VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Vaccine microarray patches (MAPs): *public summary of the VIPS Alliance Action Plan*

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

1 Executive summary

In May 2020, at the end of phase II of the Vaccine Innovation Prioritisation Strategy (VIPS) process[1], the VIPS Steering Committee selected and recommended three innovations to be prioritised to better meet country needs and improve coverage and equity. As a next step, the five partner organisations of the VIPS Alliance[2] will engage with these priority innovations to advance development, policy and access.

Microarray patches (MAPs) were ranked as the highest priority of these three innovations;[3] they were considered to be truly 'transformational' innovations that have the potential to address many of the immunisation barriers identified by low- and middle-income countries (LMICs) during the VIPS process. They are also highly relevant for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine implementation and for pandemic preparedness and response in general.

During the second half of 2020 and into Q1 of 2021, the VIPS Working Group (WG) drafted and endorsed a five-year Action Plan for vaccine MAPs. This document is a summary of the methodology used, and the key activities contained in the plan.

The full version of the Vaccine MAP Action Plan, which is available on request:[4]

- Identifies activities for the VIPS Alliance and other organisations to undertake to accelerate development and future uptake of vaccine MAP products for LMIC use.
- Considers the context of existing activities by the VIPS Alliance and other stakeholders.
- Has the aspiration to advocate for vaccine MAPs in general and attract the interest of other global health partners to benefit the development of vaccine MAP products of highest value for LMICs.

The VIPS Alliance's long-term vision for vaccine MAPs is to:

Implement MAP products for priority vaccines to overcome immunisation barriers to ensure equitable access to, and improved effectiveness of, vaccines in LMICs and contribute to global health security.

The VIPS Alliance is aware that widespread implementation of vaccine MAPs will not be achieved within the five-year timeframe of the Action Plan; therefore, the five-year goal of the Action Plan is to:

[1] https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy.

[2] The VIPS Alliance is a partnership between Gavi, the Bill and Melinda Gates Foundation, PATH, UNICEF and the World Health Organization.

[3] The other prioritised innovations were heat-stable and controlled temperature chain qualified vaccines, and barcodes on primary packaging

[4] Please contact Tiziana Scarna tscarna@gavi.org to access the full version of the Action Plan

Accelerate development and future country uptake of MAPs as a platform technology for vaccine delivery in LMICs.

Five measurable target outcomes (TOs) have been developed, with 21 underlying activities needed to achieve this five-year goal. These activities will be undertaken by the VIPS Alliance and other organisations during 2021–2025, and in case of gaps the VIPS Alliance will advocate for the relevant activities to be on other funders' agenda The TOs are:

1. Provide guidance to industry, funders and countries by clarifying the needs and demand for, and the value of, vaccine MAPs.
2. Create an enabling environment for vaccine MAPs by understanding the need for market incentives, and addressing the challenges linked to the business case for vaccine MAPs for LMICs.
3. Expand the evidence base to demonstrate the potential of MAPs as a platform technology for delivering vaccines, including for pandemic preparedness and response.
4. Advance at least one LMIC vaccine MAP product to phase 3 clinical trials.
5. Cross-cutting (shared with Action Plans for other VIPS priority innovations): secure resources and set-up engagement and coordination mechanisms with key stakeholders and establish a continuous learning environment.

2 Background to vaccine MAPs

MAPs consist of an array of hundreds to thousands of micro-projections on a patch or backing. The micro-projections can be coated with, or are composed of, vaccine in a dry formulation. MAPs are either applied to the skin without an applicator or by using an applicator. After MAP application, the vaccine is delivered into the dermis and/or epidermis of the skin, which are rich in antigen-presenting cells. The two main types of vaccine MAPs being developed are:

- **Solid-coated**: the micro-projections are formed of a solid substance, such as polymer, steel or silicon, and are coated with vaccine.
- **Dissolving**: sometimes referred to as dissolving microneedles; the micro-projections are formed from a mixture of vaccine and excipients that provide sufficient structural strength to enable the projections to penetrate the skin.

Phase II of VIPS prioritised MAPs because:

- They were recognised as having the potential to address many of the immunisation barriers identified by countries during phases I and II of VIPS.
- This is due to their:
    - Potential for improved thermostability.
    - Better ease of use.
    - Avoidance of reconstitution and the associated errors and risks.
    - Improved safety.
    - The fact that they are single-dose presentations.

Additionally:

- Vaccine MAPs are applicable to a range of immunisation use-cases including routine, supplemental, house-to-house, outbreak immunisation and pandemic response. In these settings, vaccine MAPs could be delivered by health-care workers, community health workers or by self-administration, with or without assistance.
- They could also have a positive impact on life-course immunisation for broader populations beyond children, such as adolescents and adults, including those who are pregnant or older.
- The attributes of vaccine MAPs could make them particularly valuable for pandemic preparedness and response. They could be developed for use with licensed or pipeline vaccines against SARS-CoV-2, and with prototype vaccines to prepare or respond to a future pandemic with influenza, a coronavirus or pathogen X.

Phase II of VIPS noted, however, that there are still significant technical and commercial barriers to overcome before vaccine MAPs can be implemented, particularly for vaccines intended for use in low-resource settings.

2.1 Landscape of vaccine MAPs

In Q3 2020, the pipeline of vaccine MAPs known to be in preclinical and clinical development and in the public domain was reviewed for the initial draft of the Vaccine MAP Action Plan and updated in Q2 2021. The pipeline is discussed in more detail in the full version of the Vaccine MAP Action Plan.

In summary, preclinical development of vaccine MAPs is ongoing with a number of vaccine MAPs for LMICs, including

- **Measles–rubella (MR):** The Bill and Melinda Gates Foundation (BMGF) is supporting preclinical development, phase 1 and phase 2 clinical trials of MR MAPs by two MAP developers (MDs), Micron Biomedical and Vaxxas. Phase 1 clinical trials are expected to start in Q2/Q3 2021.
- **Inactivated poliovirus vaccine (IPV):** The World Health Organization (WHO) and BMGF have been supporting two MDs (Micron Biomedical and Vaxxas). In 2017, the programs had stalled due to the global shortage of IPV antigen for clinical studies.
- Micron Biomedical is manufacturing MAPs containing **inactivated rotavirus vaccine** for the US Centers for Disease Control and Prevention.[5]
- In Q1 and Q2 2020, the Biomedical Advanced Research and Development Authority (BARDA) announced funding to support three MDs (University of Connecticut; Vaxess

[5] https://micronbiomedical.com/micron-biomedical-progresses-with-clinical-evaluation-of-its-technology-for-measles-rubella-vaccination-2-2/

and Verndari) to work on **SARS-CoV-2** vaccine MAPs,[6] and for one MD (Vaxxas) to develop a **pandemic influenza** vaccine MAP.[7]

MDs and vaccine manufacturers (VMs) also have internal programmes in preclinical development, details of which are not often in the public domain.

Three MDs have tested MAPs for delivery of influenza vaccines in phase 1 clinical trials and have published data.[8],[9],[10],[11] One further MD has announced completion of a clinical study, but the data are not available.[12] Another MD is known to have completed a phase 1 trial with hepatitis B virus vaccine.[13]

2.1.1 Status of vaccine MAP manufacturing

MDs have advanced their manufacturing processes to varying degrees, ranging from proof of concept through to the capability to produce vaccine-loaded MAP prototypes suitable for phase 1 clinical trials using manual processes. One MD has announced an alliance to develop the world's first high-throughput, aseptic manufacturing line for production of MAPs for vaccine delivery, which could produce up to 5 million vaccine MAPs/week.[14] Developing the processes and facilities that can produce vaccine MAPs at large scale are activities on the critical path to product availability, assuming clinical trials are successful.

2.1.2 Timelines for vaccine MAP development

The dates by which the first vaccine MAPs primarily for LMIC use will be approved and available for implementation are very uncertain. The most advanced candidates are believed to be the MR MAPs from two MDs that are due to enter phase 1 clinical trials in Q1/Q2 2021. Estimates by the VIPS WG and other stakeholders suggest that in a best-case scenario, WHO prequalification (PQ) for MR MAPs could possibly be achieved is ~2026 at the earliest, but this would only be for MR MAPs produced using a pilot-scale process. PQ MR MAPs produced at

---

[6] https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx

[7] https://www.businesswire.com/news/home/20201005005168/en/Vaxxas-Announces-22-Million-Award-from-U.S.-Government-to-Advance-Vaxxas-Needle-Free-HD-MAP%E2%84%A2-Vaccine-Patch-Technology-for-Pandemic-Response

[8] Forster AH, Witham K, Depelsenaire ACI, Veitch M, Wells JW, Wheatley A, et al. Safety, tolerability, and immunogenicity of influenza vaccination with a high-density microarrqay patch: Results from a randomized, controlled phase I clinical trial. PLoS Med. 2020 Mar;17(3):e1003024.

[9] Hirobe S, Azukizawa H, Hanafusa T, Matsuo K, Quan Y-S, Kamiyama F, et al. Clinical study and stability assessment of a novel transcutaneous influenza vaccination using a dissolving microneedle patch. Biomaterials. 2015 Jul;57:50–8.

[10] Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet. 2017 12;390(10095):649–58.

[11] Fernando GJP, Hickling J, Jayashi Flores CM, Griffin P, Anderson CD, Skinner SR, et al. Safety, tolerability, acceptability and immunogenicity of an influenza vaccine delivered to human skin by a novel high-density microprojection array patch (Nanopatch™). Vaccine. 2018 18;36(26):3779–88.

[12] https://www.zosanopharma.com/partnering/vaccines/covid-19/

[13] Stefan Henke, LTS Lohmann and Ravi Menon, Serum Institute of India Ltd, personal communication.

[14] https://www.businesswire.com/news/home/20200528005214/en/Harro-Höfliger-Vaxxas-Announce-Alliance-Develop-Industrial-scale

commercial-scale are not likely to be available until 2028–2030 at the earliest. These are optimistic timelines without contingencies. They assume adequate resources are available throughout the programmes, and they do not account for any impacts of the COVID-19 pandemic on the development process.

The development of vaccines in response to the COVID-19 pandemic has shown that the traditional vaccine-development timelines can be dramatically shortened given political will and sufficient funding. It is possible that the development of SARS-CoV-2 MAPs could also be accelerated, with products possibly available as early as 2025–2026.

2.1.3 Ongoing vaccine MAP activities by existing VIPS Alliance partners and other stakeholders

The BMGF and the WHO have been supporting preclinical and clinical development of MR- and IPV MAPs. WHO has supported an acceptability study for MR MAPs,[15] and coordinates an MR-MAP WG.

The MAP Center of Excellence co-ordinated by PATH and funded by the UK Foreign Commonwealth and Development Office is undertaking a number of activities to assist development of MAPs for vaccine- and non-vaccine applications.[16]

UNICEF is supporting MAP-related activities, and funding an initial full value for vaccines assessment (FVVA) for MR-MAPs.

BARDA has announced funding for MDs to develop MAPs for SARS-CoV-2 and pandemic influenza vaccines.[6,7]

2.2 Why an Action Plan is needed

MAPs have been in development by many academic laboratories and companies for around 20 years but, to date, only a handful of candidate vaccine MAPs have entered early-phase clinical studies.[17] The rate of progress reflects the technical and commercial challenges involved in developing and manufacturing these complex products that are a combination of delivery device and vaccine.

It is likely that the first vaccine MAPs will be approved ~2026–2027, but these will probably be for vaccines with markets primarily in high-income countries, such as seasonal influenza vaccine. It is possible that SARS-CoV-2 vaccine MAPs might be available sooner than this. Most stakeholders agree, however, that the development of vaccine MAP products of most value for LMICs won't happen without a clear and integrated strategy, with the end goal in mind, and with new funding, including for procurement.

---

[15] Guillermet E, Alfa DA, Phuong Mai LT, Subedi M, Demolis R, Giersing B, et al. End-user acceptability study of the nanopatch™; a microarray patch (MAP) for child immunisation in low and middle-income countries. Vaccine. 2019 Mar 16

[16] https://www.path.org/resources/path-center-excellence-microarray-patch-technology/

[17] Badizadegan K, Goodson JL, Rota PA, Thompson KM. The potential role of using vaccine patches to induce immunity: platform and pathways to innovation and commercialisation. Expert Rev Vaccines. 2020 Feb;19(2):175–94

The full Vaccine MAP Action Plan aimed to:

- Review vaccine MAP development for LMICs and assess what remains to be done by VIPS Alliance partners and other organisations to develop vaccine MAP products of value for LMICs and accelerate their introduction to LMICs.
- Identify activities that the VIPS Alliance can undertake to address gaps and obstacles within the entire development process of vaccine MAPs through an end-to-end approach: from improving partnering and communication between funders, VMs and MDs, through to late-stage clinical testing, procurement, and preparation for the use of vaccine MAP products in LMICs.

3 Methodology

The scope and steps involved in the development of the Vaccine MAP Action Plan included

- A review of the landscape of vaccine MAPs based on work in VIPS phases I and II.[18] This work had focussed on vaccines for endemic pathogens for LMICs but, from Q1 2021, the review also considered vaccine MAPs in the context of the COVID-19 pandemic and for pandemic preparedness and response in general.
- A review of current vaccine MAP workstreams and activities of VIPS Alliance partners.
- Consultations, by telephone interview or e-mail in Q2–Q3 2020, with:
    - A panel of six MDs and six VMs.
    - A panel of other key partners including representatives from civil society organisations, global health organisations, funders, and industry reviewed lessons learned from the development of other vaccine-product innovations. Comments that were specific to, or could be applied to, MAP development were captured.
- In Q3 2020, the findings from the consultations and VIPS WG were consolidated to identify key challenges facing development of vaccine MAPs.
- The challenges were reviewed by VIPS Alliance partners and a list of activities that were not being addressed and were considered important for the acceleration of vaccine MAP development were identified and grouped into five measurable TOs.
- From Q3 2020, the Vaccine MAP Action Plan was reviewed and endorsed by the five VIPS partner organisations and this public summary prepared.

The findings from the consultations as well as the consolidated list of challenges are described in the full Vaccine MAP Action Plan.

[18] A summary of the technical notes produced for MAPs for phases 1 and 2 of VIPS is available at https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy

4 Summary findings from consultations

4.1 Consultations with MDs and VMs

There was a wide range of responses from VMs and MDs to the consultations conducted in Q2–Q3 2020, with some common themes:

- VMs had a wide range of levels of interest and enthusiasm for MAPs, with some being very interested and actively involved in their development, while others were not convinced of their potential.
- All the MDs were interested, at least in principle, in developing vaccine MAPs for use in LMICs, because they wanted to have a positive impact on global health.
- Some MDs expressed concern about how commercially sustainable this would be for them, and if there is a business model to support development of these LMIC products.
- Some MDs considered that the current approaches for push-funding are not sufficiently attractive and involve too much risk.
- Some VMs were concerned that vaccine MAPs will be more costly to produce, that future procurement is not guaranteed, and the prices offered will not provide a return on their investment.
- Most, if not all, VMs and MDs considered that demonstrating that MAPs can be produced at commercial scale is a significant challenge that still needs to be addressed.
- VMs, and to an even greater extent, MDs, considered there to be regulatory hurdles to be addressed, and that guidance on key regulatory issues is required. Most thought that an important question is whether sterile/aseptic manufacture of vaccine MAPs will be required, or whether production under low bioburden conditions will be acceptable, at least for early stages of clinical development. Aseptic manufacture is very likely to significantly increase the cost of goods (CoGs).
- There was no clear consensus on which vaccines, or even which vaccine types, should be prioritised for use with MAPs. Guidance from Alliance partners would be welcomed by MDs and VMs.
- MAPs have several attributes that would be useful for SARS-CoV-2 vaccines, but in Q2-Q3 2020, MDs and VMs felt that MAPs were not yet sufficiently mature for use with first-generation COVID-19 vaccines. They thought that the level of investment in SARS-COV-2 vaccines, and increased awareness of pandemics, could benefit all vaccine development and vaccine MAPs in the short- to long-term. MDs and VMs cited self-administration as an important potential benefit of MAPs.
- There was a wide range of suggestions for ways in which the Alliance partners might accelerate vaccine MAPs for use in LMICs. Advocacy of vaccine MAPs as a platform technology was often cited.

4.2 Consultations with key partners (KPs)

In the Q2–Q3 2020 consultations with KPs some of the points that were raised about vaccine-product innovations in general were also relevant to vaccine MAPs, these included

- There is a need for vaccine-specific and vaccine-innovation specific, full value of vaccine assessments (FVVAs) to stimulate early and sustained investment. They could include: use cases, pricing and total systems trade-offs to incorporate willingness to pay and return on investment for donors, funders and industry.
- In general, technology solutions should be based on clear demand from countries, with clear articulation of programmatic and cost/benefit. The demand signal should be generated early enough to be compelling for investment. Where possible, country assessments should include preferences for product attributes.
- In general, a 'fast-fail process' is needed, against predefined criteria so technology development that does not have potential for impact or uptake can be stopped.
- Push-funding of partnerships between MDs and VMs, including developing country vaccine manufacturers (DCVMs), is needed.
- Deploying differentiated vaccine products within a single immunisation programme could be a logistical challenge.
- Implementation research should be conducted in parallel to product development if possible. This could help avoid post-licensure delays in policy recommendation and vaccine introduction.
- MAPs could be used with 'next generation' SARS-COV-2 vaccines, including in LMICs.
- Vaccine-MAPs could be one way to reach the goals for 'zero-dose' children in Immunisation Agenda 2030 (IA2030).

5 VIPS Alliance vision and goal for vaccine MAPs and related activities for 2021–2025

The VIPS Alliance's long-term vision for MAPs is to:

Implement MAP products for priority vaccines to overcome immunisation barriers to ensure equitable access to, and improved effectiveness of, vaccines in LMICs and contribute to global health security.

This vision cannot be achieved with the five-year time frame of the Vaccine MAP Action Plan; therefore, the overall five-year goal is to:

Accelerate development and future country uptake of MAPs as a platform technology for vaccine delivery in LMICs.

Five measurable target outcomes (TOs) have been developed, with 21 underlying activities needed to achieve this five-year goal. These activities will be undertaken by the VIPS Alliance and other organisations during 2021–2025, and in case of gaps the VIPS Alliance will advocate for the relevant activities to be on other funders' agenda.

The Action Plan is not a roadmap or product development plan incorporating all stages of the development of a vaccine MAP. It describes activities that are required to address the challenges

that were identified in the consultation process, and that the VIPS WG consider will accelerate development and future country uptake of vaccine MAPs for LMIC use. The plan acknowledges that in order to implement vaccine MAP products in LMICs that are recommended by WHO and PAHO, the activities will need to continue beyond the five-year duration of the plan.

The TOs are:

TO 1: Provide guidance to industry, funders and countries by clarifying the needs and demand for, and the value of, vaccine MAPs.

VMs and MDs and some funders would like guidance on the vaccines that global health funders, countries and procurement agencies consider of value for use with MAPs, so that appropriate products for LMICs are developed. One way to do this is by an in-depth analysis using the WHO format of FVVAs. Components of FVVAs include analyses of potential use-cases and preferred product attributes, demand forecasting and economic modelling.

Activities

1. Identify priority vaccines to be used with MAPs for LMICs.
2. Identify and quantify potential use-case scenarios and size the demand for at least two vaccine MAPs relevant and/or important to LMICs.
3. Estimate the cost of goods of vaccine MAPs for at least two vaccines relevant to LMICs.
4. Model the broad economic impact, and the potential impact on coverage and equity of MAPs used with at least two vaccines relevant to LMICs.
5. Conduct willingness-to-pay and willingness-to adopt analyses for at least two vaccines relevant to LMICs
6. Provide guidance on the preferred product attributes for LMICs for at least two vaccines relevant to LMICs.
7. Develop and communicate FVVAs for MAPs for at least two vaccines relevant to LMICs.

TO 2: Create an enabling environment for vaccine MAPs by understanding the need for market incentives, and addressing the challenges linked to the business case for vaccine MAPs for LMICs.

Currently, the business cases for some vaccine MAPs, especially for use in LMICs, are not well-understood, and might not be sufficiently compelling to attract investment. Push- and pull-funding mechanisms are likely to be required to support and incentivise MDs and VMs to develop vaccine MAPs for LMICs. Early involvement of policy makers and vaccine implementers could help reduce overall costs and avoid delays between licensure and implementation.

Activities

8. Understand the challenges related to the business models for vaccine-MAP development, and support as appropriate.
9. Investigate the need for, and possibly design new push- and pull-funding mechanisms for vaccine MAPs for LMICs.

10. Define the regulatory, policy, procurement, financing, and introduction pathways for vaccine MAPs for LMIC use.

TO 3: Expand the evidence base to demonstrate the potential of MAPs as a platform technology for delivering vaccines, including for pandemic preparedness and response.

MAPs are a platform technology that are potentially applicable to a wide range of vaccines, especially vaccines for pandemic preparedness and response. The preclinical and clinical evidence base with current MAP formats and vaccines is, however, relatively limited. Additional preclinical and clinical data, with a range of vaccines relevant for LMIC use are needed to inform on the breadth of applicability of vaccine MAPs. Combined with evidence from implementation research, this should help to guide further investment in vaccine MAPs for LMIC use.

Activities

11. Conduct implementation research to inform delivery strategies for at least two vaccine MAPs relevant to LMICs.
12. Conduct preclinical studies to evaluate the applicability of MAPs to different vaccine types, using exemplar vaccines.
13. Understand expectations from key stakeholders for clinical trial data and optimise trial design and support for at least two vaccine MAPs relevant to LMICs.
14. Conduct clinical trials with at least four vaccine MAPs relevant to LMICs, ideally using different MAP platforms.

TO 4: Advance at least one LMIC vaccine MAP product to phase 3 clinical trials.

Given the status of the vaccine MAP pipeline, product development needs to be accelerated if phase 3 trials with the first vaccine MAP for LMIC use are to start within the timeframe of the Vaccine MAP Action Plan. To achieve this, other critical obstacles will need to be addressed including funding for commercial-scale manufacturing and a regulatory strategy for phase 3 and market approval.

Activities

15. Understand the challenges facing scale-up of vaccine-MAP manufacturing, and financially support a proposed solution, if necessary.
16. Develop preferred policy profiles for at least two vaccine MAPs relevant to LMICs.
17. Fund or support phase 3 trial(s) with at least one vaccine MAP relevant to LMICs.

TO 5 (cross-cutting): secure resources and set-up engagement and coordination mechanisms with key stakeholders and establish a continuous learning environment.

The success of the VIPS Alliance Action Plans for the three VIPS priority innovations will depend on collaborating with stakeholders beyond the existing VIPS Alliance partners, including global-health funders, immunisation implementation partners and other country- and regional-level stakeholders. This will require ongoing communication, engagement on, and advocacy for vaccine MAPs.

Activities

A. Define and implement an Action Plan funding strategy, including engagement with new funders to secure resources and/or commitments to carry out all the Action Plan activities.
B. Establish a mechanism for country and regional engagement to inform the Action Plan activities.
C. Establish a mechanism to regularly engage and coordinate with key stakeholders and identify areas of collaboration.
D. Set up a learning environment.

The TOs in the Vaccine MAP Action Plan are ambitious, but the VIPS WG considers them and the underlying activities to be necessary if the most valued vaccine MAPs are going to be developed and available in LMICs, including for pandemic preparedness and response, as soon as possible.