VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Phase I executive summary: Heat-stable/Controlled Temperature Chain (CTC) qualified dry formulations

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Gavi The Vaccine Alliance

World Health Organization

BILL & MELINDA GATES foundation

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

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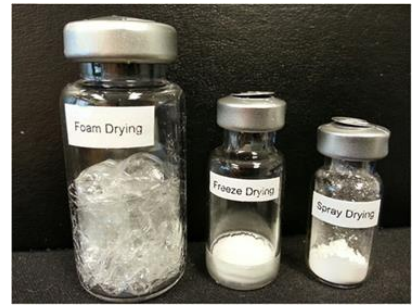
About Heat-stable/CTC qualified dry formulations

- Dry formulations that are **heat-stable and CTC-qualified** have attributes enabling them to be **exposed to ambient temperatures below a defined threshold without losing their potency**.
- CTC-qualification allows vaccines to **be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time** under monitored and controlled conditions.
- CTC qualification involves **regulatory approval and prequalification by WHO**.
- Dry formulations vary in their sensitivity to heat and suitability for use in a CTC.
- Currently all dry vaccine formulations that are commercially available require reconstitution with a diluent and are delivered as a liquid (injectable and oral routes).
- **Common drying processes include:**
  - **Freeze-drying (lyophilisation)** is a complex multi-stage process used on an industrial scale, in particular for live-attenuated vaccines. The steps involve (i) freezing, (ii) primary drying and (ii) secondary drying, resulting in a dried cake in the final container.
  - **Foam-drying** is a desiccation process whereby a solution is transformed into a dried foam structure by boiling or foaming under reduced vapour pressure followed by rapid evaporation. Unlike lyophilisation, there is no freezing step, so it can be used with freeze-sensitive vaccines.
  - **Spray-drying**, spray-freeze drying, and supercritical fluid drying are processes that can be used to produce ‘free-flowing’ dry-powders with defined particle sizes.

Lovalenti [a]

Lyophilised formulation



Lovalenti [a]

Foam-dried, freeze-dried, and spray-dried formulations

[a] Lovalenti, P.M., Anderl, J., Yee, L. et al. Pharm Res (2016) 33: 1144. https://doiorg.ezp.welch.jhmi.edu/10.1007/s11095-016-1860-1.

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

Stage of development

- The **freeze drying process is commonly used for commercially available vaccines**.
    - One freeze-dried vaccine (**the meningococcal A conjugate vaccine, MenAfriVac**) has **received regulatory and WHO prequalification approvals for use in a CTC.**
- Dry-powder formulations created by the other drying processes are **not currently used for commercially available vaccines** and are still at the **early testing phases of R&D.**

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

Comparators: Current liquid and lyophilised formulations

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Quality of evidence: Low to moderate

VIPS Criteria		Indicators	Comparators: Liquid formulations	Comparators: Lyophilised formulations	Priority indicators - Country consultation: RI* Facility	RI* Community	Campaigns
Primary criteria	Health impact	Ability of the vaccine presentation to withstand heat exposure	Better	Better	+	++	++
		Ability of the vaccine presentation to withstand freeze exposure	Better	Neutral			
	Coverage & Equity impact	Ease of use [a]	Worse	Neutral	+	+	++
		Potential to reduce stock outs [b]	Worse	Neutral			
		Acceptability of the vaccine presentation to patients/caregivers	Better	Better		+	+
	Safety impact	Likelihood of contamination	Worse	Neutral			+
		Likelihood of needle stick injury	Worse	Neutral			
	Economic costs	Total economic cost of storage and transportation of commodities per dose	Mixed	Better	+		
		Total economic cost of the time spent by staff per dose	Worse	Neutral	++	++	+
		Total introduction and recurrent costs [c]	Neutral	Neutral			
Secondary criteria	Potential breadth of innovation use	Applicability of innovation to one or several types of vaccines	All vaccines that are currently dry and thermostable.				
		Ability of the technology to facilitate novel vaccine combination	No				

* RI : Routine immunisation

++	Given significantly more importance
+	Given more importance
	Kept neutral

[a] Ease of use can prevent missed opportunities and impact ability for lesser trained personnel to administer the vaccine, including self-administration

[b] Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities

[c] Total economic cost of one-time / upfront purchases or investments required to introduce the innovation and of recurrent costs associated with the innovation (not otherwise accounted for)

Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Antigen applicability

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- Heat stable/CTC qualified dry formulations could be applied to **any vaccine that is currently or can potentially be reformulated into a thermostable dry presentation**.
- Developing heat-stable/CTC-qualified dry formulations will be **technically challenging for some vaccines**. No single formulation method will stabilise all vaccines; each vaccine requires a customised approach.
- Some drying process **might not be compatible with aluminum-salt-based adjuvants**.
- Vaccines that are **currently liquid and adequately heat-stable would not be appropriate for this innovation** since their current liquid format has benefits in terms of ease-of-use and lower costs (e.g., **HPV vaccine**).
- The **benefits of CTC-qualification** are greatest for vaccines that are used in **campaigns or special strategies** (e.g. **meningococcal group A conjugate vaccine**).
- **Ebola and MR** are other VIPS antigens that could be suitable for this innovation.

Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Assessment outcomes

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KEY BENEFITS

✚✚ **Improving the heat stability** of vaccines can **protect against damage caused by inadvertent heat-exposure**. In some cases, a dry formulation will be more heat-stable and **less freeze-sensitive** than the same formulation as a liquid.

- Depending on the vaccine format, heat stability/CTC qualification can **potentially increase coverage and equity by enabling alternative delivery scenarios** where the vaccine is transported and stored outside of the cold chain – easing cold chain logistics for health care workers.

✚✚ May **increase acceptability** among caregivers/vaccinees due to increased access to the vaccines.

✚ Potentially **reduce storage and transport volume in the cold chain and associated costs** since both the diluent and dry formulation could be **stored outside the cold chain during the last mile.**

- **Broad applicability** to all vaccines that are currently dry and thermostable.

✚✚ Important attribute for at least 2 settings or for the 3 settings based on the country consultation (see slide 3)

✚ Important attribute for campaigns or routine facility-based immunisation based on country consultation (see slide 3)

KEY CHALLENGES

- **Rated lower than liquid formulations comparator on some aspects of coverage and equity:**

✚✚ May **reduce ease of use**: dry formulations that require reconstitution are more complex in terms of preparation.

- May **increase stock-outs** due to **more components** required for reconstitution (diluent and reconstitution syringe).

✚ May **reduce safety compared to liquid formulations** due to increased **risk of contamination** and **needle-stick injuries** during reconstitution.

- **Rated lower than liquid comparator for delivery costs:**

✚ **May increase out of the cold chain volume and associated storage and transport costs** due to the greater space required for the reconstitution diluent and syringe.

- May **increase health care worker time** to deliver the vaccine.

- In multidose presentations, dry formulations without preservative **increase vaccine wastage and missed opportunities** as the reconstituted vaccine must be discarded at the end of the vaccination session. When used in a CTC, the drop in heat stability after reconstitution might also limit the length time the vaccine can be used in a session further increasing wastage.

Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Rationale for prioritisation

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- Based on the analysis, dry heat stable CTC formulations are included in a '**maybe**' category for prioritisation and **the Steering Committee is requested to provide advice on whether this innovation should be prioritised or not for Phase II.**
- Dry heat stable CTC formulations have advantages over existing dry formulations in terms of **ability to withstand heat exposure and reduction in the need for cold chain during the last mile** resulting in decreased logistics and storage/transport costs. However CTC use of dry formulations is **likely most appropriate for vaccines that are in single dose formats.**
- A number of innovations recommended for prioritisation in phase II are single dose dry formulations that could be CTC-qualified – microarray patches, solid dose implants, dual chamber devices – and have the advantage of not requiring reconstitution. Therefore **it may not be necessary to advance dry heat stable CTC formulations as a separate VIPS innovation**.
- Dry heat stable CTC formulations have clear **coverage and equity, safety, and cost disadvantages in comparison to heat stable liquid formulations** and it is important to not signal heat stability and CTC qualification as a standalone objective without taking into account these many negative tradeoffs.