VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Phase II executive summary: Heat stable/Controlled temperature chain (CTC) qualified liquid formulations

March 2020

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Heat-stable/controlled temperature chain (CTC) qualified liquid formulations

About heat-stable/CTC qualified liquid formulations

- This innovation refers to liquid vaccine formulations that are sufficiently heat stable to be kept in a CTC. CTC use of vaccines allows a single excursion of the vaccine into ambient temperatures not exceeding +40°C for a **minimum** of 3 days, just prior to administration.
- Heat-stable vaccines differ in the length of time they can be in a CTC and the maximum temperature they can endure while retaining potency. The necessary CTC duration is vaccine and context specific.
- WHO has prioritised vaccines used in **campaigns or special strategies** for CTC qualification because the benefits of CTC cannot be fully realised for routine vaccines that are stored and transported together unless all these vaccines are qualified for CTC use.

Stage of development

- As of February 2020 there are **two heat stable liquid vaccines qualified for CTC use**.
  - Merck's **Gardasil® 4 (quadrivalent human papillomavirus vaccine)**
  - **Shantha Biotechnics Shanchol™ (oral cholera vaccine).**
- Other vaccine manufacturers are in the **process of qualifying their existing and pipeline liquid vaccines for CTC use.**
- Several developers have created approaches, some of which are proprietary, that may be applicable to a variety of vaccines to improve their heat stability in liquid formulations.

Summary of key insights (1/2)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Potential public health impact of innovation

Applicability to vaccines

- All liquid vaccines are potential candidates, as well as some lyophilised vaccines providing they can be **formulated as liquid with sufficient heat stability** to receive CTC qualification.
- However, WHO currently recommends CTC only for **vaccines delivered** in **campaigns or special strategies.**

Public health benefits

- Heat stable/CTC qualified liquid vaccines provide several **public health benefits** for a **broad array of vaccines** including the possibility to **improve coverage and equity** by easing logistics for outreach and **reduce vaccine damage due to heat/freeze exposure**.
- Benefits of **avoiding the risks and complexity of vaccine reconstitution** are also achieved in cases where lyophilised vaccines are reformulated into heat stable liquid vaccines, although this is likely to be **technically challenging.**

Vaccine problem statements

- The innovation addresses several of the top 5 problem statements identified for **hepatitis B birth dose, HPV, MR, Men A, rabies, and typhoid vaccines**.
- The key problems identified were **heat and freeze exposure** and **cold chain requirements** for **liquid vaccines** and **reconstitution complexity and safety** for **current lyophilised vaccines**.

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Summary of key insights (2/2)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Barriers to realise the innovation's potential impact

Costs

- **Whether or not CTC qualification increases vaccine prices will be product dependent.**
- Countries will have to purchase **threshold indicators** to monitor vaccines used in a CTC, but these costs are minimal and may be offset by **logistical costs savings due to not using a cold chain**.

Technology Readiness

- **Low technical challenges for inherently heat stable liquid vaccines and moderate to high technical challenges for vaccines requiring new formulations, particularly lyophilized vaccines.**
- **No or minor impact on manufacturing complexity.**
- A **few vaccine manufacturers** are pursuing CTC qualified liquid vaccines in cases where the technical challenges are minimal.

Commercial feasibility

- **Demonstrated country interest in** CTC use of **hepatitis B birth dose** and **oral cholera vaccines, but mixed interest** in CTC use of **HPV vaccine**.
- **Challenges for commercialisation** include **manufacturers' uncertainties around demand** and **concerns about pricing strategies** especially if CTC qualification will increase the cost of goods.

Countries interest

- Heat stable liquid formulations / CTC qualified was **ranked 3rd innovation amongst the 9 tested by countries** during the VIPS country consultations.

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Heat-stable/CTC qualified liquid formulations have broad applicability to vaccines

Applicability to vaccines

	VIPS Phase II analysed vaccines	Vaccine Type	Presentation	Route
Vaccines **technically compatible** with heat-stable/CTC liquid formulations and analysed in Phase II.	**Licensed vaccines**			
	Penta (or DTP containing)	Adjuvanted Inactivated subunit plus PS-PCV	Liquid	IM[2]
	Hepatitis B (birth dose)*	Adjuvanted sub-unit	Liquid	IM
	HPV*	Adjuvanted sub-unit	Liquid	IM
	MR (or MCV)*	Live attenuated,	Lyophilised	SC[5]
	N. Men A (or N. Men A,C,W,Y,X)*	Conjugate, adjuvant in diluent	Lyophilised	IM
	Polio, IPV	Whole inactivated	Liquid	IM or ID[6]
	Rabies*	Whole inactivated,	Lyophilised	IM or ID
	Rota (Oral)	Live attenuated virus	Liquid	Oral
	Typhoid, conjugate (TCV)*	Conjugate, no adjuvant	Liquid	IM
	Pipeline vaccines			
	Ebola (rVSV-ZEBOV)[7*]	Live vector	Liquid (FROZEN)	IM
	ETEC (ETVAX)	Whole inactivated organism	Liquid vaccine, lyophilised buffer and adjuvant	Oral
	HIV (bivalent subtype C gp120 boost only)[8]	Adjuvanted recombinant protein	Liquid	IM
	Influenza (pandemic,VAL-506440)*	Lipid nanoparticle, modified RNA,	Liquid	IM
Vaccines **not technically compatible** & not analysed in Phase II	**Yellow fever** (YF)	Live attenuated	Lyophilised	SC
	Malaria (RTS,S)	Adjuvanted recombinant protein	Lyophilised, liquid adjuvant	IM
	HIV (ALVAC prime only) [8]	Live recombinant virus	Lyophilised	IM
	MTb (next gen.,VPM1002)	Live recombinant BCG	Lyophilised	ID
	RSV (Pre-F)	Recombinant protein	Lyophilised	IM

13 vaccines are technically compatible and have therefore been assessed (out of 17 in scope) in Phase II

Vaccine applicability:

- **All liquid formulations** are potential candidates for heat-stable/CTC qualified liquid formulations.
- **Lyophilised vaccines where there is some evidence for, or demonstrated interest in developing a stable liquid formulation,** have been included.
- ***These vaccines are currently WHO CTC Working Group priority vaccines for CTC use because they are delivered in campaigns or special strategies.**
- Technical feasibility was assessed based on data, when available, and expert opinion. Key considerations included the natural route of infection, vaccine type, use of adjuvants and preservatives, and context of use.

Comparators:

To assess innovations against both ‘best practice’ and ‘current practice’, comparators were defined as:

- **Single dose vial (SDV)[4] presentation** and auto-disable (AD) N&S[5],
- If available, the **MDV[6] presentation** commonly procured by LMICs.

[2] Intramuscular; [3] Single-dose presentation; [4] Auto-disable needle & syringe; [5] Subcutaneous; [6] Intradermal. [7] At the time of the assessment, Ebola vaccine was not yet licensed and has been analysed as a pipeline vaccine. [8] 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.

Beyond the 17 vaccines analysed through VIPS, heat-stable (HS) / CTC qualified liquid vaccines could be applicable to a range of other vaccines

Applicability to vaccines

**Pipeline vaccines*

VIPS vaccines assessed with HS/CTC liquid formulation	Vaccine type	Other vaccines likely to be compatible with HS liquid formulation
HepB; pentavalent; *HIV (gp120 boost)*	Subunit, liquid, adjuvant	dT; TT; DTwP; DTaP; hexavalent; *non-replicating rotavirus; GAS; next generation malaria; CEPI vaccine platform (clamp); Shigella; ETEC*
HPV	VLP or inactivated virus, liquid, adjuvant	JE (inactivated); hepA; *non-replicating rotavirus; RSV*; *improved or universal influenza; influenza (pandemic)*
IPV	Inactivated virus, liquid	Influenza (seasonal); *RSV*
Men A	Polysaccharide-protein conjugate, lyophilised	Men ACWY(X)
MR	Live attenuated virus, lyophilised	MCVs; JE (live attenuated); dengue; influenza (seasonal); *CEPI vaccine platforms (live recombinant vectors); chikungunya, HSV; next generation malaria; RSV*
Rabies	Inactivated virus, lyophilised	*R&D Blueprint vaccines*
Rotavirus	Liquid (oral)	Oral cholera vaccine (liquid); novel oral poliomyelitis virus vaccine (*nOPV2); Shigella; ETEC*
Typhoid	Polysaccharide-protein conjugate, liquid	Pneumo. conjugate vaccine; Hib, Men ACWY (liquid); *GBS*; *Shigella*
Ebola	Live vector, liquid,	*CEPI vaccine platforms (rVSV); R&D Blueprint vaccines; HSV; next generation malaria; RSV*
Flu (pandemic)	Nucleic acid, liquid	*CEPI vaccine platforms (DNA, RNA), HSV*
ETEC (ETVAX)	Inactivated (liquid) vaccine, lyophilised buffer, lyophilised adjuvant (oral)	Rotavirus (live attenuated)

Overview of Heat Stable /CTC qualified liquid vaccine public health benefits based on Phase II analysis

Public health benefits

Vaccine with an elimination agenda **Current CTC or priority for CTC qual. vaccines**

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

[1] Based on availability of the innovation in a single-dose presentation or multi-dose with preservative; [2] To patients/caregivers; [3] Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities; [4] per person vaccinated; [5] VAL 506440; [6] gp120 boost;

Phase II confirms heat-stable/CTC[1] qualified liquid formulations' potential public health benefits for a range of compatible vaccines

Public health benefits

Based on the VIPS primary indicators assessment applied to vaccines, heat-stable/CTC qualified liquid formulations can **potentially address a number of immunisation challenges for a range of compatible vaccines**, including:

- **Ability to withstand accidental or intentional (i.e. CTC use) heat exposure** likely resulting in **greater effectiveness** and **reduced vaccine wastage.** The degree of heat stability will be vaccine- and formulation-dependent.
- **Reduction in the likelihood of freeze-sensitive vaccines being exposed to freezing temperatures during CTC use,** this could also improve **effectiveness** and **reduce vaccine wastage**.
- **Improved immunisation coverage**; there is evidence that storing hepatitis B birth dose vaccine outside of the cold chain (but not in the CTC) increases immunisation coverage in health facilities and home births in comparison to vaccine stored in the cold chain.
- **If they can be developed**, heat stable liquid presentations offer **ease of use and safety benefits for vaccines that are currently lyophilised by reducing the complexity of vaccine preparation, likelihood of needle-stick injury, risks of reconstitution-associated errors,** and **greater waste** associated with products requiring reconstitution**.**
- **Acceptability of the vaccine schedule** may be improved due to **increased access to vaccines** enabled by use in a CTC. Without the constraints of the cold chain, vaccines can be transported over longer distances and for longer durations allowing them to reach vaccine recipients in a more timely and convenient manner.

[1] CTC can be applied to a routine immunisation setting only when all of the vaccines being transported or stored together have common CTC qualifications.

Overview of the ability of heat-stable/CTC qualified liquid formulations to address vaccine specific problems identified in the VIPS online survey[1]

Vaccine problem statements

Vaccine with an elimination agenda

Current CTC or priority for CTC qual. vaccines

	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	Ebola	ETEC	HIV[4]	Influ-enza[3]
Vaccine ineffectiveness/wastage due to **heat exposure**	2	2	4	1	3	2	2	1	1				
Vaccine ineffectiveness/wastage due to **freeze exposure**[2]	1	1	1			1		2	5				
Cold chain requirements during outreach[2]	4	3	3	4	2	3		3					
Vaccine wastage or missed opportunities due to **multi-dose vial**[2]				2	1		4	5	2				
Reconstitution related **safety issues**[2]				3	4								
Reduced acceptability due to painful administration[2]	3	5	2			4	3						
Difficult preparation requiring trained personnel[2]		4	5				1		4				
Negative impact on the environment due to waste disposal practices[2]						5		4					
Needle-stick injuries[2]				5	5		5						
Contamination risk due to multi-dose vial[2]	5												
Difficult to deliver vaccine to correct injection depth[2]									3				

[1] Based on an online survey with 209 global experts and country-level stakeholders across 54 countries conducted in Q4 2019 – Q1 2020, top 5 reported challenges per licensed vaccine were selected as 'vaccine problem statements' to be specifically analysed. Numbers in the table refer to the ranking order of top 1 to 5 problem statements. For pipeline vaccines, problem statements were defined by VIPS WG.
[2] Scoring based on product attributes. [3] VAL 506440; [4] gp120 boost.

No data available for assessment | No difference with the comparator | Better than the comparator

Heat-stable/CTC qualified liquid formulations have the potential to address several top 5 vaccine problem statements for a range of vaccines

Vaccine problem statements

The overlay of the top 5 problem statements by vaccines with the VIPS primary indicators assessment shows that heat-stable/CTC-qualified liquid formulations **have the potential to address several top 5 vaccine problem statements for a range of vaccines:**

- **Vaccine ineffectiveness/wastage due to heat exposure** is addressed through more heat stable products **–** *Identified as a top 5 problem for 9 vaccines including **HepB, HPV, Men A, Rabies, MR, and TCV** vaccines which are priority vaccines for CTC use, as well as for **penta, IPV and rota** which are not priorities for CTC use. Data supporting this have been obtained to date with HepB and HPV.*
- **Vaccine ineffectiveness/wastage due to freeze exposure might be reduced**, as vaccines in the CTC are less likely to be exposed to freezing temperatures. *This was ranked as a top 5 problem for **HepB, HPV** and **TCV, which are priority vaccines, as well as penta, IPV and rota**.*
- **Cold chain requirements during outreach -** *Identified as a top 5 problem for **HepB, HPV and MenA**, which are priority vaccines for CTC use, as well as **penta, IPV and rota**.*
- Assuming sufficiently heat-stable liquid formulations can be developed for vaccines that are currently lyophilised, then **reconstitution-related safety issues** would be avoided. Needle-stick injuries should also be reduced as there would be no reconstitution step. *These were identified as problems for **MenA, MR vaccines and rabies**.*
    - Developing heat-stable liquid formulations of lyophilised vaccines will be **technically very challenging** however.

Some CTC qualified vaccines may be more costly, however there is opportunity for delivery cost savings with CTC use

Costs

Commodity costs[1, 2]	Delivery costs[1, 3]	Introduction and recurrent costs[1]
Slightly increased (HPV) and no data (all other vaccines): • **To date, CTC qualification (e.g. for HPV vaccine) has not increased vaccine prices,** but **some manufacturers may increase prices** if higher initial potency levels are required or if costs associated with re-formulation and/or additional stability testing are passed on. The **magnitude of these price increases is unknown**. • No change is expected in safety box costs. • **Delivery device costs will increase by <$0.01 per vial because of the need for a separate threshold indicator (TI)**, but this TI is shared across several vials and reusable if it has not reached endpoint. **If a VVM-TI is mandated, commodity costs would increase by $0.03 to $0.05 per vial.** • Change in presentation from a lyophilised to liquid vaccine (if achieved) would eliminate the need for a reconstitution syringe, which could reduce costs.	**Reduced:** • **Costs of cold chain storage and transport would be reduced,** with the **greatest savings in logistics costs being for facilities without existing cold chain equipment.** A study of CTC use of Men A vaccine in Togo showed **average reductions in logistics costs of $0.06 per dose** for such facilities. • **Costs of time for vaccinators is reduced with CTC use of vaccines**, as staff would save time because they no longer have to spend time freezing and conditioning icepacks before leaving for a vaccination session. • No change expected in the economic costs of out of cold chain storage and transportation and costs of time for stock management staff.	**Introduction costs due to training needs:** • There are **training costs** as vaccinators need to be trained on CTC use of vaccines. • There are no other upfront costs or other recurrent costs.

[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;

Technical challenges related to developing heat-stable/CTC qualified liquid formulations are low for some vaccines but moderate to high for others

Technology Readiness

Vaccine with an elimination agenda Current CTC or priority for CTC qual. vaccines

VIPS Criteria	Indicators	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	Ebola	ETEC	HIV[6]	Influenza[5]
Secondary criteria	Technology readiness[1]	Clinical development pathway complexity	Low	Not complex	Not complex	Low	Low	Low	Low	Low	Low	High	High/Very high	High	Low
		Technical development challenges	Moderate	Low	Low	High	Moderate	Moderate	Moderate	Moderate	Low	High	Moderate	Moderate	Moderate
		Complexity of manufacturing the innovation	Not complex												
		Robustness: multiple developers of the technology	No data	Moderate	Moderate	Not robust	No data	No data	No data	No data	Moderate	No data	No data	No data	No data
		Robustness: multiple suppliers/manufacturers of the vaccine	High	High	Moderate	Moderate	Not robust	Not robust	Moderate	Moderate	Not robust	Not robust	Not robust	Not robust	Moderate

- **There are moderate to high technical development challenges** related to achieving a sufficiently heat stable liquid product for vaccines requiring **new formulations** or **increase in potency** when the vaccine is released. The former will be more challenging for vaccines that are currently lyophilised.
- **There are low technical development challenges** for liquid vaccines that are inherently heat stable.
- There should be **no/minor impact on manufacturing complexity** if the existing liquid formulation is CTC-compatible, and potentially a **minor impact** for formulations incorporating new excipients. Manufacturing complexity might **decrease in complexity** if lyophilised vaccines are reformulated as liquids.
- **There are varied levels of robustness** for developers improving the heat stability of specific vaccines and/or pursuing heat stable/CTC qualified liquid formulations.

[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] VAL 506440; [6] ALVAC prime

Challenges to develop heat stable/CTC qualified liquid vaccine formulations are greater for vaccines that would require re-formulation and for lyophilised vaccines

Technology Readiness

Regulatory	Technical	Manufacturing	Vaccines

• **Clinical development**. **complexity varies** depending on the **current status and format of the vaccine.**
  • Commercially available liquid vaccines that are **already heat stable may only require stability studies to produce sufficient data for CTC qualification.** Clinical studies may not be required.
  • Vaccines needing reformulation may require non-inferiority trials.
  • For pipeline vaccines, CTC qualification should not affect the clinical development pathway.
• If **CTC-qualification** is achieved by **increasing the initial potency of the vaccine,** then **additional safety studies might be required.**
• CTC labelling (in package insert) is approved through licensure and WHO prequalification.
	• Some products may require new **formulations** to be developed to achieve the necessary stability. Whether or not this is possible will be vaccine-specific**.**
	• Developing **heat-stable liquid formulations of currently lyophilised vaccines** (particularly live vaccines) is **likely to be technically challenging.**
	• **Preservative efficacy at elevated temperatures** must be assessed for multidose vials of preserved vaccines being submitted for CTC qualification.
	• Conducting **additional stability studies** may be required for CTC qualification.
		• **No significant manufacturing challenges** are expected. Addition of heat-stabilising excipients will result in minor changes to the manufacturing process, but new equipment and/or novel processes are unlikely to be needed.
		• If heat stable liquid formulations of lyophilised vaccine are developed, then fill/finish will change to the standard and less complex processes for liquid vaccines.
			• Of the existing liquid vaccines under VIPS, **HepB, HPV and TCV** are priority vaccines for CTC use determined by the WHO's CTC Working Group.
			• Development of heat stable liquid vaccine formulations for all pipeline vaccines could be encouraged, particularly for vaccines that are not envisaged to be delivered only though routine delivery strategies such as **Ebola, pandemic flu, and the HIV liquid booster**.

The commercial opportunity for heat stable/CTC qualified liquid vaccine formulations in LMICs is unclear and some manufacturers will need incentives to move the innovation forward

Commercial feasibility

Vaccine with an elimination agenda Current CTC or priority for CTC qual. vaccines

VIPS Criteria	Indicators	Penta	Hep B BD	HPV	MR	Men A	IPV	Rabies	Rota	TCV	Ebola	ETEC	HIV[1]	Influenza[2]
Secondary criteria: Commercial feasibility	Country stakeholders' interest based on evidence from existing data	No data	Demon-strated interest	Mixed interest	No data	Demon-strated interest	No data							
	Potential breadth of the target market	Large	Large	Large	Large	Moderate/ Large	Moderate	Small/ Moderate	Large	Small/ Moderate	Small	Moderate	Large	Small
	Existence of partnerships to support development and commercialisation	No known interest	Significant interest	Significant interest	Mixed interest	No known interest	No known interest	No known interest	No known interest	Significant interest	No known interest	No known interest	No known interest	No known interest
	Known barriers to global access to the innovation	No data	No known barriers	No known barriers	No data	No data	No data	No data	No data	No known barriers	No data	No data	No data	No data

- There is **demonstrated country interest** for **Men A vaccine** given broad CTC use in initial introductions and for **Hep B vaccine** birth dose which was and is still given out of cold chain use for birth dose outreach. In addition, a number of countries are proactively adopting CTC use of **oral cholera vaccine[3]** on their own. **There is mixed interest for HPV vaccine:** one country has conducted pilots and others have expressed interest, but uptake is low, possibly due to reluctance to add CTC implementation to the complexities of introducing this vaccine.
- While some of the potential markets for CTC vaccines are large, **demand for the innovation is likely only in LMICs** and, in some cases possibly focused on **specific subsets of the market in LMICs** (e.g., areas where health facilities lack cold chain or where target outreach is needed to homes or communities).
- **Some vaccine manufacturers are pursuing CTC qualification (i.e., for HPV, OCV, TCV)** based on expression of need from WHO and/or to increase product competitiveness.
- However, the **key challenges** facing commercialisation of heat-stable CTC liquid vaccines are due to **pricing strategies (especially if the innovation negatively impacts COGS) and the lack of clarity on the market potential and value proposition.**

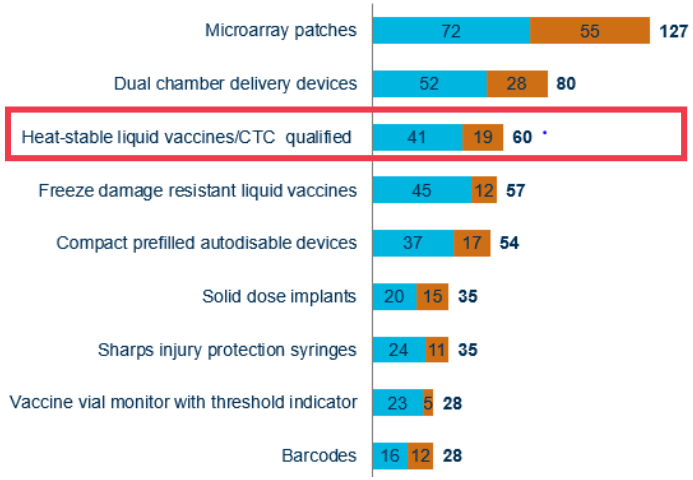
[1] gp120 boost; ; [2] VAL 506440;; [3] Vaccine was not evaluated in VIPS

Based on VIPS country feedback[1], there is strong interest from countries in heat-stable/CTC qualified liquid formulations

Countries interest

Feedback from in-person country interviews

Innovations' ranking



- Heat-stable/CTC qualified liquid formulations are rated by both immunisation staff and decision makers as the **#3 innovation amongst the 9 tested**, in terms of potential impact in helping address their immunisation programme's current challenges.

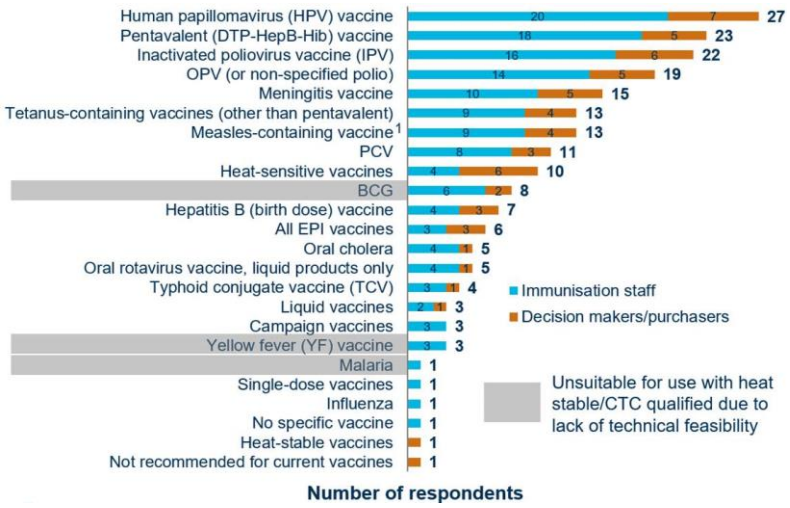
Perceived benefits

- Potential to keep vaccines **out of cold chain**, **reduce cold chain logistics** and **wastage** due to heat damage**;**
- Facilitate **delivery outside health facility;** and potential to **improve coverage;**
- Save **health worker time;**
- **Reduce wastage** due to freeze damage**.**

Perceived challenges

- Overall **cost;**
- Risk of **increased wastage due to heat damage/exceeding CTC duration limit**;
- Immunisation staff : **complexity of CTC protocol; not enough CTC** qualified vaccines**;** potential of creating **carelessness / confusion in vaccine management;** risk of **reduced acceptability to community;**
- Decision makers: **increase in price per dose** and **training needs**.

Vaccines' ranking for heat stable/CTC qualified liquid formulations



[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

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

What could VIPS do to accelerate heat-stable/CTC qualified liquid vaccine development for LMICs	Risks of not prioritising heat-stable/CTC qualified liquid vaccines through VIPS
If this innovation were to be prioritised by VIPS, stakeholder inputs would be sought to identify follow-up activities that would have the **greatest impact on accelerating** development. These could include: • **Strengthened global coordination** (e.g., through the WHO CTC working group) to provide clarity on priorities, specifications, use cases, and the value proposition for CTC vaccines and assistance to manufacturers and countries; • **Increased resources at global level** to advance the CTC agenda; • **Market shaping to incentivise vaccine manufacturers;** and • **Assistance to countries with CTC introductions** and **support for generating impact data**.	• Not prioritising this innovation would be **at odds with ongoing work at WHO and GVAP[1] recommendations to qualify and introduce CTC vaccines** to help achieve immunisation coverage and equity targets. • WHO and vaccine manufacturers **might abandon development** of heat-stable formulations and/or CTC qualification.

[1] Global Vaccine Action Plan

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