VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Phase II executive summary: Combined Vaccine Vial Monitor (VVM) and Threshold Indicator (TI)

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Gavi The Vaccine Alliance

World Health Organization

BILL & MELINDA GATES foundation

PATH

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Combined Vaccine Vial Monitor (VVM) and Threshold Indicator (TI)

About Combined VVM-TIs

- **Currently, VVMs and TIs are not integrated. VVMs are placed on primary containers and standalone TIs are used in addition to VVMs when vaccines are kept in a controlled temperature chain (CTC).** These TIs must be purchased and initially distributed separately from the vaccine and kept at temperatures below their threshold. They are placed in vaccine carriers and cold boxes (without icepacks) during CTC storage and transport.
- Although a **VVM alone changes colour in response to cumulative heat exposure, its response is not rapid enough at higher temperatures (e.g. above 37°C or 40°C),** whereas the TI reacts rapidly if exposed at or above a defined threshold temperature.
- A combined VVM-TI on primary containers undergoes gradual colour change up to a specified peak threshold temperature and rapidly reacts if exposed at or above the threshold temperature.
- There are two potential types of VVM-TIs:
  - **VVM and TI together:** both indicators are placed on the same label and require a review of VVM and TI separately. There are no examples of the technology in this format.
  - **TI is integrated into the VVM:** combined features of both VVM and TI in one indicator, which looks and is interpreted identically to the existing VVMs. This type is commercially available.

Reading of integrated VVM-TI

Stage of development

- **WHO prequalification (PQ) specification and verification protocols** have been **developed and published.**
- One **VVM-TI has received WHO prequalification (PQ)**, however this product does not have the appropriate specifications for currently qualified CTC vaccines.
- Other integrated VVM-TIs have been developed but will need to pass WHO PQ approvals as standalone products. Vaccine manufacturers adding VVM-TIs to their vaccine products will need to seek national regulatory and WHO PQ approvals for the label change.

Summary of key insights (1/2)

Potential public health impact of innovation

Applicability to vaccines

- It would be **technically feasible to add VVM-TIs to all vaccines** as they are **more accurate heat exposure indicators** than the existing VVMs, however they are **most appropriate for use with vaccines used in a controlled temperature chain (CTC)** that are intentionally exposed to ambient temperatures for a limited time period.

Public health benefits

- **In comparison to use of VVMs and separate TIs for CTC vaccines, VVM-TIs:**
  - **Ease logistics** by reducing the need to procure, distribute, and use/interpret separate TIs; thereby **removing a barrier to CTC use of vaccines;**
  - **Reduce the potential for TI stockouts and the environmental impact of disposal of TIs** since TIs are no longer needed.

Vaccine problem statements

- VVM-TIs **do not address vaccine-specific problems** as their main benefit is to facilitate CTC use of vaccines.

Summary of key insights (2/2)

Barriers to realise the innovation's potential impact

Costs

- The **cost of a VVM-TI will be up to 75% more** than use of a VVM with a separate TI; **especially for vaccines in single-dose containers** where one dose bears the full cost of the VVM-TI and wastage is extremely low. This cost will not be offset by the expected savings from having to purchase, distribute, monitor, use, and provide training on separate TIs for CTC vaccines.

Technology Readiness

- VVM-TIs face **minimal technical development and manufacturing challenges** as: suitable VVM-TIs could be WHO prequalified and available to vaccine manufacturers in a relatively short time frame (e.g., less than one year) and vaccine manufacturers can label vaccines with VVM-TIs using existing VVM labeling equipment.
- However, there is only **a single VVM-TI supplier**.

Commercial feasibility

- **No known market demand** as countries aren't familiar with the innovation.
- The **market potential** is **likely to be limited to CTC-qualified vaccines** given the **cost premium.**
- **One vaccine manufacturer** plans to place a VVM-TI on **their rotavirus vaccine** (but not for CTC use).

Countries interest

- In the VIPS country consultations, **VVM-TIs were rated 7th** overall together with barcodes out of the 9 innovations in terms of ability to address immunisation programme challenges.

VVM -TIs are applicable to all vaccines, but are most suitable for vaccines qualified for controlled temperature chain (CTC) use

Applicability to vaccines

Vaccines **technically compatible** with barcodes and analysed in Phase II

VIPS Phase II analysed vaccines	
Licensed vaccines	**Penta (or DTP containing)**
	Hepatitis B (birth dose)*
	HPV*
	MR (or MCV)*
	N. Men A (or N. Men A,C,W,Y,X)*
	Polio, IPV
	Rabies*
	Rota (Oral)
	Typhoid, conjugate (TCV)*
	Yellow fever (YF)*
Pipeline vaccines	**Ebola (rVSV-ZEBOV)[1*]**
	ETEC (ETVAX)
	HIV (ALVAC-HIV + bivalent Subtype C gp120)[2]
	Influenza (pandemic,VAL-506440)*
	Malaria (RTS,S)*
	MTb (next gen.,VPM1002)*
	RSV (Pre-F)*

VVM-Tis are technically compatible with all vaccines including the 17 vaccines in scope of Phase II but are most useful for vaccines intended for CTC use.

- **Antigen applicability: technically feasible to apply VVM-TIs as a substitute for existing VVMs on all vaccines,** including those reviewed in the VIPS Phase II analysis.
- **Primarily useful for vaccines intended for CTC use** as these are **intentionally exposed to ambient temperatures** for a limited time period in order to facilitate vaccine outreach.
  - Currently available **CTC vaccines include MenA, HPV and oral cholera.**
  - Other priority vaccines for CTC qualification include **hepatitis B (birth dose), MR, rabies, typhoid, YF, Ebola, HIV, influenza, malaria,** and **MTb.**
- **Comparator:** VVM with stand-alone TI

* Currently available CTC vaccines and priority vaccines for CTC qualification

[1] At the time of the assessment, Ebola vaccine was not yet licensed and has been analysed as a pipeline vaccine. [2] HIV vaccine consists of two different components: a virus vector for priming doses and a subunit protein plus adjuvant. The prime and boost were therefore assessed separately.

Overview of VVM-TI public health benefits based on Phase II analysis

Vaccine with an elimination agenda

Current CTC or priority for CTC qual. vaccines

Public health benefits

VIPS Criteria	Indicators	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	YF	Ebola	ETEC	HIV[4]	Influ-enza[5]	Malaria	M. Tb[6]	RSV[7]
Primary criteria																		
Health impact	Vaccine efficacy	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Vaccine effectiveness	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	Ability of the vaccine presentation to withstand heat exposure	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Ability of the vaccine presentation to withstand freeze exposure	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Coverage & Equity impact	Number of fully or partially immunised (relative to target population)	Neutral	No data	No data	No data	No data	Neutral	No data	Neutral	No data	No data	No data	Neutral	No data	No data	No data	No data	Neutral
	Ease of use: clinical perspective based on product attributes	Neutral	Better	Better	Better	Better	Neutral	Better	Neutral	Better	Better	Better	Neutral	Better	Better	Better	Better	Neutral
	Ease of use: ability of a lesser trainer personnel to admin. / self-admin.	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Ability to facilitate dose sparing	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Avoid missed opportunities and reduce vaccine wastage	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Acceptability of the vaccine presentation and schedule[1]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Potential to reduce stock outs[2]	Neutral	Better	Better	Better	Better	Neutral	Better	Neutral	Better	Better	Better	Neutral	Better	Better	Better	Better	Neutral
Safety Impact	Number of vaccine product-related AEFIs	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Likelihood of contamination and reconstitution errors	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Likelihood of needle stick injury	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Economic costs	Commodity costs of the vaccine regimen[3]	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse	Worse
	Delivery costs of the vaccine regimen[3]	Neutral	Better	Better	Better	Better	Neutral	Better	Neutral	Better	Better	Better	Neutral	Better	Better	Better	Better	Neutral
	Introduction & recurrent costs of the vaccine regimen[3]	Neutral	Better	Better	Better	Better	Neutral	Better	Neutral	Better	Better	Better	Neutral	Better	Better	Better	Better	Neutral
Environmental impact	Waste disposal of the vaccine regimen[3] and delivery system	Neutral	Better	Better	Better	Better	Neutral	Better	Neutral	Better	Better	Better	Neutral	Better	Better	Better	Better	Neutral

[1] To patients/caregivers; [2] Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities; [3] per person vaccinated; [4] ALVAC-HIV + bivalent Subtype C gp120; [5] VAL-506440; [6] VPM 1002; [7] Pre-fusion F protein

Phase II confirms that VVM-TIs offer targeted public health benefits, especially for vaccines used in a CTC

Public health benefits

Based on the VIPS primary indicators assessment, VVM-TIs can **potentially address a few immunisation challenges when compared to use of CTC vaccines with VVMs and separate TIs.**

- **VVM-TIs would ease logistics** as they would replace the stand-alone TIs that are currently distributed with vaccines in a CTC. Health workers would not have to deal with **storage and transport of separate TIs** and **interpretation of two indicators** (the VVM and separate TI). They would only need to refer to the VVM-TI which is interpreted identically to existing VVMs.
- **Training on TI interpretation is currently a barrier to CTC implementation;** VVM-TIs would remove this barrier**.**
- The use of VVM-TIs avoids the need to purchase and distribute separate TIs to health facilities for use with vaccines in a CTC therefore **reducing the potential for stockouts of TIs and** removing the **need for forecasting, procurement and distribution of stand-alone TIs,** which is **currently a barrier to CTC implementation.** VVM-TIs **would not impact the risk of stock-outs of vaccines** or needles and syringes.
- VVM-TIs are **better in terms of environmental impact** as standalone TIs require disposal when they are no longer usable. There would be no change in the waste disposal of vaccines, however.

A VVM-TI will have a significantly higher cost than a VVM with a stand-alone TI because the increase in commodity costs will outweigh any savings in delivery cost

Costs

Commodity costs[1, 2]

Commodity costs expected to be more expensive:

- VVM-TI will result in **up to a 75% price premium** (equivalent to a price increase of $0.03–$0.04 per unit) **compared to a VVM alone without a TI**. The price per dose will be spread among the number of doses per vial (or other primary container). The price-premium might therefore be significant for vials with one or few doses.
- A VVM-TI would cost more than use of a separate VVM and TI (estimated cost $0.25 - $0.50 per vaccine carrier which can be <$0.01 per dose since it is shared among several doses and reusable if it has not reached endpoint).
- Price reductions are possible when VVM-TI demand increases beyond 50 million units.
- No change in delivery device and safety box purchase costs.

Delivery costs[2, 3]

Delivery costs expected to be reduced due to costs of time spent by vaccinators:

- Reduction in time spent by vaccinators on monitoring vaccines used in a CTC since they will only have to monitor one indicator instead of two.

No cost savings for vaccines not used in a CTC.

Introduction and recurrent costs[1]

No introduction costs for non-CTC vaccines:

- There is minimal training required since a VVM-TI is interpreted identically to the existing VVM.

Reduced introduction costs for CTC vaccines:

- **Less training required during CTC implementation** as training on separate TIs would not be required with use of VVM-TIs.

[1] Of a vaccine regimen (per person vaccinated); [2] Includes the purchase cost of a vaccine regimen and delivery devices (injection syringes or other components needed for vaccine preparation and administration) accounting for wastage, and safety box costs; [3] Includes costs of in and out of cold chain storage and transport for a vaccine regimen including delivery technology(ies), time spent by vaccinators when preparing and administering the vaccine and by staff involved in stock management.

VVM-TIs are “downstream” and could be available to vaccine manufacturers in a relatively short timeframe

Technology Readiness

VIPS Criteria	Indicators	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	YF	Ebola	ETEC	HIV[5]	Influenza[6]	Malaria	M. Tb[7]	RSV[8]
Secondary criteria	Technology readiness[1]	Clinical development pathway complexity	No complexity															
		Technical development challenges	Low complexity															
		Complexity of manufacturing the innovation	No complexity															
		Robustness: multiple developers of the technology	Not robust															
		Robustness: multiple suppliers/manufacturers of the vaccine	Not robust															

- **Minimal technical development challenges** as the technology is established: **one VVM-TI type is WHO prequalified** and **a VVM-TI appropriate for CTC use is ready for prequalification** and could be available in less than one year.
- **No manufacturing complexity** as the **VVM supplier** can **use existing VVM manufacturing equipment** to produce VVM-TIs and **can scale capacity** beyond the current single shift **to meet demand**. **Vaccine manufacturers can use existing VVM labeling equipment** to label vaccines with VVM-TIs.
- The **innovation-vaccine pipeline is not robust** as there is only **one supplier of VVM-TIs** and only **one vaccine manufacturer actively pursuing use of VVM-TIs** on a lyophilised rotavirus vaccine (though not for CTC use).

[1] VIPS assessment of the Technology Readiness criteria was informed by consultations with the WHO/PATH Delivery Technology - WG for each innovation assessed under Phase II, as well as with consultations with regulators. [5] ALVAC-HIV + bivalent Subtype C gp120; [6] VAL-506440; [7] VPM 1002; [8] Pre-fusion F protein

Most development challenges have already been overcome for VVM-TIs

Technology Readiness

Regulatory	Technical	Manufacturing	Vaccines
• **No clinical development** is required for application of a VVM-TI as there is no change in the formulation, route of administration, or delivery mechanism (needle and syringe). • The **label change** would require identification of the correct VVM-TI for each vaccine followed by regulatory and WHO prequalification approvals.	• **Low technical complexity:** Proof of concept established and **one VVM-TI is already WHO prequalified**. • Vaccine manufacturers would need to **identify appropriate VVM-TIs for each vaccine** and **conduct internal testing of the VVM-TIs** as they do for current VVMs.	• **The manufacturing process for VVMs is well suited for large scale production of VVM-TIs**. • **Vaccine manufacturers** surveyed verified that there are **minimal technical challenges with labeling products with VVM-TIs.**	• It is technically feasible to apply VVM-TIs to **all vaccines.** • **'Best' vaccines** from a programmatic suitability perspective will be those used in a CTC: • **Current CTC vaccines** include: **HPV, MenA, and oral cholera vaccine (OCV)***. • **Future CTC vaccines** could include: **HepB, MR, rabies, typhoid, yellow fever, Ebola, HIV, influenza, malaria, and MTb.**

*OCV was not evaluated under VIPS.

The commercial opportunity for VVM-TIs in LMICs is highly uncertain

Commercial feasibility

Secondary criteria	VIPS Criteria	Indicators	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	YF	Ebola	ETEC	HIV[5]	Influ-enza[6]	Malaria	M. Tb[7]	RSV[8]
	Commercial feasibility	Country stakeholders' interest based on evidence from existing data	No data																
		Potential breadth of the target market	Small																
		Existence of partnerships to support development and commercialisation	Mixed interest																
		Known barriers to global access to the innovation	No known barriers																

- **Countries are not aware of this technology** largely because **VVM-TIs as well as CTC use of vaccines is new** and CTC introductions have been relatively limited.
- **Market potential is likely to be limited to CTC-qualified vaccines in LMIC markets** and is therefore expected to be **small**.
  - A **WHO/UNICEF requirement** would likely be needed to make the innovation available on vaccines.
  - **However, countries are not likely to be willing to pay the cost premium for VVM-TIs for vaccines, especially in small- or low-dose containers, independent of whether they are CTC-qualified or not**.
- **Mixed interest** from stakeholders **regarding development and commercialisation:**
  - **Vaccine manufacturers** surveyed by the DTWG **identified the need to understand country interest and the potential market**. The **(increased) price** was seen as the most **significant barrier** to adoption.

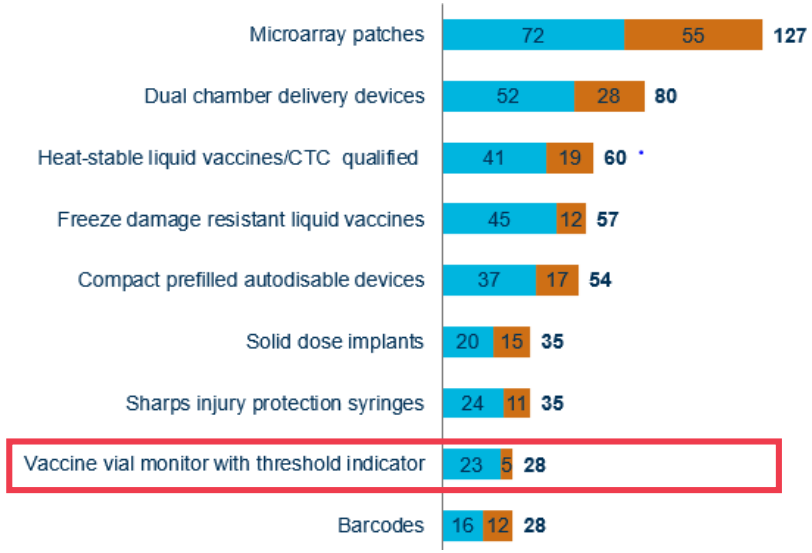
[5] ALVAC-HIV + bivalent Subtype C gp120; [6] VAL-506440; [7] VPM 1002; [8] Pre-fusion F protein

Based on VIPS country feedback,[1] there is little interest in VVM-TIs

Countries interest

Feedback from in-person country interviews

Innovations' ranking



- **Immunisation staff** ranked VVM-TIs as **#7 and decision makers #9** in terms of having the greatest potential impact to address their immunisation programme's challenges. **The overall rating is #7 together with barcodes (last)**.
- The low rating may be due to lack of experience with CTC use of vaccines with heat exposure monitoring by both VVMs and separate TIs.

Perceived benefits

- Potential to **reduce vaccine wastage** due to heat damage/suspected heat damage**;**
- Enable vaccines to be **kept out of the cold chain; i**mprove **ability to monitor vaccines** for heat exposure, helps **assuring the quality of vaccines** that are administered;
- Save **health care worker time;**
- Increase ability to **deliver vaccines outside of a health facility** and improve **ease of use.**

Perceived challenges

- Impact on **overall cost**;
- Immunisation staff: **risk of vaccine wastage**;
- Decision makers: **increase in price per dose** and **training needs.**

[1] Based on in-person interviews conducted in Q4 2019-Q1 2020 with 55 immunisation staff and 29 decision makers across 6 countries to gather feedback on the 9 innovations under final evaluation

Potential impact of VIPS prioritisation

What could VIPS do to accelerate VVM-TIs development for LMICs

- **Highlight the value proposition of VVM-TIs in the facilitation of CTC implementation** and consider linking endorsement of the two innovations together.
- **Market shaping activities** to **encourage competition in the VVM-TI market** to potentially lower prices and set up a **procurement mechanism that requires VVM-TIs on priority vaccines and facilitate procurement of the resulting higher cost products** due to the **price premium** over existing VVMs.
- Consideration could be given to **prioritising VVM-TIs for CTC vaccines used in campaigns and outbreak response in large vial sizes** to reduce the cost per dose.

Risks of not prioritising VVM-TIs through VIPS

- **Missed opportunity to incorporate VVM-TIs** into an **ongoing process to qualify vaccines for CTC use.** CTC was one of the highest rated priority innovations in the VIPS country consultation.
- **Vaccine manufacturers are unlikely to voluntarily apply VVM-TIs to their products – whether CTC qualified or not** so a requirement/incentive is needed and may not occur without concrete attention/support.