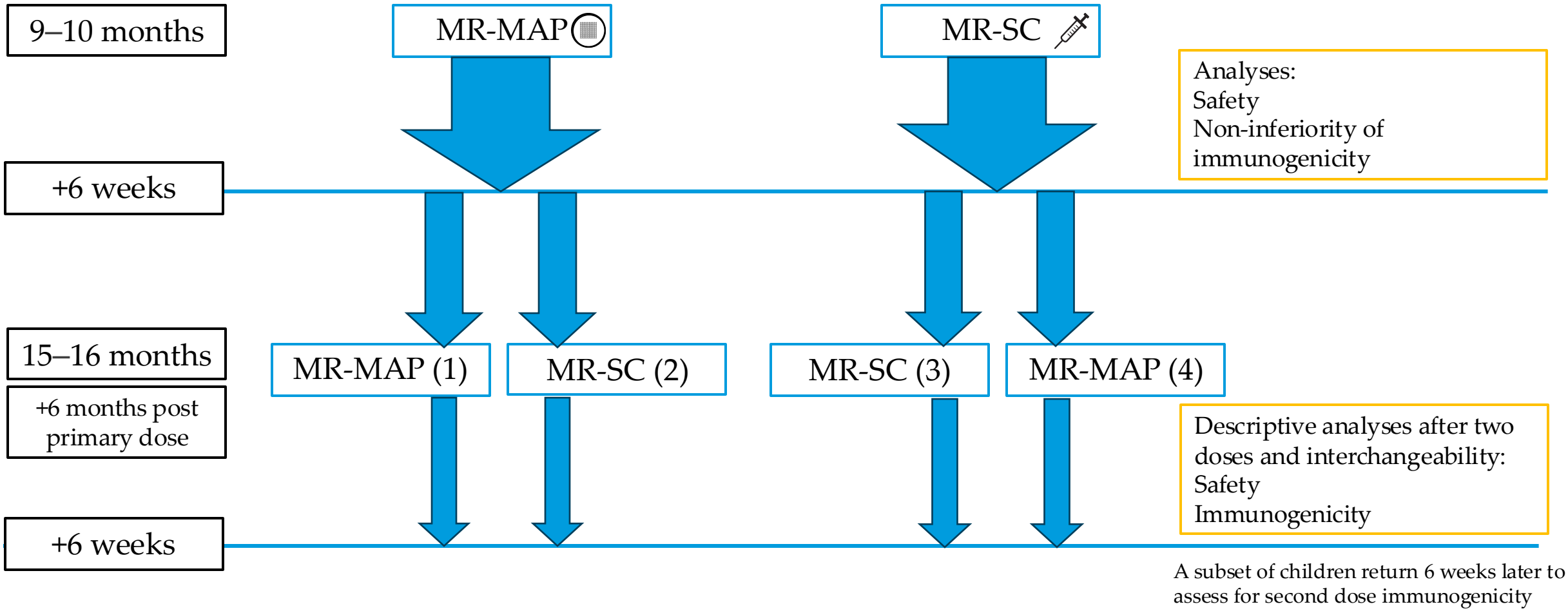
Citation: Zehrung, D.; Innis, B.L.; Suwantika, A.A.; Ameri, M.; Biellik, R.; Birchall, J.C.; Cravioto, A.; Jarrahian, C.; Fairlie, L.; Goodson, J.L.; et al. Measles–Rubella Microarray Patches Phase III Clinical Trial Framework: Proposal and Considerations. Vaccines 2024, 12, 1258. https://doi.org/10.3390/vaccines12111258

Academic Editor: Ralph A. Tripp

Received: 3 September 2024
Revised: 23 October 2024
Accepted: 25 October 2024
Published: 6 November 2024

Abstract: Background: The Measles–Rubella Microarray Patch (MR-MAP) is an important technology that is expected to reduce coverage and equity gaps for measles-containing vaccines (MCVs), reach zero-dose children, and contribute to elimination of measles and rubella. MR-MAPs are anticipated to be easier to deploy programmatically and could be delivered by lesser-trained health workers, thereby increasing immunization coverage. The most advanced MR-MAP has reached clinical proof-of-concept through a Phase I/II trial in the target population of infants and young children. The World Health Organization (WHO) and partners have developed the Phase III clinical trial framework for MR-MAPs presented in this article. **Objectives and Methods**: The purpose of such framework is to inform the considerations, design and approach for the pivotal clinical trial design, while considering the anticipated data requirements to inform regulatory approval, WHO prequalification, and policy decision. **Results**: The proposed Phase III trial would compare the immunogenicity and safety of an MR-MAP with MR vaccine delivered subcutaneously in 9- to 10-month-old infants. An analysis of non-inferiority (NI) of immunogenicity would occur six weeks after the first dose. Should regulatory agencies or policy makers require, a proportion of infants could receive a second dose of either the same or alternate MR vaccine presentation six months after the first dose, with those children returning six weeks after the second dose for a descriptive assessment of immunogenicity, and then followed up six months after the second dose for evaluation of safety and immunogenicity. It is anticipated that this proposed pivotal Phase III trial framework would generate the required clinical data for regulatory licensure and WHO prequalification (PQ) of MR-MAPs. However, the trial design would need to be reviewed and confirmed by a national regulatory authority (NRA) that will assess the product for regulatory licensure and the WHO PQ team. Additional research will likely be required to generate data on concomitant vaccine delivery, the safety and immunogenicity of MR-MAPs in other age groups such as children 1–5 years and infants younger than 9 months of

Proposed Phase III trial design for MR-MAPs



Measles–Rubella Microarray Patches Phase III Clinical Trial Framework: Proposal and Considerations

Examples of data anticipated to inform policy decision for MR-MAPs

Vaccine indication and schedule: Data on immunogenicity and safety for the primary dose in children aged 9–18 months (**minimum**) and expanded to younger (6 months) and older age groups (up to 5 years) (**optimal**), aligning with routine immunization schedules and campaign-specific applications.

Populations:

Minimum: children 9-18 months

Optimum: older children under 5, infants 6-9 months, children HIV+ and malnourished

Vaccine co-administration: Immunogenicity and safety data are required to ensure MR-MAP compatibility with EPI vaccines, particularly for simultaneous administration or within a month, considering potential interactions with live vaccines.

Storage and handling: Evidence is needed to confirm MR-MAP thermostability under controlled temperature chain (CTC) conditions, with a shelf life exceeding 24 months, and compatibility with current cold chain infrastructure, reducing wastage and improving logistics.

Acceptability and equity:

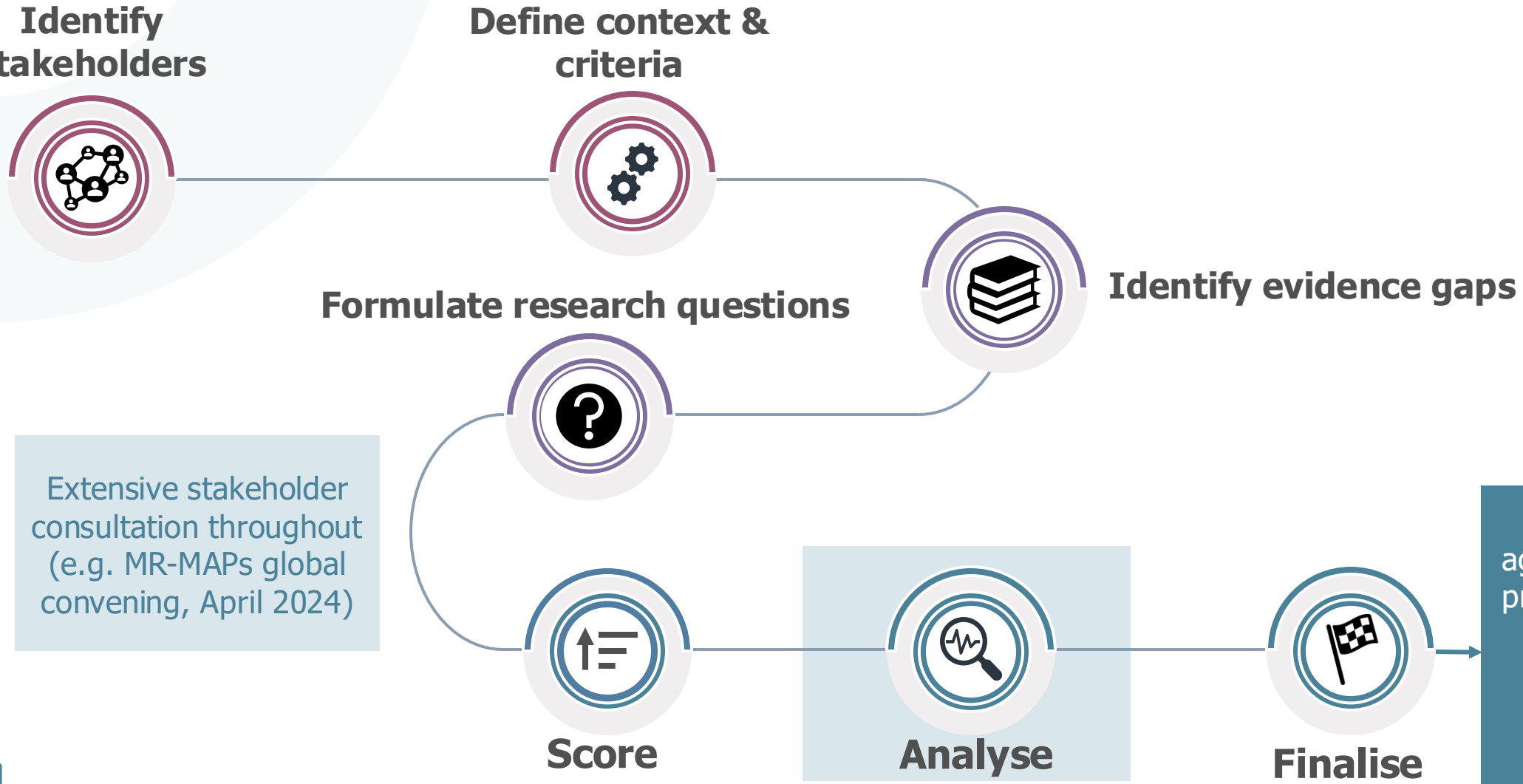
Minimum: data demonstrating acceptability of MR-MAPs among healthworkers and caregivers

Optimum: data supporting MR-MAPs' potential to increase coverage

MATEUSZ

Methodology to identify implementation research needs for MR-MAPs

CHNRI: Child Health and Nutrition Research Initiative Priority Setting



GLOBAL HEALTH CONSULTING

Criteria to identify implementation research needs for MR-MAPs

1 **Answerability**

Is the proposed research question answerable in the countries and communities by 2035?

2 **Impact**

Is the proposed research question likely to positively impact the uptake and coverage of MR?

3 **Equity**

Is the proposed research question likely to reduce inequities?

4 **Relevance**

Is the proposed research question relevant to the defined research context?

5 **Potential for translation**

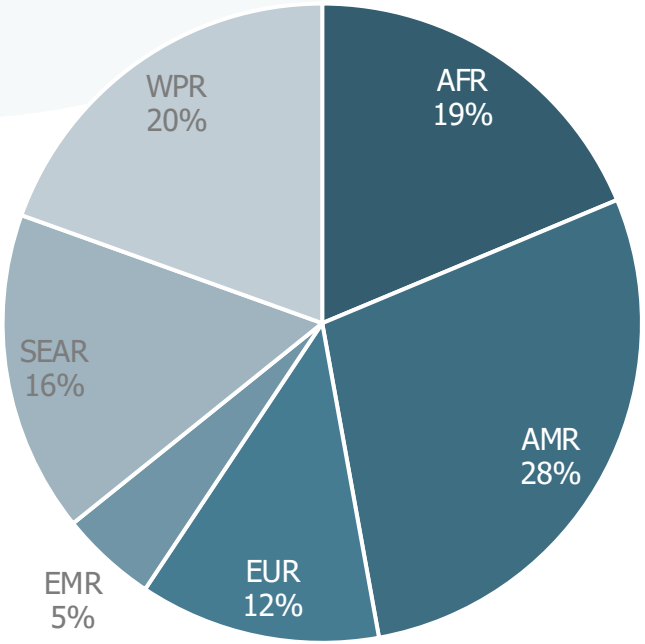
Is the proposed research question translatable to different country contexts and communities?

Respondents will be asked to review each RQ and to respond “Yes”, “No”, “Partially”, and “Don’t know” to each criteria

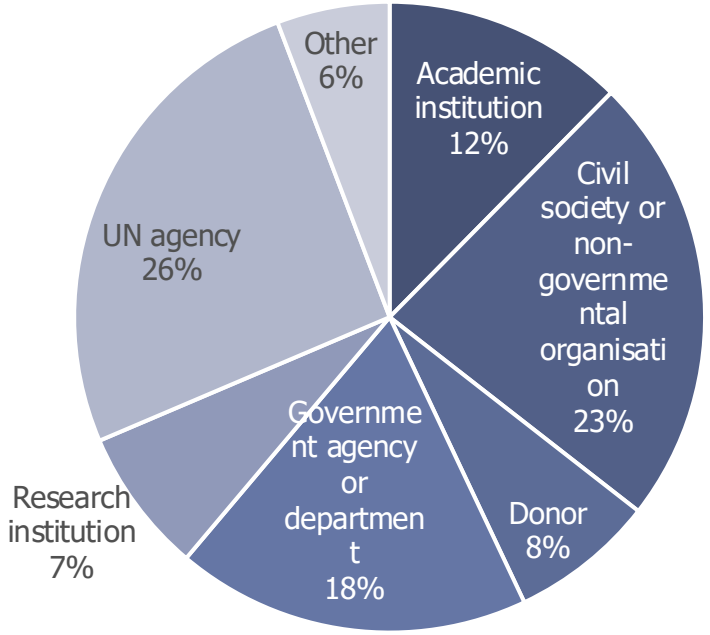
Respondent demographics

Survey sent to 190 experts (MR, vaccine programme implementation, MAPs, from country to global)
91 respondents fully completed the survey, and 30 respondents provided partial responses

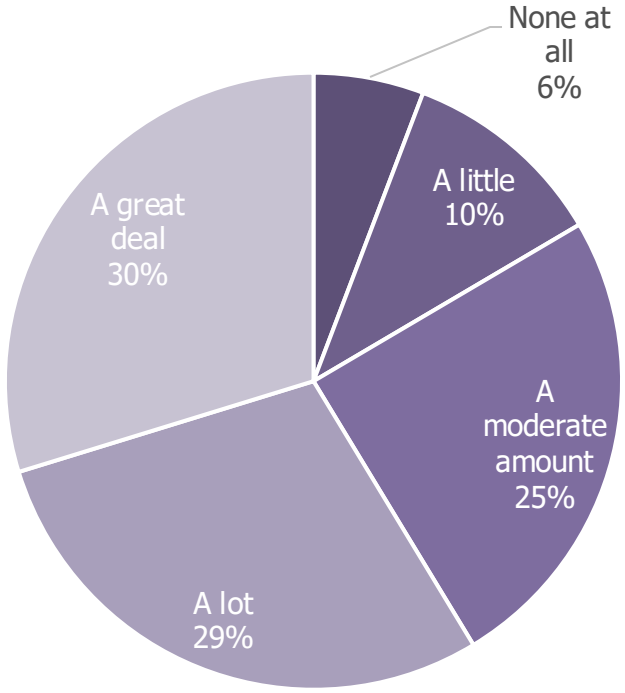
Respondent regional location



Respondent organisational affiliation



Respondents' experience of implementing in LMICs



Results: top 10 priority questions by category (1 of 3)

Average score	Acceptability, uptake and coverage
89%	Can the use of MR-MAPS reduce missed opportunities for vaccination (MOV), improve compliance in people with needle phobia, or reach children in hard-to-vaccinate communities? If so, by how much and what is the estimated impact on overall coverage?
87%	How can MR-MAPs improve MR vaccine uptake by and access to un- and under-vaccinated children, and to what extent, compared to the injectable vaccine?
84%	What are the caregiver and vaccinator perceptions on the risks, challenges, and opportunities of MR-MAPs that could affect acceptability and/or uptake?
82%	Can MR-MAPs reduce refusals related to multiple injections in one visit, if so, what is the frequency?

Results: top 10 priority questions by category (2 of 3)

Average score	
	Administration
84%	What are the caregiver and vaccinator perceptions on the risks, challenges, and opportunities of co-administration of MR-MAPs with other vaccines and/or with other health interventions (e.g., Vitamin A, deworming)?
	Supply chain and CTC
86%	What conditions and criteria need to be met to enable the optimal use (e.g., increase coverage while minimizing wastage) of MR-MAPs under controlled temperature conditions or the ability to tolerate ambient temperatures of at least +40°C for a minimum of three days?
85%	What would be the incremental benefit on vaccine coverage of having thermostable MR-MAPs (e.g., ability to tolerate ambient temperatures of +40°C for a minimum of three days or vaccine vial monitors with high stability of 30 days at +37°C)?

Results: top 10 priority questions by category (3 of 3)

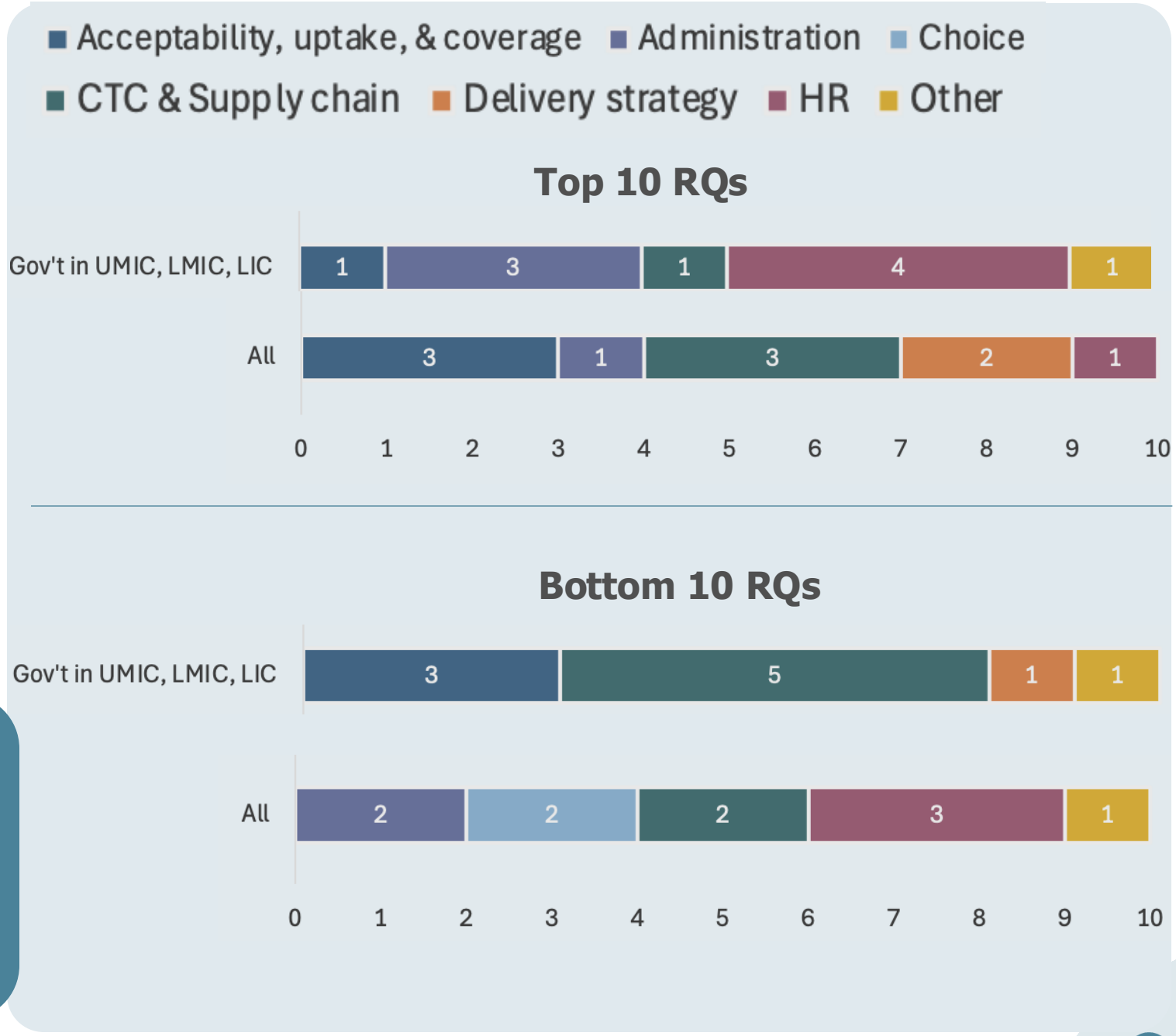
Average score	
	Delivery strategy
85%	What would be the role of MR-MAPs be in facilitating a timely response to measles or rubella outbreaks?
83%	What are the drivers of costs of MR-MAP in different delivery strategies, and contexts relative to the full benefits such as increase in coverage and reduction in measles cases compared with injectable MR vaccines?
	HR
87%	What is the impact of MR-MAPs on human resources (e.g., delivery strategies, team numbers, team composition, use of lesser trained personnel) planning for routine and SIAs?

Prioritized questions differed considering the stakeholders

- All stakeholders **prioritized** acceptability, coverage and uptake, and CTC & supply chain
- LMIC gov't reps **prioritized** Administration and HR and **deprioritised** acceptability, coverage and uptake, and CTC & supply chain

IMPLICATION:

- While the sample size from LMIC gov't representatives is small, there is a clear differentiation in the prioritization
- It is important to consider their perspectives to ensure appropriate implementation of MR-MAPs



COURTNEY

World Health Organization

Priority List of Vaccine Targets for MAPs

- **Rationale:** Current vaccine presentations have limitations in low- and middle-income countries (LMICs) due to cold chain requirements, complex administration, and waste from multi-dose vials, and MAPS could help to overcome these challenges
- **Method:** a prioritization process to identify high-priority vaccines for MAPs, focusing on LMICs, considering programmatic impact, regulatory complexity, and financial sustainability to support MAP development in LMICs
- **Results:** A final list of 11 high-priority vaccines was established, including vaccines for hepatitis B, measles, rubella, HPV, and influenza, among others.
- **Expected impact:** alignment of MAP development with public health needs.

PRIORITY LIST OF VACCINE TARGETS FOR MAPS

	VACCINE TARGET (DISEASE OR PATHOGEN)
Priority group 1	Hepatitis B
	Measles-rubella (MR)/measles, mumps and rubella (MMR)
	Human papillomavirus (HPV)
	Rabies
	Yellow fever
	Influenza virus: seasonal and pandemic
	COVID-19
Priority group 2	Group B streptococcus (GBS), *S agalactiae*
	Meningococcal A,C,W,Y,(X)
	Salmonella Typhi
	Streptococcus pneumoniae

Vaccine MAP pipeline

Prioritized, not in development

- Yellow fever
- Group B streptococcus
- Neisseria meningitidis
- Streptococcus pneumoniae

Preclinical

- HPV
- Rabies
- IPV
- Pentavalent/ Hexavalent

Phase 1

- **Hepatitis B**
  LTS Lohmann — Adult booster study, MAP had no adjuvant
- **Influenza**
  Seasonal and pandemic, multiple developers — Adults, demonstrated dose sparing
- **Hepatitis B***
  QuadMed — Planned for 2025
- **Typhoid conjugate***
  Vaxxas — Planned for 2026
- **Japanese encephalitis**
  Fuji Films — Adults
- **Rotavirus**
  Micron – Planned for 2025

Phase 2

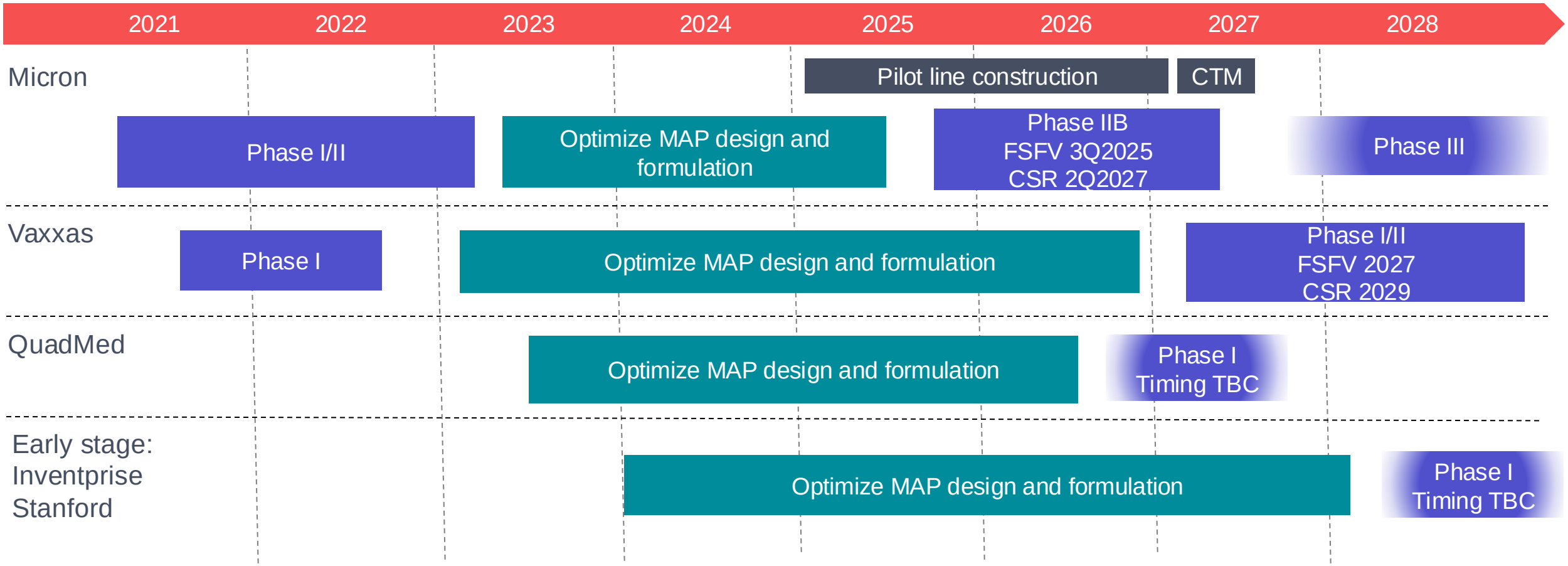
- **Measles-rubella**
  Micron — Adult, toddler, and infants in the Gambia
- **Measles-rubella***
  Micron* — 2b study in infants in the Gambia; Planned for 2025
- **Seasonal flu***
  Vaxxas —Planned for 2025
- **COVID-19***
  Vaxxas —Planned for 2026
- **Measles-rubella***
  Vaxxas — Adult, toddler, and infants in the Gambia; Planned for 2027

Key

- Prioritized
- Not prioritized
- * Trial planned and funded, not yet completed

List is not inclusive. Only the most advanced candidates for each vaccine antigen are shown.

Timeline for development of MR MAPs

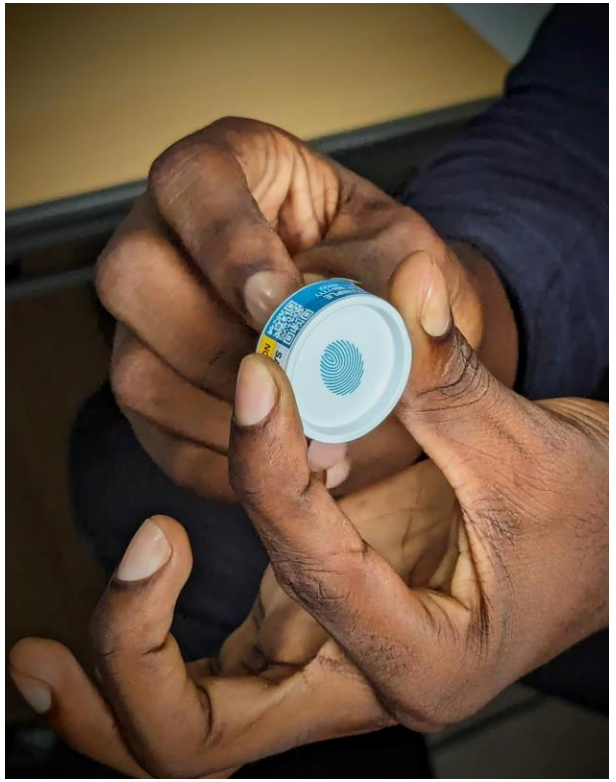


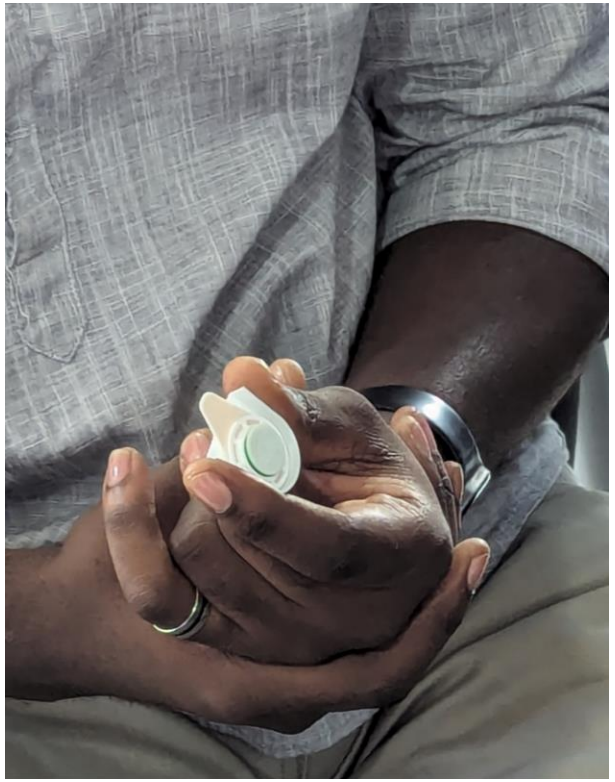
Device Development
Clinical
CMC/Manufacturing
Potential future activities

Abbreviations: CMC, Chemistry, Manufacturing, and Controls; CTM, clinical trial manufacturing; TBC, to be confirmed.

PATH's 2025 vaccine MAP plans

- Publish findings from MR MAP studies completed in 2024:
    - Human factors (Micron/Vaxxas)
    - Thermostability/CTC (Micron)
- Initiate Micron Phase 2b clinical trial
- Develop clinical study design and protocol for Vaxxas Phase 1/2 clinical trial
- Develop integrated manufacturing, clinical, regulatory, and policy timeline for an MR MAP





MATEUSZ

MAPs activities for 2025

- Publication of **TCV-MAPs FVVA** (incl. manuscripts on use cases and cost-effectiveness)
- Publication of a **manuscript on VIPS priority vaccines for use with MAPs**
- Update of **MR-MAPs demand modelling** based on **targeted use**
- Finalisation of **MR-MAPs public health impact** associated with **targeted use**
- **Country consultations**/deep-dives to define tailored **introduction scenarios**
- **End-to-end mapping** of all required activities **up to in-country introduction**

- Finalisation and publication of the **evidence anticipated to inform WHO policy decision** on MR-MAPs
- **Publication** of priority **implementation research**
- **Conducting** priority **implementation research** through partners
- Engagement with Expert Committee on Biological Standardization to **identify a pathway to WHO prequalification**

Summary

- Microarray patches have been prioritised by VIPS alongside thermostable vaccines and barcodes, and **continue to be a priority innovation**;
- A framework with **considerations for the design of a phase III trial** has been published– highlighting data likely required to inform regulatory decisions
- Summary of **anticipated evidence to inform WHO policy decision** will soon be revised by SAGE and WHO Technical Advisory Group on MR-MAPs and later published.
- **Implementation research priorities have been identified** and studies to collect data on implementation **research should start in 2025**.
- **Priority list of vaccine MAPs** has been identified and will soon be published.
- There are **increasing number of candidates in the vaccine MAP pipeline**– with two phase 1 studies, and two phase two studies to commence in 2025.
- Construction of the pilot line for the leading MR-MAP candidate is ongoing.

Thank you!

- Are there other key activities that WHO and/or VIPS partners should be leading to accelerate the product development of MR-MAP, or to diversify the pipeline?
- Are there additional activities that WHO or VIPS partners could / should do to strengthen the investment case for vaccine-MAPs more broadly?