The VIPS Prioritisation Process: Methodology and Outcomes

Contents

INTRODUCTION

Rationale for VIPS

Innovative approaches are needed to help to address immunisation barriers and achieve immunisation coverage and equity goals. Vaccine product innovations offer important means to simplify logistics, increase the acceptability and safety of immunisation, minimise missed opportunities, and facilitate outreach. There is increasing recognition of the need to employ targeted solutions to extend vaccine access to reach the unreached. This may require the use of differentiated vaccine products or technologies for these focused efforts and a willingness to pay a price premium to reduce vaccine coverage inequities. Work by industry; individual technology developers; academic institutions; and governmental, non-governmental, and international agencies has contributed to the advancement of specific vaccine product innovations yet it has often been insufficiently coordinated, focused on higher income markets, and/or lacking in the market shaping efforts required to ensure that promising technologies reach those who need them most.

VIPS Background and Goal

In the 2016-2020 Supply and Procurement Strategy, Gavi, the Vaccine Alliance reaffirmed innovation as one of three priorities[1] in shaping markets to better meet country needs and support Alliance goals on immunisation coverage and equity. In 2017, the Gavi Secretariat convened an Alliance Working Group (WG) including the World Health Organization (WHO), Bill & Melinda Gates Foundation (BMGF), United Nations Children's Fund (UNICEF), and PATH, that developed a single integrated framework to drive priority vaccine product innovations forward.

The resulting Vaccine Innovation Prioritisation Strategy (VIPS) represents an unprecedented three-year collaboration amongst the aforementioned organisations, involving in-depth research, stakeholder consultations, and development and application of a framework capable of evaluating a variety of technologies at different stages along the product development pipeline continuum. The work required understanding countries' needs to consider the expected financial and non-financial impacts of innovations; developing common principles across the Alliance to measure the long-term benefits of product innovations; and convening a platform to articulate a clear and aligned perspective on priority product innovations. By prioritising innovations in vaccine products and communicating these priorities, the goal of VIPS is to provide greater clarity to manufacturers and partners to inform and influence investment decisions. VIPS outcomes will also represent a first step to mobilise key decision-makers and funders and chart a strategic pathway forward for the prioritised innovations.

Purpose of this Document

This document describes the methodology developed by VIPS to prioritise vaccine product innovations as well as the outcomes.

[1] Other priorities included ensuring adequate and secure supplies and reducing prices to appropriate and sustainable levels.

STRUCTURE OF VIPS

Alliance Working Group

VIPS is a close Alliance-wide collaborative effort that leverages the existing capabilities and comparative advantages of five key organisations that cover the entire product development to uptake spectrum, from research and development to policy, procurement, access and impact, and have complementary roles along this continuum. The VIPS Alliance Working Group (WG) consists of representatives from the five organisations (BMGF, Gavi, PATH, UNICEF and WHO), who worked collaboratively to identify the scope of innovations to be considered, conducted in-depth background research on each innovation, developed and executed the methodology for prioritising the innovations, consulted with relevant stakeholders, determined final outcomes (informed by recommendations from the Steering Committee), and communicated the progress along the way. The work would not have been possible without the strong commitments from each organisation and dedication of resources to create a sophisticated and coherent process for evaluation and decision-making.

Steering Committee

A VIPS Steering Committee (SC) was formed in June 2018 to offer independent and expert advice to the VIPS WG across multiple dimensions and provide recommendations regarding the prioritised innovations. The committee is comprised of 16 members with strong technical, programmatic and/or global health expertise. Members bring independent and broad-ranging perspectives on the issues pertinent to VIPS analyses, the innovations under consideration and prioritisation. Members are not expected to represent their affiliated institutions' positions and recused themselves from making recommendations if potential conflicts of interest were identified.

The SC members (see Appendix A) have expertise in the following domains:

- National immunisation programme financing and immunisation service delivery challenges, including supply chain and logistics, with a focus on understanding lower- and middle-income country (LMIC) needs
- Coverage and equity barriers and challenges
- Infectious disease epidemiology/vaccine-preventable disease control (especially with regard to increasing coverage rates and reducing morbidity and mortality)
- Health impact analysis/modelling
- Vaccine innovations, pipeline developments related to vaccine manufacturing and delivery technologies, and development of value propositions for new products.

As the VIPS SC operates on an existing foundation established by the WHO's Immunisation Practices Advisory Committee (IPAC) and the Product Development for Vaccines Advisory Committee (PDVAC) and to ensure alignment with existing initiatives, half of the SC members are also members from these two committees. Two SC subgroups were also formed and provided feedback on the evaluation methodology and country consultations.

Stakeholder Engagement

The VIPS evaluation process included broad stakeholder engagement to inform the prioritisation process, obtain input and alignment with other ongoing initiatives, and raise awareness.

Country stakeholders were consulted via surveys and in-person interviews to ensure that VIPS prioritised innovations could best address barriers to immunisation faced by countries.

Technology developers were asked to review and comment on documents about innovations relevant to their product pipeline and portfolio to verify the data presented.

Vaccine industry representatives were consulted to ensure the accuracy of the assumptions on technologies that impacted vaccine products through a series of meetings and interactions with the Delivery Technologies Working Group (DTWG) that is co-chaired by WHO and PATH. DTWG members include vaccine manufacturers from both the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the Developing Countries Vaccine Manufacturers Network (DCVMN). In addition, meetings were held with IFPMA and DCVMN representatives to provide regular updates on the VIPS process.

Regulators and regulatory consultants were engaged to obtain feedback on and validation of assumptions related to the regulatory pathway for each innovation and the clinical development pathway where relevant.

International agencies and other interested parties were kept informed about VIPS throughout the prioritisation process via presentations and regular updates including to the WHO Strategic Advisory Group of Experts on Immunization, IPAC, and PDVAC as well as to the Coalition for Epidemic Preparedness Innovations and other stakeholders.

Further details on these consultations can be found in the Phase I and Phase II descriptions below.

OVERVIEW OF THE VIPS PROCESS

Description of Phases and Timeline

The VIPS prioritisation process is summarised in Figure 1 and consisted of:

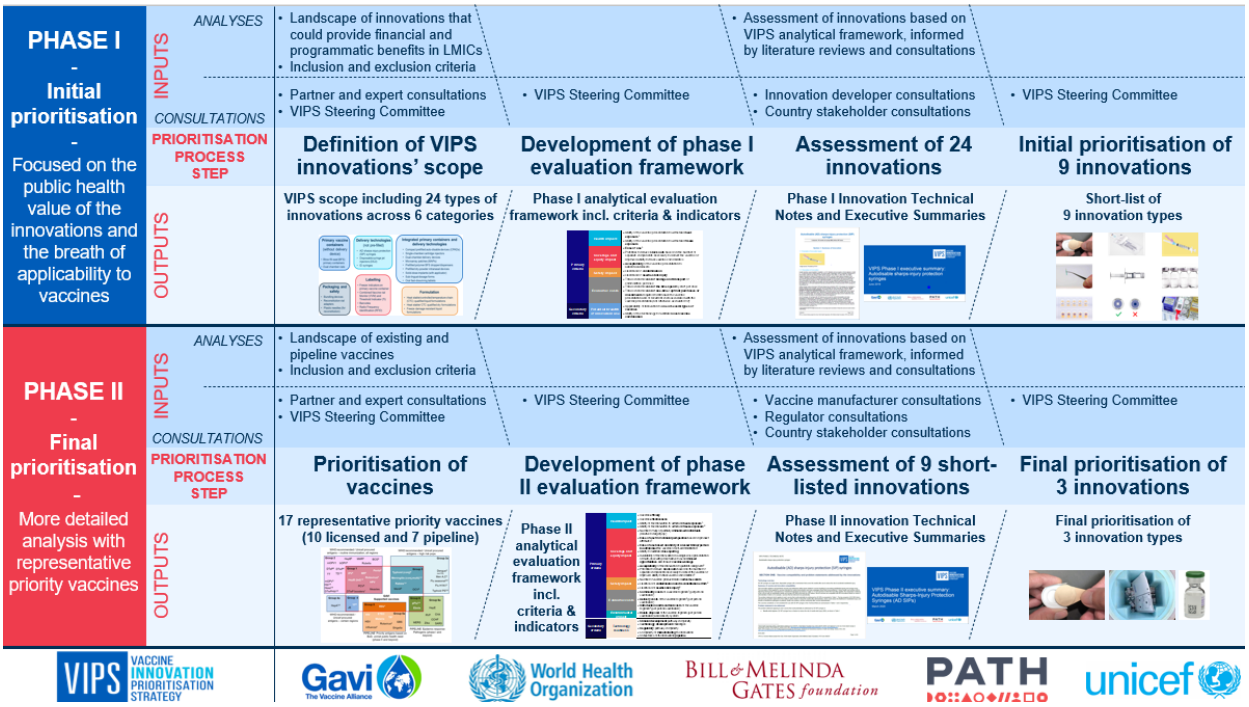
- **A preparatory phase** from January to November 2018 that focused on work planning and resourcing during which an innovation landscaping and an initial landscaping of vaccines was conducted, the scope of innovations was defined, and the SC's terms of reference and membership were finalised. The innovation landscaping exercise, informed by partner and expert consultations, as well as SC recommendations, enabled the identification of 24 innovations for consideration in phase I that fit within the scope of VIPS. These included existing and potential future vaccine product innovations that could provide measurable financial or programmatic benefits to LMICs. During the preparatory phase, the VIPS WG also

designed a country consultation approach to better understand country immunisation barriers that could be addressed by vaccine product innovations.

- **A phase I** from December 2018 to June 2019 during which the initial list of 24 innovations were evaluated based on their characteristics or design features and potential public health value, as well as their potential 'breadth of use' (applicability to several antigens) resulting in a short list of 9 innovations that progressed to phase II.

- **A phase II** from July 2019 to May 2020 during which the 9 shortlisted innovations were analysed in more detail and in the context of a set of priority vaccines to identify the final list of vaccine product innovations determined to have the highest potential to address immunisation issues and improve coverage and equity.

Figure 1: VIPS Prioritisation Process



Scope of Innovations

The scope of vaccine product innovations included in VIPS is defined as completely new products or adaptations to existing products that provide measurable financial or programmatic benefits to LMICs, such as increased coverage and equity (e.g., by overcoming a 'last mile' barrier) or vaccine effectiveness. The scope was informed by partner and expert consultations.

The 24 innovations that were defined as in-scope can be grouped into 6 categories:

- **Primary vaccine containers**: The immediate receptacles in direct contact with the vaccine as distributed for sale.
- **Delivery technologies (not prefilled)**: Stand-alone technologies used to administer a vaccine by a specific vaccine administration route.
- **Integrated primary containers and delivery technologies**: Prefilled devices that act both as the primary container and delivery device.
- **Packaging and safety**: The containers that enclose or protect vaccine products for distribution or items that facilitate safe administration but are not the actual delivery device.
- **Labelling on primary packaging**: Text, symbols, data or other visual cues provided on the primary packaging of a vaccine.
- **Formulations:** This category only included formulation improvements with the objective of improved thermostability.

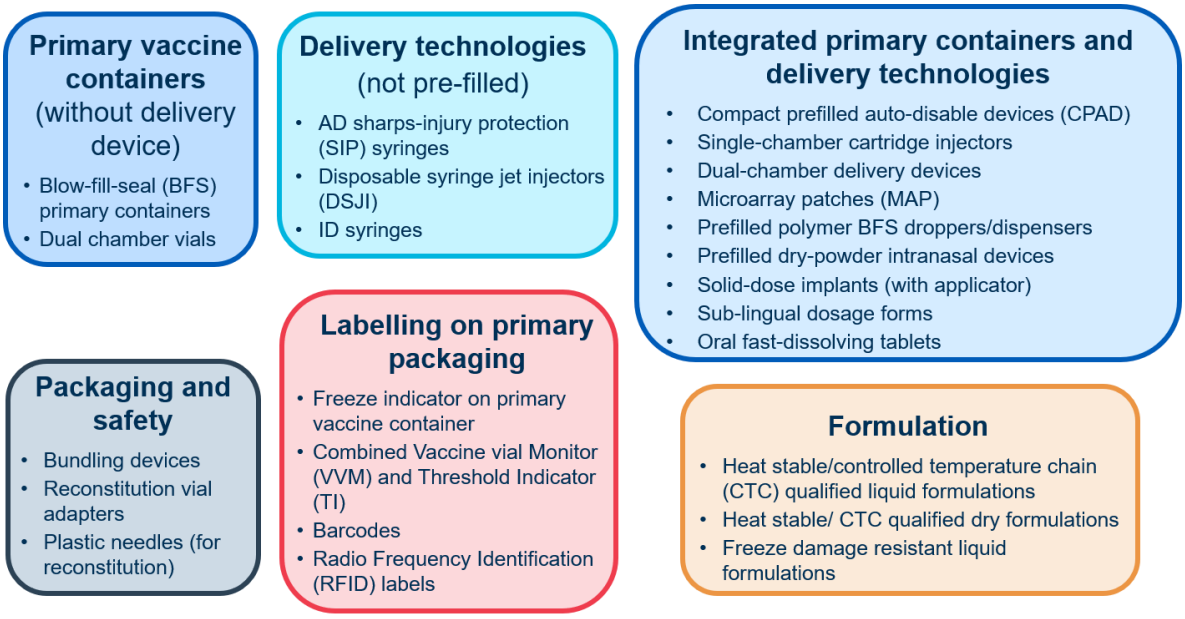
Innovations determined to be out of scope included supply chain innovations and cold chain equipment as these categories are covered by other mechanisms, global working groups, and market-shaping efforts including the Cold Chain Equipment Optimisation Platform. Innovations that relate to the type of antigen or vaccine (subunit, virus-vector, nucleic acid etc.) or immuno-enhancers were also determined to be out of scope as these are vaccine-specific and covered by PDVAC and the Gavi Vaccine Investment Strategy.

In addition, three exclusion criteria were defined and applied to focus the scope of innovations:

1. **Innovations were excluded, if WHO Programmatic Suitability for Vaccines Prequalification criteria for the innovation already exist but were not met by the innovation**. For example, prefilled syringes that are not compact or lack auto-disable features.
2. **Innovations that already have a mechanism for product development and will come to market without Alliance interventions were excluded**. For example, innovations that are already widely available including: prefilled syringes, intranasal spray nozzles, prefilled intranasal spray dispensers, and prefilled, preformed containers for oral/intranasal vaccines.
3. **Innovations for which development has been discontinued were excluded** including dry-powder jet injectors.

Figure 2 lists the initial 24 innovation categories that were evaluated in phase I of VIPS.

Figure 2: Innovations Assessed in Phase I



PHASE I

Overview of the VIPS Phase I Evaluation Framework

A VIPS evaluation framework was developed by the VIPS WG with oversight and guidance from the VIPS SC. The framework was meant to:

- Objectively and transparently assess and compare the added value of different types of innovations taking into consideration financial and non-financial trade-offs for countries to the extent possible,
- Allow for an aligned prioritisation across different stakeholders, and
- Achieve a balance between granularity and rigor on one hand, and simplicity on the other.

The evaluation framework included primary and secondary criteria as shown in Figure 3.

Figure 3: VIPS Assessment Criteria Definitions

Primary criteria	**Health impact**	Beneficial impact of a vaccine product innovation on health of the population receiving the vaccine.
	Coverage and equity impact[2]	Beneficial impact of a vaccine product innovation regarding increased access and utilisation of the vaccine for all populations.
	Safety impact	Potential impact of a vaccine product innovation on the safety of the population administering or receiving the vaccine.
	Economic costs	Potential impact of the vaccine product innovation on costs such as price of the vaccine and delivery technologies, cold chain, transport and health worker time costs, and introduction and recurrent costs.
	Environmental impact	Potential impact of vaccine product innovation on waste treatment management used in resource-limited settings (incineration/disinfection).
Secondary criteria	**Potential breadth of innovation use**	Potential breadth of an innovation's applicability to vaccines based on technical feasibility.
	Technology readiness	Readiness and complexity of a vaccine product innovation from clinical, technological, regulatory & manufacturing perspectives.
	Commercial feasibility	Commercial feasibility of an innovation in terms of market size, interests and barriers.

Indicators were then created for each of the criteria categories as described in Figure 4.

[2] Although coverage and equity measures are typically a subset of the health impact criteria, given the importance of improved coverage and equity as one of the ultimate objectives of VIPS, it was decided to have Coverage and Equity as a separate criterion.

Figure 4: VIPS Phase I Criteria Indicators

Primary criteria	**Health impact**	• Ability of the vaccine presentation to withstand **heat exposure**[3] • Ability of the vaccine presentation to withstand **freeze exposure**
	Coverage and equity impact	• **Ease of use**[4] • Potential to reduce **stock outs** based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • **Acceptability** of the vaccine presentation to patients/caregivers
	Safety impact	• Likelihood of **contamination** • Likelihood of **needle-stick injury**
	Economic costs	• Total economic **cost of storage and transport** of commodities per dose • Total economic **cost of the time spent** by staff per dose • Total economic **cost of one-time / upfront purchases or investments** required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)
Secondary criteria	**Potential breadth of innovation use**	• Applicability of innovation to **one or several types of vaccines** • Ability of the technology to facilitate **novel vaccine combination**

Parameters were then defined to qualitatively measure each innovation against each indicator. Due to the diversity of innovations being evaluated under VIPS, direct comparisons across innovations were difficult (e.g., comparing compact prefilled auto-disable devices to barcodes). To overcome this issue, each innovation was assessed for each primary criteria parameter using a comparator. The comparator represented the best or standard practice that most closely matched the innovation in terms of features, attributes, and use. When the comparator included existing vial presentations of liquid or lyophilised vaccines, single dose vials, rather than multi-dose vials were used for the comparator, because in most cases the innovation being considered was a single-dose presentation. Using single-dose vials made the incremental gains/losses easier to compare. *For example, the comparator for the dual chamber delivery device includes all the*

[3] Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.

[4] Ease of use can prevent missed opportunities resulting from the complexity of preparation and administration procedures, hence no indicator on missed opportunities from that perspective is included in the framework. Ease of use also affects timeliness of vaccination (vaccine doses given within the recommended age range); however, it was decided that timeliness of vaccination should be captured under vaccine effectiveness based on country data.

components required to reconstitute and deliver a lyophilised vaccine, i.e., a single dose vial of lyophilised vaccine, diluent vial, reconstitution syringe, and auto-disable syringe. In this manner, each assessment against each parameter resulted in a score, using a magnitude of impact where possible, that rated the innovation in comparison to best or standard practice. The scoring methodology, although qualitative, ultimately allowed the innovations to be compared and ranked. The secondary criteria parameters were also assessed qualitatively; however, they were not assessed against a comparator but in an absolute manner. Secondary criteria were used to provide additional contextual information for each innovation.

In some cases, sub-categories of innovations needed to be assessed when the product attributes of one sub-category resulted in a different scoring outcome than the product attributes of another sub-category. *For example, four types of compact prefilled auto-disable devices (CPADs) were evaluated: preformed, Blow-Fill-Seal (BFS) pre-assembled, BFS user-assembled, and other types.* Assessments were made at the level of the technology category (or sub-category), not at the level of individual products.

Evaluation of the 24 Innovations in Phase I

Country Consultation to Inform the Phase I Evaluation

Country stakeholder inputs were critical in guiding the VIPS phase I evaluation. An online survey[5] was therefore launched, requesting inputs from country representatives on immunisation implementation barriers and vaccine product attributes countries value the most. The survey was fully completed by 500 country representatives across a total of 61 Gavi-supported and non-Gavi-supported countries, including immunisation programme managers, procurement staff, logistics/supply chain staff, data managers, senior policy makers, healthcare service providers, implementing partners, UNICEF and WHO country/regional office staff, and in-country research/university partners.

Survey respondents were asked to select their top 5 priority implementation barriers to immunisation that could be addressed by vaccine product innovations, and top 5 most valuable vaccine product attributes, across three different use-settings: routine facility-based immunisation, routine community-based immunisation and campaigns. Based on the analysis of the results, the VIPS WG assigned qualitative levels of importance to the phase I indicators of the evaluation framework that were taken into account during the prioritisation process.

Technical Notes and Executive Summaries

Each innovation was assessed using the phase I evaluation framework and the assessments were consolidated into documents called **phase I Technical Notes**. These detailed notes not only consolidate the evidence (or expert opinions) behind the scoring on each parameter but also provide background and other relevant information on the innovations.

[5] Survey results are reflected in the Executive Summaries of each innovation and a detailed publication on all VIPS country consultations will be published in Q3 2020.

Literature reviews were conducted on each innovation category using publicly available sources and databases (such as PubMed, manufacturer websites, clinical trial databases) and additional information was gathered from Alliance partners and international experts. Where needed, manufacturers and technology developers were queried with targeted questions to fill data gaps. In all cases, data sources were referenced, and only non-confidential data were used that could be transparently shared.

The phase I assessments, documented in the Technical Notes, were drafted by technical experts from the VIPS WG and consultants with background in the innovation being assessed.

Regular consultations and rigorous review of the Technical Notes by VIPS WG members and independent technical experts helped to ensure alignment and consistency in application of the scoring methodology across the 24 innovations. In addition, the content of each Technical Note without the scoring was reviewed by up to 3 relevant technology developers or manufacturers to ensure accuracy of the information upon which the scoring was based. Once all Technical Notes were developed, a final consistency check was conducted for all indicators across the innovations to ensure they were assessed in a consistent manner.

Key findings from the phase I Technical Notes were summarised in **phase I Executive Summaries** for each innovation.

All Technical Notes and Executive Summaries for the 24 innovations assessed in Phase I can be found on the following link: https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy.

At the end of phase I, the VIPS WG held a series of meetings to analyse the findings of the phase I assessment and develop initial recommendations to present to the SC. These initial recommendations are reflected in the phase I Executive Summaries.

Selection of Innovations Shortlisted for Phase II

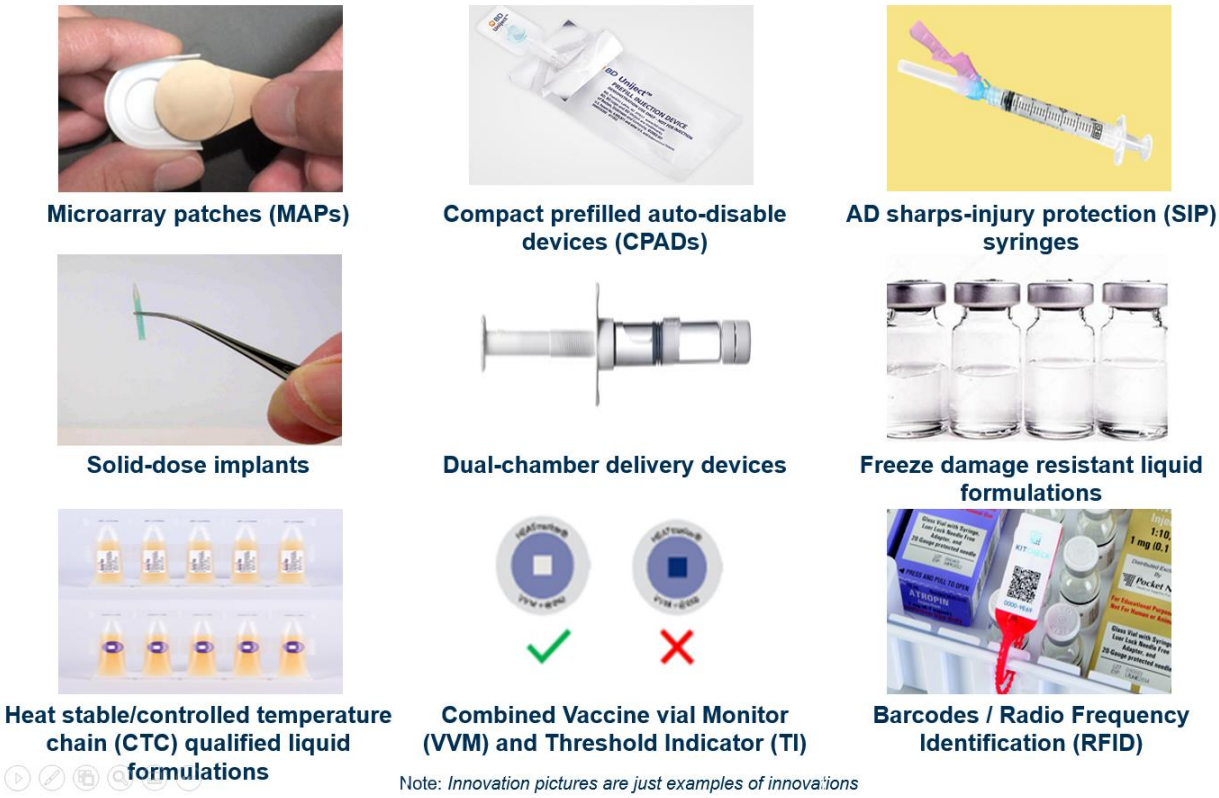
A two-day VIPS SC meeting was held in June 2019 during which the results of the phase I evaluation were discussed, and recommendations were made for innovations to be further assessed in phase II. The process was informed by several steps of analysis and discussions:

1. Assessing the potential public health benefits of each innovation using the primary criteria and indicator scores, while paying attention to the indicators that were given more importance by countries, and prioritising innovations with the highest or broadest potential public health benefits.
2. Applying the insights from secondary criteria, especially the breadth of antigen applicability based on technical feasibility.
3. Analysing the relative benefits across innovations, i.e., comparing innovations with similar benefits and prioritising those with the broadest benefits or applicability.

4. Leveraging additional insights and expert knowledge from the group that may influence the prioritisation.

The SC then recommended proceeding to phase II with 9 innovations (see Figure 5) and these were endorsed by the WG.

Figure 5: 9 Innovations Shortlisted for Further Analysis in Phase II



Note: *Innovation pictures are just examples of innovations*

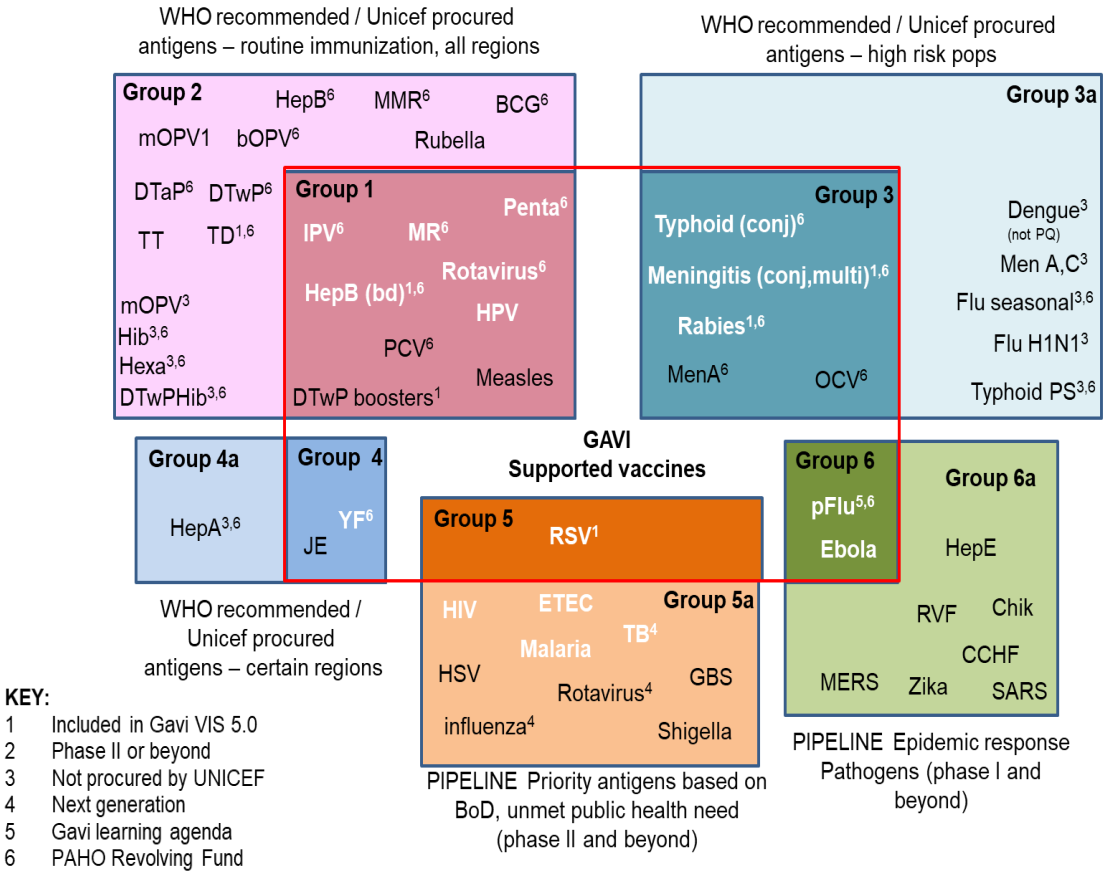
PHASE II

Overview of the Phase II Evaluation Framework

In the second phase of VIPS, the 9 shortlisted innovations were further assessed in the context of specific vaccines they could be applied to and the vaccine-specific implementation challenges and issues they could potentially address in combination with those vaccines. As it was not possible to analyse the innovations in combination with the full vaccine landscape, a list of 10 licensed vaccines and 7 pipeline candidates were identified as 'priority vaccines' to be analysed in phase II to provide a representative picture of the broader vaccine universe based on vaccine type, formulation and presentation. These 17 vaccines are shown in white text in Figure 6. Note

that Ebola vaccine was subsequently licensed in November 2019. However, the VIPS analysis continued to refer to it as a pipeline vaccine as this was its status for the majority of the process.

Figure 6: Prioritised 17 Representative Vaccines and Categorisation



These vaccines were selected by the VIPS WG based on a thorough four-stage process that included applying specific inclusion and exclusion criteria: (1) landscaping to define a preliminary long list of all licensed vaccines, (2) categorisation of vaccines by characteristics, (3) application of primary inclusion criteria as proposed by the VIPS SC, and (4) application of secondary inclusion and exclusion criteria based on additional analysis and considerations. A landscape of pipeline vaccines was also assessed based on the WHO PDVAC and R&D Blueprint priority pathogens.

As in phase I, phase II assessed a diversity of innovation types, making direct comparisons across innovations very difficult. To overcome this issue, each vaccine-innovation combination was assessed against a comparator presentation to allow a direct comparison for each indicator. For

phase II, the comparator presentation chosen for each vaccine included the single dose vial presentation, but also included comparison to the multi-dose vial presentation in cases where it is the most-commonly procured presentation by LMICs. This enabled an assessment of the innovations against both 'best practices' but also 'current practices'.

The phase I analytical framework was further expanded for the phase II assessment (see Figure 7) given that the phase II assessment was conducted for each vaccine-innovation combination which allowed for greater specificity and deeper analysis. An additional primary criterion was added on environmental impact aimed at assessing the potential impact of vaccine product innovations on waste management. Two new secondary criteria were also added: technology readiness and commercial feasibility. The technology readiness criterion assessed the innovation's development status (i.e., clinical development status and regulatory, technological and manufacturing complexity), while the commercial feasibility criterion assessed the commercial opportunity for the innovation (i.e., potential market, country stakeholder interest, existence of partnerships). As in phase I, secondary criteria were not assessed against a comparator but in an absolute manner and were used to provide additional contextual information for each innovation.

Figure 7: VIPS Phase II Criteria Indicators

Primary criteria	**Health impact**	• Vaccine **efficacy** • Vaccine **effectiveness** • Ability of the innovation to withstand **heat exposure**[6] • Ability of the innovation to withstand **freeze exposure**[6]
	Coverage and equity impact	• Number of fully or partially **immunised individuals** (relative to target pop) • **Ease of use from a clinical perspective** based on product attributes[7] • **Ease of use based on the ability of a lesser trainer person to administer** the vaccine or self-administration[7] • Ability to facilitate **dose sparing** • Availability of the innovation in a single-dose presentation or multi-dose with preservative to avoid **missed opportunities** and reduce **vaccine wastage** • **Acceptability** of the innovation to patients/caregivers[6] • Potential to reduce **stock outs** based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities[6]

[6] Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing
[7] This indicator is re-assessed in Phase II only when the comparator for a specific vaccine is a multi-dose vial, requiring a new evaluation – The comparator single-dose vial is assessed in Phase I

	Safety impact	• Number of vaccine product-related **adverse events** • Likelihood of **contamination and reconstitution errors**[6] • Likelihood of **needle stick injury**[6]
	Economic costs	• **Commodity costs** of a vaccine regimen[8] (per person vaccinated) • **Delivery costs** of the vaccine regimen[8] (per person vaccinated) • **Introduction and recurrent costs** of the vaccine regimen[8] (per person vaccinated)
	Environmental impact	• **Waste disposal** of the vaccine regimen (per person vaccinated) and delivery system
Secondary criteria	**Technology readiness**	• **Clinical development** pathway complexity • **Technology development** challenges • **Regulatory** pathway complexity • Complexity of **manufacturing** the innovation • Robustness of the innovation **pipeline**
	Commercial feasibility	• Potential breadth of **market size** • Existence of **partnerships** to support development and commercialisation • Known **barriers to global access** to the innovation • **Stakeholders' interest**

As in phase I, specific parameters were developed to enable scoring for each indicator and the scoring methodology used a magnitude of impact where possible. The difference in phase II was that each vaccine-innovation combination was assessed for each parameter against the relevant comparator.

Evaluation of the 9 Innovations in Phase II

Country Consultations

In phase II, two country consultations, an online survey and in-depth interviews, were conducted to support the final prioritisation of the VIPS 9 shortlisted innovations and to complement the first online survey conducted in phase I.

Phase II online survey:

An online survey[9] was conducted to identify and evaluate vaccine-specific immunisation challenges that could be addressed by VIPS innovations and to collect additional information on

[8] Vaccine regimen cost refers to the vaccine product and innovation cost times number of doses for complete immunisation

[9] Results are reflected in the Executive Summaries of each innovation and a detailed publication on all VIPS country consultations will be published in Q3 2020.

the use of electronic recordkeeping systems for vaccine inventories or patient vaccination records to support the barcode analysis. The survey was targeted to experts in vaccination strategies and existing vaccine products in both Gavi-supported and non-Gavi supported-countries as well as global experts. Participants were provided with a standard list of challenges developed by global experts for the 10 licensed vaccines analysed through VIPS and were asked to select the top three challenges for all vaccines they had knowledge about. 209 participants responded to the survey across a total of 54 Gavi-supported and non-Gavi-supported countries.

The top five challenges for each vaccine based on the frequency of selection (the number of times a challenge was selected as a top three challenge by respondents from a list of 11 challenges) were reported in the assessments as 'vaccine problem statements'. These vaccine problem statements were mapped to the VIPS phase II evaluation indicators and for all vaccine-innovation combinations the assessments of indicators that relate to the problem statements were highlighted. For the pipeline vaccines, problem statements were defined by the VIPS WG based on current knowledge of the vaccine presentation and/or expected use case and delivery setting.

As detailed in the phase II Technical Notes and Executive Summaries, the online survey helped to clarify and highlight each innovation's ability to address the most important problem statements identified by countries for each vaccine. It also brought visibility to problem statements that apply to multiple vaccines in the VIPS analysis**.**

Phase II in-depth interviews:

In-depth face-to-face interviews[9] were also conducted to collect feedback on the 9 shortlisted VIPS innovations from country decision makers, i.e., stakeholders with decision-making authority or influence over vaccine purchase decisions (national and regional levels), and immunisation staff (health care workers, district and frontline staff, and logistics staff). 84 respondents were interviewed across 6 countries: Ethiopia, Mozambique, Nepal, Nigeria, Senegal and Uganda.

Interviewees were first briefed about each innovation (with no information provided on benefits and challenges), and then, per innovation, were asked open-ended questions about foreseen benefits and challenges and specific vaccines for which each innovation could be particularly useful. Lastly, they were asked to select the top three innovations that have the greatest potential to address their immunisation programme challenges.

The in-depth interviews provided perspective from country stakeholders on the perceived relevance of VIPS innovations for their immunisation programmes. In particular, the results helped in understanding which innovations could help address current challenges faced by immunisation programmes (innovation's ranking), how each innovation could help (perceived benefits) and which challenges they may bring (perceived challenges). Country stakeholders also identified which vaccines they thought would benefit the most from each innovation (vaccines' ranking). The results were used to inform the assessment of the VIPS phase II secondary criteria on commercial feasibility in terms of country interest and feedback for each innovation.

Industry consultations

The VIPS WG also conducted a series of consultations with the WHO- and PATH-led Delivery Technologies Working Group (DTWG), consisting of a broader set of immunisation stakeholders including industry experts. The objective of these consultations was twofold: to update these stakeholders on VIPS and to collect feedback on the specific innovations. The key features of each innovation were presented, and detailed background information was shared. DTWG members were then asked to complete an on-line survey focused on the technology readiness and commercial feasibility of each innovation and this feedback was used to inform the assessment of these VIPS phase II secondary criteria.

Regulator consultations

As recommended by the VIPS SC, the VIPS WG also engaged in early consultations with several regulators and regulatory consultants to inform the secondary criteria on technology readiness. The input collected informed the assessment of the regulatory pathway complexity indicator. Two types of consultations were held:

- **Consultations with United States Food and Drug Administration (FDA), European Medicines Agency, African Vaccine Regulatory Forum, and Paul Ehrlich Institute officials:** VIPS technical experts gathered feedback/validation on assumptions related to endpoints/surrogate markers for vaccines and the complexity of clinical development used in evaluation of vaccine-innovation products.
- **Consultations with ex-FDA officials:** VIPS technical experts gathered feedback from ex-FDA consultants on VIPS assessments of technical development and manufacturing challenges on a vaccine innovation product basis from a regulatory perspective.

Technical Notes and Executive Summaries

As in phase I, phase II assessments were documented in detailed **phase II Technical Notes** which consolidated all the information collected relevant to the 9 shortlisted innovations. These documents include the assessment of vaccine-innovation combinations against the comparator presentations and provide consolidated evidence behind the scoring of indicators as well as additional relevant information not easily captured by scores.

To develop the Technical Notes, the VIPS WG conducted additional literature reviews where needed to identify relevant data to assess the indicators added to the evaluation framework in phase II. Technical Notes also include data collected from consultations with countries, industry, and regulatory agencies as described in detail above – that informed relevant criteria and associated indicator scoring.

As in phase I, the Technical Notes went through a rigorous review process where all VIPS technical experts conducted multiple reviews of the indicator assessments and scores to ensure consistency and manage subjectivity of scoring. Additionally, the essential information from the Technical Notes was summarised in **phase II Executive Summaries** that crystallise essential findings along the following dimensions:

- **Potential public health impact of the innovation**: Expected applicability of the innovation to the VIPS priority vaccines (licensed and pipeline), public health benefits (assessed along the VIPS primary criteria indicators), and vaccine problem statements addressed by the innovation (identified via the country survey data).
- **Barriers to realise the innovation's potential impact**: Cost considerations, technology readiness and commercial feasibility (assessed along the VIPS secondary criteria indicators) and countries' feedback on the innovation (based on in-depth interviews with countries).

All Technical Notes and Executive Summaries for the 9 short-listed innovations further analysed in Phase II can be found on the following link: https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy.

Selection of Innovations for Final Prioritisation

The VIPS WG again held a series of meetings and deliberations following the review of the final results, documented in the Technical Notes and Executive Summaries, of the phase II assessments of the 9 innovations. Proposed guiding principles were also developed for the SC including suggestions to consider:

- Prioritising innovations that may increase coverage and equity for priority vaccines that have an elimination or eradication agenda, i.e., measles-rubella, inactivated polio, and human papillomavirus vaccines.
- De-risking the portfolio of VIPS prioritised innovations by including both lower risk and higher risk innovations.
- The effort/complexity/feasibility and resources required to ensure access of the innovation to LMIC markets and the trade-offs in terms of expected public health impact.
- Highlighting specific synergistic pairings of innovations which may add incremental value.
- The impact/risks of not prioritising a specific innovation through VIPS.
- Seeking 'win-win' scenarios by prioritising innovations with potential to both increase equitable coverage for existing vaccines, particularly during post-COVID-19 catch-up immunisations, and be valuable for COVID-19 vaccine delivery. The WG was cognizant that the COVID-19 pandemic might create potential funding opportunities for innovations that are relevant for both COVID and other priority vaccines and could accelerate their product development and/or implementation.

At the VIPS SC meeting held in May 2020, the SC selected and recommended 3 innovations to be prioritised and these were endorsed by the WG.

VIPS OUTCOMES

Prioritised innovations

Three innovations were ultimately selected (listed below in order of priority) for which VIPS will engage in advancing their development and access:

1. Upstream novel delivery devices – **Microarray patches (MAPs):** MAPs are seen as truly 'transformational' innovations that have the potential to address many immunisation barriers identified by countries due to their improved thermostability; better ease of use; avoidance of reconstitution and the associated errors and risks; improved safety (as they are sharps-free); and the fact that they are single-dose presentations, thereby avoiding missed opportunities due to the reluctance to open a multi-dose vial. Additionally, MAPs are applicable to a number of use cases including routine, supplemental, house-to-house and outbreak immunisation. Therefore, the development of MAPs should be encouraged for use with several vaccines, including pipeline vaccines and those with elimination and eradication agendas. They are also innovations that may have a positive impact on 'life-course' immunisation for broader populations beyond children, including adolescents, adults and older adults. While MAPs are unlikely to be ready for implementation with the first COVID-19 vaccines developed in response to the current pandemic, they could be co-developed with vaccines to be positioned for future emergency response, or for use with COVID-19 vaccines in the longer term. However, it was noted that there are still significant technical, biological and commercial barriers to overcome before MAPs can be implemented, particularly for vaccines intended for use in low resource settings, which will require substantial funding. Additionally, it is not known whether the prices for vaccines on MAPs will be acceptable to end-users, despite the expectation that they may reduce costs at the delivery level and assist with overcoming immunisation barriers.

2. A combined formulation, regulatory, and programmatic approach to vaccine management – **Heat stable and Controlled Temperature Chain (CTC)[10] qualified vaccines.** Thermostability was identified as the top priority by countries consulted on barriers to immunisation and this innovation directly addresses equity concerns by virtue of improving access to harder to reach communities and alleviating cold chain constraints for health care workers. As such, the Alliance has prioritised heat stable and CTC-qualified vaccines, including both liquid and dry formulations. Enhanced thermostability is a desirable feature for all vaccines to improve vaccine effectiveness and, where possible and appropriate, to enable higher temperature storage and transport in a CTC. Vaccine candidates for CTC use, whether liquid or dry, should have the following attributes: adequate heat stability to achieve regulatory and WHO prequalification for CTC with the longest CTC duration possible (e.g., days, weeks or months), contexts of use that benefit from CTC, and formats that do not increase vaccine wastage or safety risks when used in a CTC. Dry formulations are of interest if coupled with

[10] CTC-qualified vaccines are approved by regulatory authorities and WHO for use up to a specified threshold temperature for a **minimum** of 3 days prior to administration.

technologies that offer additional benefits such as removing the issues associated with manual reconstitution – as would be the case with dual delivery chamber devices, solid dose implants or MAPs. This innovation category is also synergistic with VVM-TIs to facilitate temperature monitoring. VVM-TIs could be further evaluated as part of a future scope. This innovation may be a relatively 'quick win' for existing thermostable vaccines and emerging pipeline vaccines. However, thermostability represents a higher hurdle for existing vaccines that require reformulation; in such instances greater heat stability and/or CTC could be pursued if vaccines undergo reformulation for another reason.

3. A programme implementation and system technology – **Barcodes on primary packaging:** Track and trace is considered a priority for vaccines on secondary packaging by Gavi and UNICEF and 2D barcodes on primary packaging would allow for greater accuracy in tracking vaccine products, especially when they are removed from their secondary packaging at lower levels of distribution. It would also support the eventual transition to electronic record keeping, in line with the objectives of advancing digital health in Primary Health Care. Barcodes on primary packaging are seen as highly valuable in terms of tracking inventory and immunisation coverage, and follow-up of AEFIs, and this is particularly true for deployment of novel vaccines. While this is a mature technology in general, an analysis of the implications of barcodes on primary packaging and a 'push' for implementation based on the analysis of the implications could build upon the existing efforts to place barcodes on vaccine secondary packaging and spur wider implementation of systematic monitoring and surveillance systems. The COVID-19 pandemic may provide an opportunity to leverage investment to catalyse manufacturing of vaccines with barcodes and it was felt that VIPS may be the right avenue to help advocate and support the advancement of this technology. Implementation of barcodes for COVID-19 vaccines is likely not feasible for the current pandemic and the first vaccine deployments, but they may be for later phases of vaccine deployment; and while it will take time to ensure country readiness, a few countries with advanced electronic recordkeeping could benefit from their availability on secondary packaging almost immediately and on primary packaging in the coming years. There is a clear recognition that barcodes themselves are not an innovation but part of a broader innovation ecosystem that will need coordination and integration within the realms of vaccine standards, manufacturing, regulatory, procurement, distribution, and in-country recordkeeping. It was noted that in order to capture the full benefits from barcodes on primary packaging, electronic inventory and health records transitioning will be required in LMICs which could be a challenging and lengthy process in many countries.

Shortlisted innovations

While VIPS has the capacity to focus on only a few innovations in the coming years, the 6 short-listed innovations that were not prioritised have strengths and merit and remain of high interest to VIPS. The intention is to continue to monitor their status for future consideration. These are (in alphabetic order):

Auto-disable sharps injury protection syringes (AD-SIPs): These devices are broadly available and improve safety by reducing the likelihood of needlestick injury and transfer of bloodborne pathogens to patients, health workers and the community after vaccine administration. VIPS supports WHO's intention to require use of syringes with SIP features in the expanded programme of immunisation in the near future.

Combined vaccine vial monitor and threshold indicators (VVM-TIs): VVM-TIs are particularly useful for vaccines used in a controlled temperature chain (CTC). The technology offers increased ease of use, fewer components, and saving of staff time in comparison to current use of VVMs with separate TIs to monitor higher temperature exposure of vaccines used in a CTC. Their adoption is likely to be determined by the size of the incremental price premium.

Compact prefilled auto-disable devices (CPADs): CPADs have many potential public health benefits, broad applicability to liquid parenteral vaccines, and proven utility in facilitating vaccine outreach. They have the benefits of greater ease of use, single-dose presentations, and can be synergistic with CTC if filled with appropriately licensed vaccines. Previous concerns regarding high cost may be overcome by new manufacturing techniques, including blow-fill-seal (BFS). The current efforts of the US government to advance and scale up BFS compact prefilled devices (although without AD features that would be required in LMICs) may help to advance this technology platform. Overall, CPADs warrant close monitoring given the potential value of this innovation.

Dual chamber delivery devices: Dual chamber delivery devices offer some of the same safety benefits as MAPs since they are appropriate for vaccines that must be formulated dry. They ease the process of reconstitution and dosing, largely eliminate reconstitution errors, and for some formulations may enable vaccines to be heat-stable until immediately prior to administration. They can also be used with vaccines that have liquid components that require mixing. Most dual chamber device formats are early in development and face significant technical and manufacturing challenges. This innovation was not selected in this VIPS cycle primarily given the need to limit the number of innovations that are early in development. Future adoption is also likely to be determined by the eventual cost of these devices.

Freeze damage resistant liquid formulations: Exposure of freeze-sensitive vaccines (particularly those with aluminium-salt-based adjuvants) to freezing temperatures during storage and distribution continues to be an important issue for countries and this was verified in the VIPS country consultations. The addition of low-cost excipients to these vaccines can prevent freeze-damage. There are some technical and clinical development hurdles yet to be overcome, as well as potentially significant acceptability issues associated with adding an excipient. As with heat stability improvements, reformulating existing vaccines was flagged as a challenge and pipeline vaccines could represent a better opportunity. In addition, VIPS recognised that alternative measures exist to address the freeze exposure problem, including improved cold chain equipment and temperature monitoring as well as vaccine management training. The prioritisation of heat stable and CTC qualified vaccines also may address some challenges related to freeze sensitivity by enabling end users to reduce a vaccine's exposure to the cold chain.

Solid dose implants: These devices have the potential to address many of the same barriers to immunisation as MAPs and dual chamber delivery devices, and might not be associated with the same degree of local reactogenicity as MAPs (though data are needed on this point). However, they have other drawbacks such as the need for a separate applicator and are earlier in development than MAPs. They were also viewed as less favourable in the VIPS country consultations than other innovations – including MAPs and dual chamber delivery devices – which also deliver dry vaccines. Solid dose implants could represent an alternative to MAPs and dual chamber delivery devices and manufacturers are encouraged to continue to generate new data, especially on country/user acceptability.

Conclusion and next steps

The VIPS partners (BMGF, GAVI, PATH, UNICEF, WHO) will now focus on defining end-to-end strategies including clear action plans to accelerate the advancement of the 3 prioritised innovations. This work will be informed by targeted consultations with technology developers and manufacturers to address key roadblocks and gaps to innovation development and uptake and will build on the ongoing efforts by VIPS partners and other stakeholders. Additionally, VIPS Alliance partners will work to create an enabling environment for vaccine innovation in terms of policy, procurement and programme implementation, and continuous learning/evaluation in alignment with Gavi's 2021 to 2025 strategy.

APPENDIX A: VIPS STEERING COMMITTEE MEMBERS

Member	Affiliation	Title
Alejandro Cravioto	Facultad de Medicina Universidad Nacional Autónoma de México	Professor; SAGE Chair
David Robinson	Bill and Melinda Gates Foundation	Deputy Director of Vaccine Development and Surveillance, Chemistry Manufacturing and Controls
Christopher Morgan	Jhpiego (from June 2020) *and* Burnet Institute	Senior Technical Advisor (Immunization) *and* Honorary Senior Principal Research Fellow
David Kaslow	PATH	Vice president, Essential Medicines
Jean-Pierre Amorij	UNICEF Supply Division	Vaccine Technology Specialist
Jerome Kim	International Vaccine Institute	Director General
Jon Abramson	Wake Forest School of Medicine	Professor of Paediatric Infectious Diseases
Kelly Moore	Vanderbilt University School of Medicine	Adjunct Associate Professor of Health Policy
Mark Jit	London School of Hygiene and Tropical Medicine	Professor, Vaccine Epidemiology
Mark Papania	Global Immunization Division, Centers for Disease Control	Medical Epidemiologist
Michael Free	Independent	Independent Consultant; Senior Advisor Emeritus, PATH
Nora Dellepiane	QRB Consultants Sàrl	Independent consultant
Ramanan Laxminarayan	Center for Disease Dynamics, Economics and Policy	Director
Ruth Karron	John Hopkins University	Professor, International Health
Samir Sodha	WHO	Routine Immunisation Officer
Shelley Deeks	Public Health Ontario	Chief, Health Protection Officer

Member of the Immunization Practices Advisory Committee (IPAC) – WHO

Member of the Product Development for Vaccines Advisory Committee (IPAC) - WHO