VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Phase I executive summary: Sublingual dosage forms

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Gavi The Vaccine Alliance

World Health Organization

BILL & MELINDA GATES foundation

PATH

unicef

Sublingual dosage forms

About Sublingual dosage forms

- Sublingual dosage forms are **tablets and thin films that are placed under the tongue** and rapidly dissolve to **form a gel in a small amount of saliva.**
- The gel is **absorbed via the mucosal surfaces under the tongue** inducing systemic immunity, similar to an injectable vaccine, and potentially inducing robust mucosal immunity.
- In contrast to oral ingestion vaccination, **sublingual dosage forms are not intended to be swallowed or delivered to the intestinal tract.**

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Gel-forming sublingual tablet being placed under the tongue

Stage of development

- Sublingual dosage forms are in **early-stage preclinical development for several vaccines including HIV Env protein and ETEC.** The mucosal adjuvant dmLT is also being evaluated.
- Some have progressed to **clinical trials including a seasonal influenza vaccine** combined with a novel adjuvant in a sublingual tablet.
- Most studies of sublingual vaccines to date have **not utilised optimised sublingual dosage forms that form a gel**, which resulted in **poor immune responses.**
- Commercially available sublingual dosage forms are used to deliver allergy immunotherapies, low molecular weight drugs, and therapeutic vaccines.

Sublingual dosage forms scorecard

Comparators: Single dose vial (SDV) (liquid) and dropper or sprayer ;
SDV (lyophilised) + diluent + reuse prevention (RUP) reconstitution syringe and dropper sprayer; SDV(liquid) and autodisable (AD) needle and syringe (N&S); SDV (lyophilised) + diluent and RUP reconstitution syringe and AD N&S

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Quality of evidence: Low to moderate

VIPS Criteria		Indicators	Comparators: Oral/Intranasal: Dropper or sprayer + recon	Comparators: Oral/Intranasal: Dropper or sprayer - recon	Comparators: Injectable: SDV AD N&S + recon	Comparators: Injectable: SDV AD N&S - recon	Priority indicators - Country consultation: RI* Facility	RI* Community	Campaigns
Primary criteria	Health impact	Ability of the vaccine presentation to withstand heat exposure	Neutral	Better	Neutral	Better	+	++	++
		Ability of the vaccine presentation to withstand freeze exposure	Neutral	Better	Neutral	Better			
	Coverage & Equity impact	Ease of use [a]	Better	Better	Better	Better	+	+	++
		Potential to reduce stock outs [b]	Better	Better	Better	Better			
		Acceptability of the vaccine presentation to patients/caregivers	Neutral	Neutral	Considerably better	Considerably better		+	+
	Safety impact	Likelihood of contamination	Better	Better	Better	Better			+
		Likelihood of needle stick injury	Better	Better	Better	Better			
	Economic costs	Total economic cost of storage and transportation of commodities per dose	Considerably better	Considerably better	Considerably better	Considerably better	+		
		Total economic cost of the time spent by staff per dose	Better	Better	Better	Better	++	++	+
		Total introduction and recurrent costs [c]	Neutral	Neutral	Neutral	Neutral			
Secondary criteria	Potential breadth of innovation use	Applicability of innovation to one or several types of vaccines	All vaccines against mucosal pathogens that can be prepared in a dry format are potential candidates.						
		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)

Sublingual dosage forms: Antigen applicability

- Sublingual dosage forms can potentially be **applied to vaccines against mucosal pathogens that can be prepared in a dry format**.
- Vaccines that are **currently delivered parenterally are likely to be suitable** for this innovation, but subunit and non-live vaccines are likely to require a mucosal adjuvant (such as dmLT), and none are approved at present.
- **Live vaccines that are currently delivered intranasally may also be suitable.**
- A sublingual dosage form is an **attractive option for an HIV** vaccine.
- Examples on the VIPS priority antigen list that might also be appropriate for sublingual delivery include **HPV, IPV** (both might require a mucosal adjuvant however) and **the live VSV-vectored Ebola vaccine**.

Sublingual dosage forms: Assessment outcomes

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KEY BENEFITS

✚✚ May offer **improved heat stability and freeze resistance** over liquid vaccines given the **dried format.**

- **Potential positively impact on coverage and equity:**

✚✚ **Easy to use:** simplify preparation and delivery and may **reduce errors and improve dose control.**

- Could **enable alternate delivery scenarios.**
- May be **suitable for delivery by lesser-skilled health care workers.**

✚✚ Potential to **increase acceptability:** likely to be more acceptable due to the reduced pain of delivery (compared to injectable presentations).

- Potential to **reduce stock-outs** since the innovation has a **single component to be procured, distributed, and tracked.**

✚ May **improve safety** by reducing **risk of contamination** and **needlestick injuries**.

- **Potential to reduce overall delivery costs:**

✚ May **reduce storage and transportation costs** since sublingual dosage forms are **extremely compact and eliminate the need to store and transport any components out of the cold chain.**

✚✚ May **save health care worker time**, as easy to use.

- Have the potential to **increase immunogenicity** compared to a dropper/sprayer.

KEY CHALLENGES

- For infants and young children, the dry sublingual dosage forms **may need to be reconstituted** and then administered with a liquid dropper under the tongue to address the potential risk of choking **which negates some of the benefits for this age group**.
- **Limited applicability** for subunit and non-live vaccines unless combined with a mucosal adjuvant

✚✚ 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)

Sublingual dosage forms: Rationale for prioritisation

- Based on the analysis, sublingual dosage forms 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.**
- While the technology may yield **high public health benefits**, its **applicability to subunit and non-live vaccines is limited without the availability of a mucosal adjuvant** and advancement of adjuvants is outside of the purview of VIPS.

Additional important information to be analysed in phase II (if prioritised for Phase II)**:**

- Vaccine specific reviews of technical feasibility – especially for products requiring a mucosal adjuvant.
- Vaccine specific reviews of the public health value proposition – especially for products targeting younger age groups.