VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Phase II executive summary: Freeze damage resistant liquid formulations

March 2020

Gavi The Vaccine Alliance | World Health Organization | Bill & Melinda Gates foundation | PATH | unicef

Freeze damage resistant (FDR) liquid formulations

About freeze damage resistant liquid formulations

- **Many vaccines are freeze-sensitive**, including those containing aluminium-salt adjuvants. When vaccines containing aluminium-salt adjuvants are frozen, the antigen-adjuvant particles agglomerate (form a cluster) and sediment resulting in irreversible loss of potency.
- The **addition of excipients** (stabilising agents) to vaccine formulations **could prevent agglomeration and freeze damage; stabilising the potency of vaccines**.
- Glycerin, polyethylene glycol 300, and propylene glycol (PG) have been **demonstrated to reduce the sensitivity to damage due to freezing of hepatitis B and other vaccines containing aluminum-salt adjuvants** including diphtheria, tetanus and pertussis (DTP); and pentavalent (hepatitis B, DTP, Haemophilus influenza type b) vaccines.

www.myelomacrowd.org [a]

Freeze damage resistant liquid vaccines

Stage of development

- **Excipients that could be used to improve freeze resistance** of vaccines are known and available but are **not used in any approved vaccines** – though they are used in other parenteral drugs, including some for pediatric use.
- There have been **pre-clinical studies with freeze-damage resistant formulations of hepatitis B, pentavalent, and DTP vaccines**, but overall, the approach is at **an early phase of development.**

www.publichealthontario.ca [b]

Freeze damage resistant liquid vaccines

[a] https://www.myelomacrowd.org/wp-content/uploads/2015/05/vials.jpg
[b] https://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/PIDAC/Pages/Infection-Prevention-and-Control-for-Clinical-Office-Practice-Multidose-Vials.aspx

Summary of key insights (1/2)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Potential public health impact of innovation

Applicability to vaccines

- **The innovation is potentially feasible for application to all freeze-sensitive liquid vaccines** and **diluents**, especially those **containing aluminum adjuvants.**

Public health benefits

- Freeze damage resistant liquid formulations have the potential to **safeguard vaccine potency and decrease vaccine wastage.**

Vaccine problem statements

- **Freeze exposure** was identified as the **top problem** for 5 vaccines (**hepatitis B, pentavalent, HPV, IPV and TCV)**.
- Developing vaccine formulations that are freeze damage resistant is **one means to prevent freeze damage**. Other means include **temperature monitoring, icepack conditioning, and use of freeze free vaccine carriers and cold boxes and cold chain equipment with improved temperature control.**

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Summary of key insights (2/2)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Barriers to realise the innovation's potential impact

Costs

- The innovation would likely **add minimal costs** if the excipient addition is considered **early enough in vaccine development** or while a vaccine is **being reformulated for other reasons**.

Technology Readiness

- **Clinical development complexity** depends on the vaccine type and the timing of formulation changes and there are **moderate challenges for technical development,** with greater complexity with multivalent vaccines.
- **No complexity for manufacturing** as the excipients are readily available and should not significantly impact the manufacturing process.
- **Pipeline is not robust** as no vaccine manufacturers are known to be applying this innovation.

Commercial feasibility

- **Large potential market and strong interest from country stakeholders, but vaccine manufacturers** are **reluctant** to use the innovation based on **lack of perceived demand, concerns about acceptability of the excipients, and the impact on costs.**

Countries interest

- The innovation was ranked **4th overall in the VIPS country interviews; immunisation staff ranked it in 3rd place and decision makers ranked it in 6th place** in terms of potential to address immunisation programme challenges.

FDR liquid formulations have a broad applicability to vaccines

Applicability to vaccines

	VIPS Phase II analysed vaccines	Vaccine Type	Presentation	Route
Vaccines **technically compatible** with freeze damage resistant liquid formulations and analysed in Phase II.	**Licensed vaccines**			
	Penta (or DTP containing)	Adjuvanted inactivated subunit plus polysaccharide-protein conjugate	Liquid	IM[2]
	Hepatitis B (birth dose)	Adjuvanted sub-unit	Liquid	IM
	HPV	Adjuvanted sub-unit	Liquid	IM
	Polio, IPV	Whole inactivated	Liquid	IM and ID[6]
	Typhoid, conjugate (TCV)	Polysaccharide-protein conjugate	Liquid	IM
	Pipeline vaccines			
	ETEC (ETVAX)	Whole inactivated organism	Liquid vaccine, lyophilised buffer and adjuvant	Oral
	HIV (bivalent Subtype C gp120 boost only)[8]	Adjuvanted recombinant protein	lyophilised prime and liquid booster (gp120)	IM
	Influenza (pandemic,VAL-506440)	Lipid nanoparticle, modified RNA	Liquid	IM
	Malaria (RTS,S)	Adjuvanted recombinant protein	Lyophilised, liquid adjuvant	IM
Vaccines **not technically compatible** with freeze damage resistant liquid formulations & not analysed in Phase II.	**MR** (or MCV)	Live attenuated	Lyophilised	SC[5]
	Rabies	Whole inactivated	Lyophilised	IM or ID
	RSV (Pre-F)	Recombinant protein	Lyophilised	IM
	Yellow fever (YF)	Live attenuated	Lyophilised	SC
	MTb (next gen.,VPM1002)	Live recombinant BCG	Lyophilised	ID
	Rotavirus (Oral)	Live attenuated virus	Liquid	Oral
	HIV (ALVAC-HIV, pirme)	Live recombinant virus,		
	Ebola (rVSV-ZEBOV)[7]	Live vector	Liquid (FROZEN)	IM
	N. Men A (or N. Men A,C,W,Y,X)	Conjugate, adjuvant in diluent	Lyophilised	IM

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9 vaccines are technically compatible and have therefore been assessed with freeze damage resistant liquid formulations (out of 17 in scope) in Phase II.

Vaccine applicability:

- The technology could be applied to **all freeze-sensitive liquid vaccines** and **diluents, especially those containing aluminium adjuvants**.
- **No in-depth studies** have been conducted on the application of the formulation method to freeze-sensitive vaccines **not containing aluminium adjuvant.**
- The innovation is **best suited to vaccines in development or those being reformulated** for other reasons.
- Technical feasibility was assessed based on data, when available, and expert opinion.

Comparators:

- To assess innovations against both ‘best practice’ and ‘current practice’, comparators were defined as:
- **SDV[3] presentation** and **AD N&S[4]**
- If available, the **MDV[9] 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. 9 Multi-dose presentation

Beyond the 17 vaccines analysed through VIPS, FDR formulations should be compatible with a range of other vaccines

Applicability to vaccines

**Pipeline vaccines*

VIPS vaccines assessed to be compatible with	Vaccine type	Other vaccines likely to be compatible with AD-SIPs
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*
Typhoid	Polysaccharide-protein conjugate, liquid	Pneumococcal conjugate vaccine; Hib, Men ACWY (liquid); *GBS*; *Shigella*
Ebola[1]	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*
Rotavirus[1]	Liquid (oral)	Oral cholera vaccine (liquid); novel oral poliomyelitis virus vaccine (*nOPV2); Shigella; ETEC*
ETEC (ETVAX)	Inactivated (liquid) vaccine, lyophilised buffer, lyophilised adjuvant (oral)	

[1] Not assessed in VIPS as not sensitive to freeze-damage. However other liquid vaccines of the similar type might be sensitive to freeze-damage and compatible with the innovation

Overview of the public health benefits of FDR liquid vaccine formulations based on Phase II analysis

Public health benefits

■ Vaccine with an elimination agenda

VIPS Criteria	Indicators	Penta	Hep B BD	HPV	IPV	TCV	ETEC	HIV[5]	Influ-enza[6]	Malaria[7]
Primary criteria	Health impact	Vaccine efficacy	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Vaccine effectiveness	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	No data	No data	No data	No data	No data	No data	No data	No data
		Ability of the vaccine presentation to withstand freeze exposure	Better	Better	No data	No data	No data	No data	No data	No data	No data
	Coverage & Equity impact	Number of fully or partially immunised (relative to target population)	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	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Ease of use: ability of a lesser trainer personnel to admin. / self-admin.	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Ability to facilitate dose sparing	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
		Acceptability of the vaccine presentation and schedule[2]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Potential to reduce stock outs[3]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Safety impact	Number of vaccine product-related AEFIs	No data	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	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Likelihood of needle stick injury	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Economic costs	Commodity costs of the vaccine regimen[4]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Delivery costs of the vaccine regimen[4]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
		Introduction & recurrent costs of the vaccine regimen[4]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
	Environmental impact	Waste disposal of the vaccine regimen[4] and delivery system	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	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] ALVAC-HIV + bivalent Subtype C gp120; [6] VAL-506440; [7] RTS,S

FDR liquid formulations have the potential to safeguard vaccine potency and decrease vaccine wastage

Public health benefits

- There is **preclinical and laboratory evidence** demonstrating that the formulation approach **prevents freeze-damage** to diphtheria, hepatitis B, pertussis (acellular and whole cell), and tetanus vaccines.
- Freeze damage resistant formulations could potentially:
  - Endure exposure to freezing temperatures (e.g., when placed with unconditioned icepacks, in refrigerators with poor temperature control, or in cold climates) **without potency loss** thereby potentially improving vaccine effectiveness.
  - **Prevent vaccine wastage** when inadvertent exposure to freezing temperatures does occur.

Overview of the ability of FDR formulations to address vaccine specific problems identified in the VIPS Phase II online survey

Vaccine problem statements

Vaccine with an elimination agenda

	Penta	Hep B BD	HPV	IPV	TCV	ETEC	HIV[5]	Influenza[6]	Malaria[7]
Vaccine ineffectiveness/wastage due to **heat exposure**	2	2	4	2	1				
Vaccine ineffectiveness/wastage due to **freeze exposure**	1	1	1	1	5				
Cold chain requirements during outreach[2]	4	3	3	3					
Vaccine wastage or missed opportunities due to **multi-dose vial**[2]					2				
Reconstitution related **safety issues**[2]									
Reduced acceptability due to painful administration[2]	3	5	2	4					
Difficult preparation requiring trained personnel[2]		4	5		4				
Negative impact on the environment due to waste disposal practices[2]				5					
Needle-stick injuries[2]									
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 challenges identified by countries 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 the VIPS WG. [2] Scoring based on product attributes.
[5] ALVAC-HIV + bivalent Subtype C gp120; [6] VAL-506440; [7] RTS,S

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

FDR liquid formulations have the potential to address the top problem identified by countries for 4 vaccines

Vaccine problem statements

- **Freeze exposure** was identified as the **top problem** in the VIPS online survey for **hepatitis B, pentavalent, HPV, and IPV** and the **number 5 problem for typhoid vaccine**.
- However:
  - Even if some vaccines are made to be freeze damage resistant by application of the technology, other vaccines in the same shipments might not have this property. Therefore, **vigilance in protecting other freeze-sensitive vaccines will still be necessary.**
  - It should be noted that **other methods exist to protect vaccines from freeze damage** including temperature monitoring, icepack conditioning, use of freeze free vaccine carriers and cold boxes, and use of cold chain equipment with improved temperature control.

FDR liquid vaccine formulations will likely add minimal costs if the vaccine is being developed or for second generation products

Costs

Commodity costs[1, 2]

Likely to be similar to current vaccines in single or multidose vials for new or second-generation vaccines, potentially higher for others:

- It would likely **add minimal costs (excipient cost estimated at less than $0.001 per dose)** if the vaccine is being developed or for second generation products.
- **If the vaccine is reformulated for the sole-purpose of making a freeze-damage** resistant formulation, it could **add additional costs to the vaccine if the manufacturer passes on the additional research and clinical development costs** involved.
- No impact on delivery device and safety box purchase costs.

Delivery costs[1, 3]

Similar to current vaccines in single or multidose vials:

- As the innovation is a change to formulation only, the innovation does not affect delivery costs.

Introduction and recurrent costs[1]

No introduction or recurrent costs:

- No training likely to be required for this innovation.
- No upfront, recurrent or ongoing 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;

Moderate technical challenges are anticipated for FDR liquid formulations

Technology Readiness

Vaccine with an elimination agenda

VIPS Criteria		Indicators	Penta	Hep B BD	HPV	IPV	TCV	ETEC	HIV[2]	Influenza[3]	Malaria[4]
Secondary criteria	Technology readiness[1]	Clinical development pathway complexity	Low	Low	Low	Low	Low	High/ very high	High	Low	High
		Technical development challenges	Moderate								
		Complexity of manufacturing the innovation	No complexity								
		Robustness: multiple developers of the technology	Not robust	Not robust	No data	No data	No data	No data	No data	No data	No data
		Robustness: multiple suppliers/manufacturers of the vaccine	Highly robust	Highly robust	Moderate	Not robust	Not robust	Not robust	Not robust	Moderate	Not robust

- **Variable clinical development complexity** depending on the vaccine type and the timing of formulation changes.
- **Moderate challenges** facing the **technical development** as studies will be needed for each vaccine**;** with greater complexity for multivalent vaccines.
- **No complexity for manufacturing** as the excipients are readily available and should not significantly impact the manufacturing process. This will need to be confirmed on a case-by-case basis.
- **Pipeline is not robust** as no vaccine manufacturers are known to be applying this innovation.
- **Reformulating an existing vaccine** for freeze resistance alone **is likely not tenable** given the costs and complexity.

[1] VIPS assessment of the Technology Readiness criteria was informed by consultations with the WHO/PATH Delivery Technology - WG, as well as with regulators.
[2] ALVAC-HIV + bivalent Subtype C gp120; [3] VAL-506440; [4] RTS,S

Developing FDR formulations will come with some challenges and impact costs and will thus be more suitable to new or second-generation vaccines

Technology Readiness

Regulatory	Technical	Manufacturing	Vaccines
• **Clinical development**. For licensed vaccines, phase III non-inferiority or bridging studies with immunogenicity endpoints are expected to be sufficient. However, for novel vaccines, the same (clinical) endpoints would be required as for other formulations. • Stability studies to **confirm the shelf-life (stability)** of the new formulation will be needed. • Confirmation that the excipients are **safe and acceptable for use in healthy infants** will be required.	• **Freeze stability:** Studies with each vaccine will be needed to confirm that the formulations are freeze resistant, e.g. evaluation of the effect of the excipient on the antigen(s) and the adjuvant at various freezing temperatures and freeze-thaw cycles. • **Impact on vaccine components:** Studies will be needed to determine whether the excipient has any negative effects on other vaccine characteristics. • **Multivalent vaccines** will be more complicated to formulate.	• **Materials:** Excipients used to confer freeze resistance are readily available materials used in other pharmaceuticals. • **Manufacturing process/equipment:** No impacts anticipated, but this will need to be confirmed and documented by each manufacturer.	• Given the costs of applying this innovation, the best application is for **freeze-sensitive pipeline vaccines** and **freeze-sensitive commercial vaccines that are being reformulated** for other reasons. In these instances, a new excipient could be added with minimal cost.

The commercial opportunity for FDR liquid formulations in LMICs is highly uncertain and manufacturers will need an incentive to adopt this innovation

Commercial feasibility

VIPS Criteria		Indicators	Penta	Hep B BD	HPV	IPV	TCV	ETEC	HIV[2]	Influenza[3]	Malaria[4]
Secondary criteria	Commercial feasibility	Country stakeholders' interest based on evidence from existing data	Demonstra-ted interest	No data							
		Potential breadth of the target market	Large	Large	Large	Moderate	Small/ Moderate	Moderate	Large	Small	Moderate
		Existence of partnerships to support development and commercialisation	No known interest								
		Known barriers to global access to the innovation	No known barriers								

- A 2011-2012 study with 158 **immunisation stakeholders** in Brazil, China, India, Peru, the Philippines, and Tanzania found that respondents were **interested in vaccine products with improved freeze stability characteristics**.
- There is a **large potential market** for several vaccines.
- **Vaccine manufacturers are not aware of a demand** for freeze-resistant vaccines from countries, purchasers, or donors**.**
- Industry consultation[1] revealed **concerns** about:
  - **Potential acceptability issues** and **potential negative impact on vaccination programmes** if concerns are raised about "adding antifreeze to vaccines".
  - **Purchasers' lack of willingness to pay a premium** for freeze-resistant vaccines that would enable manufacturers to **recoup costs for relicensing**.

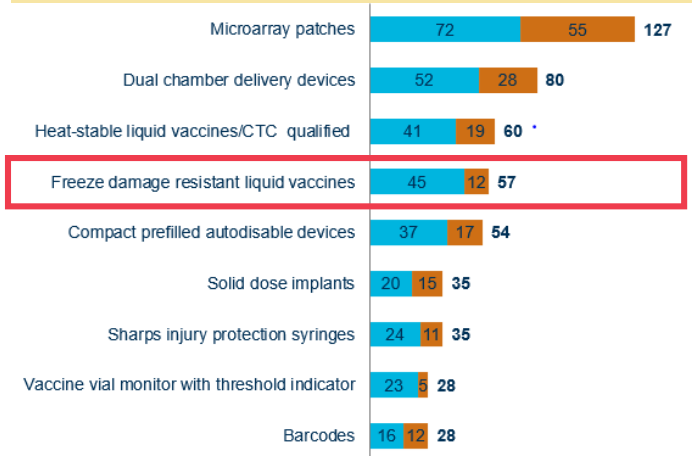
[1] The consultations with the WHO/PATH Delivery Technology – WG were also leveraged to inform the assessment of the commercial feasibility criteria.
[2] ALVAC-HIV + bivalent Subtype C gp120; [3] VAL-506440; [4] RTS,S.

Based on VIPS country feedback[1], FDR liquid formulations are especially valued by immunisation staff

Countries interest

Feedback from in-person country interviews

Innovations' ranking



- **FDR Liquid Vaccines** are **ranked overall # 4 amongst the 9 innovations** assessed in terms of potential impact in helping address immunisation programme challenges; however **immunisation staff ranked it # 3 and decision makers number 6** (based on weighted scores).

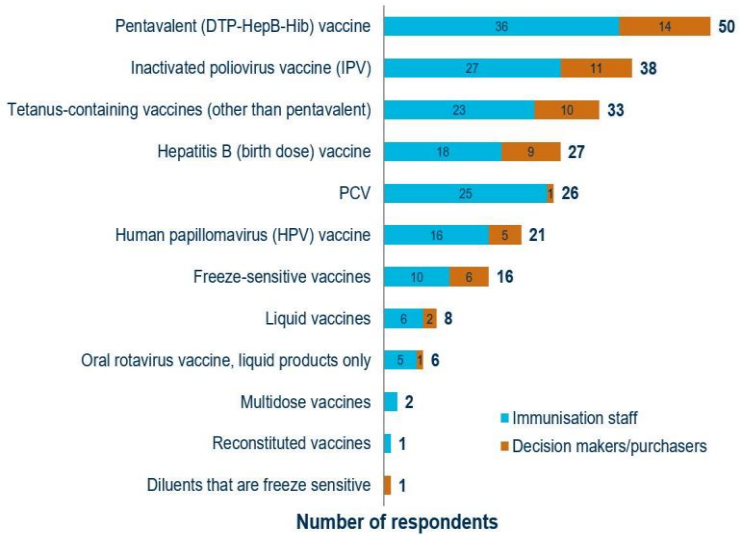
Perceived benefits

- Potential to **reduce vaccine wastage** due to suspected freezing**, save health care work time** and improve **vaccine quality/potency;**
- Makes **logistics/vaccine management** easier and reduces **worry/stress for health care workers.**

Perceived challenges

- Impact on **overall cost** and **price per dose**;
- Immunisation staff: **possibility of mishandling vaccines that are still freeze sensitive** (e.g., if one vaccine brand is freeze damage resistant and another is not), need for **community sensitisation** and **communication,** and **safety concerns regarding the added excipient.**

Priority vaccines for FDR 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

What could VIPS do to accelerate FDR liquid formulations development for LMICs

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 ensuring development of freeze damage resistant formulations**. These could include:

- Supporting/funding activities to **assess the likely acceptability** of vaccines containing **the excipients** to be used, among vaccine manufacturers, purchasers, caregivers etc.
- **Targeted signaling/advocacy** to emphasize the value for novel vaccines or vaccines that undergo reformulation for other reasons; include in **TPPs/PPCs**.
- **Identify the best opportunities** to apply the **innovation and market shaping** to incentivise manufacturers to develop freeze damage resistant formulations for second generation products for priority vaccines.

Alternatively, VIPS could highlight the problem of vaccine freeze exposure and **focus attention on other measures to address the problem**, e.g., improved cold chain equipment, training, and temperature monitoring.

Risks of not prioritising FDR liquid formulations through VIPS

- Vaccine manufacturers are not likely to adopt freeze damage resistant formulations even when opportunities arise to do so for pipeline and reformulated vaccines, and the innovation may **never be brought to market**.