Freeze Damage Resistant Liquid Formulations

SECTION ONE: Vaccine compatibility and problem statements addressed by the innovation

Technology overview:

Many vaccines are freeze-sensitive, including those containing aluminium adjuvants. When vaccines containing aluminium adjuvant are frozen, the antigen-adjuvant particles agglomerate and sediment which results in the irreversible loss of potency. Developing novel freeze stable formulations using different excipients could prevent agglomeration and stabilize the potency of vaccines. The addition of excipients such as glycerin, polyethylene glycol 300, or propylene glycol (PG) have been demonstrated to reduce the freeze sensitivity of hepatitis B vaccine (1) and other vaccines containing aluminum adjuvant including diphtheria, tetanus and pertussis (DTP); and pentavalent (hepatitis B, DTP, *Haemophilus influenza* type b) vaccines (2). Testing and pre-clinical studies using these excipients have been conducted with hepatitis B, pentavalent, diphtheria, tetanus toxoid and pertussis vaccines, but overall, the approach is at an early phase of development.

Summary of innovation applicability to vaccines:

This innovation applies only to freeze-sensitive liquid vaccines and diluents, especially those containing aluminium adjuvants. The innovation addresses the issues of vaccine freeze-damage leading to delivery of sub-potent vaccine and suspected vaccine freeze-damage leading to vaccine wastage. In the VIPS Phase II online survey of country stakeholders, vaccine freeze sensitivity was rated as the top problem for hepatitis B, human papillomavirus, inactivated poliovirus, and pentavalent vaccines; and the fifth most important problem for typhoid conjugate vaccine. The innovation is complex to apply to existing vaccines, requiring novel formulation development, characterization and immunobridging, so is best applied to pipeline freeze-sensitive vaccines during product development and existing freeze-sensitive vaccines that are undergoing reformulation for other reasons.

Problem statements to be addressed:

The problem statement that can be applied to each vaccine which could potentially be addressed by freeze damage resistant formulations is presented in Table 1. The key properties of freeze damage resistant liquid formulations that are relevant to these problem statements are:

- **Vaccine ineffectiveness/wastage due to freeze exposure:** The innovation addresses the issues of vaccine freeze-damage leading to delivery of sub-potent vaccine and suspected vaccine freeze-damage leading to vaccine wastage.

Table 1: Profile of VIPS priority[a] vaccines to be assessed for use with the innovation and the comparator presentations[b]

Vaccines	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[c]	Comparator dose(s) per container
Licensed vaccines							
Pentavalent (Diphtheria tetanus pertussis hepatitis B haemophilus inflluenzae type B inactivated poliovirus; DTP, HepB, Hib) [d]	Inactivated subunit plus polysaccharide-protein conjugated vaccine (PS-PCV)	Liquid	Yes (Aluminium -salt based)	Yes	IM	• **Vaccine ineffectiveness/wastage due to freeze exposure** • Vaccine ineffectiveness/wastage due to heat exposure • Reduced acceptability due to painful administration • Cold chain requirements during outreach • Contamination risk due to multi-dose vial	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S
Hepatitis B (birth dose)[d]	Sub-unit	Liquid	Yes (Aluminium -salt based)	Yes	IM	• **Vaccine ineffectiveness/wastage due to freeze exposure** • Vaccine ineffectiveness/wastage due to heat exposure • Cold chain requirements during outreach • Difficult preparation requiring trained personnel • Reduced acceptability due to painful administration	SDV or 10-dose vial; IM injection with an AD N&S.
Human papillomavirus (HPV)[d]	Sub-unit	Liquid	Yes (Aluminium -salt based)	No	IM	• **Vaccine ineffectiveness/wastage due to freeze exposure** • Reduced acceptability due to painful administration • Cold chain requirements during outreach	SDV or 2-dose vial and delivery by IM injection with an AD N&S.

[a] A process was developed to identify, mapped based on route, presentation and delivery strategy and the final selection of the 17 VIPS priority vaccines was based on defined inclusion and exclusion criteria to ensure a list of licensed vaccines that are WHO PQ'd, GAVI funded and UNICEF procured are included, as well as pipeline candidate vaccines. A range of vaccine families were selected based on vaccine platform, route and vaccine presentation to verify that evaluating one antigen will be representative of the others and innovations for one family member would be applicable to all. Refer to the document 'Scope of vaccines' for the detailed explanation.

[b] In all cases the comparator is the same vaccine in the same format without the innovation which consists of an additional excipient to protect the vaccine from freeze-damage.

[c] An online survey was conducted to collect information on key vaccine-specific delivery challenges faced by countries that can be addressed by innovations in the scope of VIPS. The survey was completed by 168 global and country level experts across 54 countries conducted in Q4 2019. Participants were provided with a standard list of problem statements for the licensed vaccines analysed through VIPS and top 5 reported challenges per licensed vaccine were selected as 'vaccine problem statements' to be specifically analysed. They are listed in order importance for each vaccine (most important first). Problem statements that could potentially be addressed by the innovation are shown in bold and problem statements for pipeline vaccines are in italics.

[d] Consideration could be given to making the formulations of these vaccines freeze-resistant if reformulation is occurring for other reasons.

Vaccines	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[c]	Comparator dose(s) per container
						• Vaccine ineffectiveness/wastage due to heat exposure • Difficult preparation requiring trained personnel	
Inactivated poliovirus (IPV)[d] *	Whole inactivated	Liquid	No	Yes	IM or ID	• **Vaccine ineffectiveness/wastage due to freeze exposure** • Vaccine ineffectiveness/wastage due to heat exposure • Cold chain requirements during outreach • Reduced acceptability due to painful administration • Negative impact on the environment due to waste disposal practices	• IM (0.5ml/dose): SDV or 10-dose vial • ID (0.1ml/dose): SDV (5 fractional doses) or 5-dose vial (25 fractional doses).
Typhoid (conjugate)	PS-PCV	Liquid	No	Yes**	IM	• Vaccine ineffectiveness/wastage due to heat exposure • Vaccine wastage or missed opportunities due to multi-dose vial • Difficult to deliver vaccine to correct injection depth • Difficult preparation requiring trained personnel • **Vaccine ineffectiveness/wastage due to freeze exposure**	SDV and 5-dose vial
Pipeline vaccines[e]							
Enterotoxigenic *E. coli* (ETEC) (ETVAX)	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized adjuvant	Yes (dmLT, double-mutant heat labile toxin [of ETEC])[f]	No	Oral	• *Difficult preparation requiring trained personnel* • *Reconstitution-related safety issues*	Liquid SDV that requires mixing in a cup with a foil sachet (containing recombinant protein, buffer, adjuvant) and water; and delivery by oral dropper.

[e] *Vaccines included in the 'Pipeline vaccines' section were not approved as of the beginning of the Phase II analysis, therefore the Ebola vaccine although now licensed will be assessed as a pipeline vaccine. Barriers to vaccination for these vaccines were also not evaluated through the online vaccine problem statement survey.*
[f] *Data are lacking on the freeze-sensitivity of candidate ETEC vaccines and dmLT.*

Vaccines	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[c]	Comparator dose(s) per container
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)[g]	Heterologous prime-boost. Live attenuated recombinant viral vector prime + recombinant protein booster	Lyophilized prime and liquid booster (gp120)	Yes (MF59 [oil-in-water emulsion]) (recombinant protein booster)	Not known	IM	• *Difficult preparation requiring trained personnel* • *Reconstitution-related safety issues*	As still in Phase 2b/3, assume SDV
Influenza (pandemic, VAL-506440)	Nucleic acid	Liquid	No	Not known	IM	• *Not known* • *Possibly: need to deliver the vaccine to the correct injection depth.*	SDV
Malaria (RTS,S)	Recombinant protein	Lyophilized vaccine; adjuvant in diluent	Yes (AS01E [QS21 + MPL] in diluent)	Not known	IM	• *Difficult preparation requiring trained personnel*	Dry (vaccine) SDV and liquid (adjuvant/diluent) SDV clipped together

* SDV if doses given IM; will be MDV if doses given ID.

** Must be discarded after 6 hours

Table 2: Vaccines not assessed due to technical feasibility[h]

Vaccine categories	Examples	Vaccine type	Adjuvant	Preservative	Route	Rationale
Lyophilized vaccines	Measles rubella (MR)	Live attenuated	No	No	SC	
	Rabies	Whole-inactivated	No	No	IM or ID	

[g] *Termination of the phase 2b/3 trial of this vaccine was announced in February 2020 (https://www.niaid.nih.gov/news-events/experimental-hiv-vaccine-regimen-ineffective-preventing-hiv). A similar heterologous prime-boost HIV vaccine (Ad26.Mosaic4.HIV + cladeC/Mosaic gp140 vaccine) is still in late stage trials (NCT02935686). Although this is based on a different virus vector and subunit protein, and some of the details of the assessments might be different, the overall challenges facing this type of vaccine (heterologous prime-boost) are the same, so the assessment were not re-run with Ad26.Mosaic4.HIV + clade C/Mosaic gp140 vaccine.*

[h] *Vaccines not assessed were excluded on the basis of lack of applicability of the vaccine with the innovation.*

Vaccine categories	Examples	Vaccine type	Adjuvant	Preservative	Route	Rationale
	Respiratory syncytial virus (RSV) (pre-fusion F protein)	Subunit	No	Not known	IM	Not freeze-sensitive
	Yellow fever	Live-attenuated	No	No	SC	
	Mycobacterium tuberculosis (M.tb) (VPM1002)	Live attenuated	Unknown	No	ID	
Liquid vaccines that are not freeze sensitive	Rotavirus[i]	Live attenuated virus	No	No	Oral	
	Ebola (recombinant vesicular-stomatitis virus, Zaire Ebola virus) (rVSV-ZEBOV)	Live vector	No	No	IM	
Lyophilized vaccines with diluents containing adjuvant	Meningitis A (MenAfriVac)	PS-PCV	Yes, alum in diluent	Yes**	IM	While the meningitis vaccine diluent is freeze-sensitive, it is not stored in the cold chain. It can be stored at temperatures below 40°C.

SECTION TWO: Assessment of combined vaccine-innovation products against a comparator

Note: All indicators in Phase I have also been assessed in Phase II.

1.1 Criteria on health impact

Indicator: Vaccine efficacy

Score legend: Green: Better than the comparator (The innovation improves vaccine efficacy); White: Neutral, no difference with the comparator; Red: Worse than the comparator (The innovation reduces vaccine efficacy); N/A: the indicator measured is not applicable for the innovation; Grey: no data available to measure the indicator.

[i] GlaxoSmithKline. Rotarix [package insert]. Brentford, PA: GSK; 2016. https://extranet.who.int/gavi/PQ_Web/FormAttachment.aspx?ID=2358

Table 3

Parameter assessment		
Vaccines	***Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	There is no clinical evidence that the innovation improves efficacy for any vaccine.	No data

Indicator: Vaccine effectiveness

*Score legend: Green: **Better** than the comparator (The innovation improves vaccine effectiveness); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator(The innovation decreases vaccine effectiveness); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 4

Parameter assessment		
Vaccines	**Parameter:** ***Does the innovation improve vaccine effectiveness as per the following parameters based on field or other evidence?*** ○ ***Cases averted*** ○ ***Outpatient visits averted*** ○ ***Hospitalisations averted*** ○ ***Deaths averted*** ○ ***Vaccine doses given within the recommended age range (timeliness of vaccination)***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	No effectiveness data for any of the vaccines assessed	No data

Indicator: Ability of the vaccine presentation to withstand heat exposure[j,k]

Score legend: Green: Better than the comparator (The innovation includes features that may increase heat stability or likely to enable CTC qualification ; White: Neutral, no difference with the comparator (The innovation has the same heat stability and/or CTC qualification as the current vaccine) ; Red: Worse than the comparator (The innovation

[j] *Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing*
[k] *Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.*

includes features that may decrease heat stability or less likely to enable CTC qualification); N/A: the indicator measured is not applicable for the innovation; Grey: no data available to measure the indicator.

Table 5

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?* [l]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?* [m]	*Does the innovation paired with the vaccine improve heat stability?*
Pentavalent (Liquid SDV or 10-dose vial)	Routine	No. VVM 14	No data. Unlikely given the heat stability of current products.	No, unless other routine vaccines that it is co-administered with are also qualified for CTC use.	No data. **No data**
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	Health facilities Outreach Home births	No. VVM30	Yes. CTC qualification in process for one or more vaccines.	Yes. For birth-dose outreach to homes and for storage at remote health facilities without cold chain.[n]	No data. **No data**
HPV (liquid SDV or two-dose vial)	Outreach to schools and communities	No. VVM30	Quadrivalent HPV vaccine (Merck) is qualified for CTC use (up to 3 days, below 42°C).[o]	Yes. For outreach to schools and communities.[p]	No data. **No data**

[l] *This parameter is not used for scoring purposes, it is contextual/background information.*
[m] *Vaccines used only as part of a routine schedule, involving joint delivery with other vaccines which are not thermostable, are not currently a priority for CTC.*
[n] WHO, PATH. *Controlled Temperature Chain: Strategic Roadmap for Priority Vaccines 2017–2020.* Geneva: WHO; 2018. https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1.
[o] WHO website. WHO prequalified vaccines page. Type: Human Papillomavirus (Quadrivalent). Commercial Name: Gardasil. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178. Accessed February 29, 2020.
[p] WHO, PATH. *Controlled Temperature Chain: Strategic Roadmap for Priority Vaccines 2017-2020.* Geneva: WHO; 2017. https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1.

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)? [l]*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)? [m]*	*Does the innovation paired with the vaccine improve heat stability?*
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No. VVM 7	No data. Unlikely given the heat stability of current products.	Yes, for use in campaigns	No data. **No data**
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	No. VVM 30	Yes. Likely given the heat stability of current products.	Yes. For school and community-based vaccination and outbreak response (3).	No data. **No data**
ETEC (ETVAX) (Liquid SDV)	Routine vaccine that is likely to be delivered in areas of high endemicity	No data.	No data.	No, unless other routine vaccines that it is co-administered with are also qualified for CTC use.	No data. **No data**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	No data.	No data.	Yes. For outreach and campaigns.	No data. **No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data.	No data.	Yes, for both use case scenarios.	No data. **No data**

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?* [l]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?* [m]	*Does the innovation paired with the vaccine improve heat stability?*
Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	Routine and Campaign use in areas of high endemicity.[q]cc	No. VVM14 likely.	No data.	Yes. For campaign use.[r]	No data. **No data**

Indicator: Ability of the vaccine presentation to withstand freeze exposure[s]

*Score legend: Green: **Better** than the comparator (The innovation includes features that may increase freeze resistance); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator (The innovation includes features that may decrease freeze resistance); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 6

Parameter assessment		
Vaccines	***Does the innovation paired with the vaccine prevent damage due to freeze exposure?***	**Overall score**
Pentavalent (Liquid SDV or 10-dose vial)	There is preclinical and laboratory evidence demonstrating that the freeze-resistant formulation approach prevents freeze-damage to components of pentavalent vaccines (4)(5)(6)(7).	**Better**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There is preclinical and laboratory evidence demonstrating that the freeze-resistant formulation approach prevents freeze-damage to hepatitis B vaccines (4)(5)(6).	**Better**

[q] WHO. *WHO Preferred Product Characteristics (PPC) for Malaria Vaccines*. WHO/IVB/14.09. Geneva: WHO; 2014. https://apps.who.int/iris/bitstream/handle/10665/149822/WHO_IVB_14.09_eng.pdf?sequence=1

[r] WHO. *WHO Preferred Product Characteristics (PPC) for Malaria Vaccines*. WHO/IVB/14.09. Geneva: WHO; 2014. https://apps.who.int/iris/bitstream/handle/10665/149822/WHO_IVB_14.09_eng.pdf?sequence=1

[s] *Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing*

Parameter assessment		
Vaccines	***Does the innovation paired with the vaccine prevent damage due to freeze exposure?***	**Overall score**
HPV (SDV or 2-dose vial)	There is preclinical and laboratory evidence demonstrating that the freeze-resistant formulation approach prevents freeze-damage to other freeze-sensitive vaccines containing aluminium adjuvants (4)(5)(6)(7). It is likely therefore that they will protect HPV vaccines, but no data exist.	**No data**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**
Typhoid conjugate (Liquid SDV or 5-dose)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**
ETEC (ETVAX) (Liquid SDV)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**
Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent)	While the freeze-resistant formulation approach may protect these freeze-sensitive vaccines from freeze-damage, no evidence exists.	**No data**

1.2 Criteria on coverage and equity

Indicator: Number of fully or partially immunised (relative to target population)[t]

*Score legend: Green: **Better** than the comparator (The innovation increases the overall coverage); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator (The innovation decreases the overall coverage); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 7

Parameter assessment		
Vaccines	***Does the innovation improve the overall coverage for the vaccine within a target population for one or all doses?***	**Overall Score**
All applicable freeze-sensitive vaccines and diluents	No data for any of vaccines assessed.	**No data**

Indicator: Ease of use from clinical perspective based on product attributes[u]

*Score legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[t] *For these indicators, we expect that for most of the innovations there will be no available data, therefore the score will be 'no data available'. However, when this data is available, it will be important data that should be used for the assessment*

[u] *Ease of use also affects timeliness of vaccination (vaccine doses given within the recommended age range), however it was decided that timeliness of vaccination should be captured under vaccine effectiveness based on country data.*

Table 8

Parameter assessment						
Vaccines	***Does the innovation avoid reconstitution and is that an improvement?***	***Does the innovation require fewer vaccine product components?***	***Does the innovation require fewer preparation steps and less complex preparation steps?***	***Does the innovation improve dose control?***	***Does the innovation improve targeting the right route of administration (accuracy in terms of route and/or depth of injection)?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents.	No difference. The innovation and comparator(s) are liquid vaccines that do not require reconstitution	The innovation is a liquid formulation similar to the comparator so does not impact these parameters, and there is no change relative to the comparator.				**Neutral**
	Neutral	**Neutral**				

Indicator: Ease of use based on ability of a lesser trainer person to administer the vaccine or self-administration

*Score legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 9

Parameter assessment				
Vaccines	**Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?**	***Does the innovation enable a lesser trained person (e.g. caregivers/parents/lesser trained personnel) to administer the vaccine?***	***Does the innovation enable self-administration?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents.	The innovation is for use with liquid formulations only and altering the freeze resistant properties of these vaccines will have no impact on these parameters, similar to the comparator.			**Neutral**
	Neutral			

Indicator: Ability to facilitate dose sparing

*Score legend: Green: **Better** than the comparator (The innovation improves dose sparing); White: **Neutral**, no difference with the comparator (The innovation has the same ability to facilitate dose sparing as the comparator); Red: **Worse** than the comparator (The innovation does not improve dose sparing and a higher antigen dose is required); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 10

Parameter assessment		
Vaccines	***Does the innovation improve dose sparing of the vaccine?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	The innovation is a liquid formulation only and altering the freeze resistant properties of the vaccine will have no impact on dose sparing, similar to the comparator.	**Neutral**
	Neutral	

Indicator: Availability of the innovation in a single-dose presentation or multi-dose with preservative to avoid missed opportunities and reduce vaccine wastage.

*Score legend: Dark Green: **Considerably better,** The innovation is available in a much improved presentation from the perspective of missed opportunities and reducing vaccine wastage (for example, a single dose presentation compared to a multidose presentation without preservative); Green: **Better** than the comparator, The innovation is available in an improved presentation from the perspective of missed opportunities and reducing vaccine wastage (for example, a single dose presentation compared to a multidose presentation with preservative); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator (The innovation is not available in an improved presentation from the perspective of missed opportunities and reducing vaccine wastage); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

***Note:* All SDV comparators will score neutral compared to an innovation that is a single-dose presentation**

Table 11

Parameter assessment		
Vaccines	***Is the innovation available in a single-dose presentation or multi-dose with preservative to avoid missed opportunities (e.g., due to reluctance to open a MDV) and reduce vaccine wastage?*** ***(State whether the comparator is SDV or MDV)***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	The innovation can be used with liquid vaccines in SDV and MDV. While data are lacking regarding its effect on preservatives, it is extremely unlikely that the innovation would be applied to a vaccine if it negatively affected preservative properties. Therefore, it is expected to be similar to the comparator.	**Neutral**
	Neutral	

Indicator: Acceptability of the vaccine presentation and schedule to patients/caregivers

*Score legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 12

Parameter assessment				
Vaccines	***Does the innovation include features that may improve pain experienced by the recipient following vaccination?***	***Does the innovation include features that may improve perception of ease of administration (i.e. convenience for the vaccinees/caregivers)?***	***Does the innovation include features that may improve/impact any other benefit related to acceptability by vaccinees/caregivers?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	The innovation affects the formulation of liquid vaccines only and has not yet been tested in clinical studies. While the excipients used are included in many injectable products, data do not exist on whether or not they might impact pain following vaccination.	The innovation affects the formulation of liquid vaccines only so should not impact perceptions about ease of administration, which is no different to the comparator.	Vaccinators and recipients may become aware of the added excipient and/or freeze resistance properties of the vaccine by reading the product insert. It is unknown whether the freeze resistant benefit or the excipient used will affect their perception of the acceptability of the vaccine either positively or negatively. Therefore, it is rated similar to the comparator.	**Neutral**
	No data	**Neutral**	**No data**	

Indicator: Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities

*Score legend: Green: **Better** than the comparator for one of the parameters; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator for one of the parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 13

Parameter assessment			
Vaccines	***Does the innovation require fewer components?***	***Or does the innovation include labelling that facilitates product tracking?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	The innovation does not affect the number of components. Improving the freeze resistance of the vaccine does not impact the vial presentation or delivery device, so the number of components remain unchanged and there is no change relative to the comparator.	The innovation does not impact labelling that facilitates product tracking.	**Neutral**
	Neutral	**N/A**	

1.3 Criteria on safety

Indicator: Number of vaccine product-related adverse events following immunisations[v]

*Score legend: Green: **Better** than the comparator (The innovation decreases the frequency of serious AEFIs); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator (The innovation increases the frequency of serious AEFIs); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 14

Parameter assessment		
Vaccines	***Does the innovation reduce the frequency of serious AEFIs ?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	No data for any of the vaccines assessed	**No data**

Indicator: Likelihood of contamination and reconstitution errors

(This indicator is further measured in Phase 2 only if the comparator is a MDV)

*Score legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[v] *For these indicators, we expect that for most of the innovations there will be no available data, However, when this data is available, it will be important data that should be used for the assessment*

Table 15

Parameter assessment							
Vaccines	***Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?***	***Does the innovation reduce the potential risk of reuse of delivery technology?***	***Does the innovation reduce the risk of use of nonsterile components?***	***Does the innovation reduce the risk of contamination while filling the delivery device?***	***Does the innovation require fewer preparation steps and less complex preparation steps)?***	***Does the innovation reduce the likelihood of using an incorrect diluent during reconstitution?*** [w]	***Overall score***
All applicable freeze-sensitive vaccines and diluents	The innovation has no impact on contamination risk for liquid vaccines as preparation of these vaccines does not require reconstitution. The vaccines with the innovation are prepared identically to the relevant comparator(s).	Contamination risk based on the reuse of the delivery device would be no different to the comparator.	Contamination risk based on use of nonsterile components would be no different to the comparator.	Contamination risk during filling the device would be no different to the comparator.	Contamination risk based on the preparation steps would be no different to the comparator.	The innovation has no impact on the use of an incorrect diluent, as preparation of these vaccines does not require reconstitution. The vaccines with the innovation are prepared identically to the relevant comparator(s).	**Neutral**
	Neutral	**Neutral**	**Neutral**	**Neutral**	**Neutral**	**Neutral**	

Indicator: Likelihood of needle stick injury[x]

*Score legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral,** no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[w] *Incorrect diluent – use of the wrong substance as opposed to the wrong volume of diluent.*
[x] *For all vaccines being assessed the assessment and score of this indicator remains the same as in Phase 1.*

Table 16

Parameter assessment						
Vaccines	***Does the innovation contain fewer sharps?***	***Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?***	***Does the innovation include an auto disable feature and is that better than the comparator?***	***If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?[y]***	***Does the innovation reduce the risk of injury after vaccine administration?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	As the innovation is in a liquid formulation similar to the comparator, it is assumed that the same risk of needlestick injury during vaccine delivery would apply to both and so there is no difference. An improved formulation to impart freeze resistance would have no impact on the actual administration of the vaccine in terms of route, site or depth.					**Neutral**
	Neutral					

1.4 Criteria on economic costs

Indicator: Commodity costs of a vaccine regimen[z] (per person vaccinated)

*Score legend: Red: **Worse than the comparator:** The projected wastage-adjusted total costs for vaccine, delivery device and safety box procurement costs per regimen is increased; White: **Neutral:** no difference with the comparator; Green: **Better than the comparator:** The projected wastage-adjusted total costs for vaccine, delivery device, and safety box procurement costs per regimen is reduced; N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[y] *NOTE: In Phase I, sharps-free innovations were scored as N/A for this feature since SIP features are not applicable. Scoring methodology was revised to reflect the added value of a sharps-free innovation.*

[z] *Vaccine regimen cost refers to the vaccine product and innovation cost times number of doses for complete immunization.*

Table 17

Parameter assessment				
Vaccines	***Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?***	***Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?***	***Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?***	***Score***
All applicable freeze-sensitive vaccines and diluents	No data. It is assumed that manufacturers would not reformulate existing vaccines for the purpose of improving freeze resistance alone and would only add this technology for pipeline vaccines or vaccines being reformulated for other reasons. The excipients are very inexpensive and if added during product development, this would be unlikely to affect the price of the vaccine with the innovation or would minimally increase the vaccine price. (Excipient cost estimated at less than $0.001 per dose if the vaccine is being developed or for second generation products.) Any increase in costs of manufacturing the vaccine could be offset by a likely decrease in closed-vial vaccine wastage due to suspected freeze damage. Therefore, the impact on the wastage adjusted vaccine price is likely neutral.	No change in delivery device costs because the innovation is a change to formulation only, and so the same delivery devices as with the comparator would be used.	No change in safety box purchase costs as the innovation is a change to formulation only, the waste disposal volumes and sharps waste would remain the same as with the comparator.	Overall score: **Neutral** • It is assumed that manufacturers would not reformulate existing vaccines for the purpose of improving freeze resistance alone and would only add this technology for pipeline vaccines or vaccines being reformulated for other reasons. • For pipeline vaccines or vaccines being reformulated for other reasons, the likely change in vaccine purchase cost is minimal as excipients are inexpensive ($0.001) and any price increase would be small and would likely be offset by reduction in programmatic wastage. • No impact on delivery device and safety box purchase costs.
	Neutral	**Neutral**	**Neutral**	

Indicator: Delivery costs of the vaccine regimen (per person vaccinated)[aa]

*Score legend: Red: **Worse than the comparator**: Increases the economic/delivery costs for the vaccine regimen; White: **Neutral:** no difference with the comparator; Green: **Better than the comparator**: Reduces the economic/delivery costs of for the vaccine regimen. N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 18

Parameter assessment					
Vaccines	***Does the innovation reduce the economic costs of cold chain storage and transport for a vaccine regimen?***	***Does the innovation reduce the economic costs of out of cold chain storage and transport for a vaccine regimen including delivery technology(ies)?***	***Does the innovation reduce the economic costs of time spent by the vaccinators when preparing and administering the vaccine?***	***Does the innovation reduce the economic costs of time spent by staff involved in stock management***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	No change in delivery costs as the innovation is a formulation change to liquid vaccines and does not impact any of these delivery costs.				Overall score: **Neutral** • The innovation does not impact the delivery costs.

Indicator: Introduction and recurrent costs of the vaccine regimen (per person vaccinated)

*Score legend: White: **Neutral**: There are no one-time/upfront or recurrent costs and this is not different than the comparator; Red: **Worse** than the comparator: There are one-time/upfront or recurrent costs.*

Table 19

Parameter assessment		Score
Vaccines	***How much are the introduction costs (e.g., purchase of hardware or training of health workers) and/or any recurrent or ongoing costs for this innovation, other than vaccine and delivery technology commodity costs, while taking into account the potential breadth of use of the innovation with other vaccines?***	**Score**
All applicable freeze-sensitive vaccines and diluents	Training costs: The innovation does not require training of staff.	Overall score: **Neutral**
	Neutral	

[aa] *Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing*

Parameter assessment		Score
Vaccines	***How much are the introduction costs (e.g., purchase of hardware or training of health workers) and/or any recurrent or ongoing costs for this innovation, other than vaccine and delivery technology commodity costs, while taking into account the potential breadth of use of the innovation with other vaccines?***	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs with this innovation.	• There are no training, upfront or recurrent costs with this innovation.
	Neutral	

1.5 Criteria on environmental impact

Indicator: Waste disposal of the vaccine regimen (per person vaccinated) and delivery system[bb]

*Score legend: Red: **Worse than the comparator:** Increased volume of medical and/or sharps waste and composed of materials/packaging that does not improve the environmental impact on waste disposal; White: **Neutral:** no difference with the comparator; Green: **Better than the comparator:** Reduced volume of medical and/or sharps waste and composed of materials/packaging that improves the environmental impact on waste disposal; N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator*

Table 20

Parameter assessment				
Vaccine	***Does the innovation reduce the volume of medical (biohazard) disposal waste?***	***Does the innovation reduce sharps waste disposal?***	***Is the innovation, and its packaging, composed of more sustainable materials that improves waste disposal?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	While the innovation may prevent some discards that would otherwise occur due to suspected freeze damage, the primary containers of both used and freeze-damaged vaccines would still need to be disposed of so the volume of this waste would remain the same as with the comparator.	The innovation should not have impact on sharps disposal relative to the comparator as the mode of injection will be the same.	The innovation should not have an impact on the packaging used relative to the comparator	**Neutral**
	Neutral	**Neutral**		

[bb] *This indicator is based on the assessment of waste disposal practices based on the current waste treatment management used in resource-limited settings (incineration/disinfection).*

SECTION THREE: Assessment of feasibility for vaccine innovation product development, without comparator

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity[cc]

The assessments in Table 21 are a top-level assessment of endpoints (clinical efficacy or surrogate markers) that might be used in clinical studies.

- These are based on published data and input from regulatory consultants.
- Only endpoints related to efficacy have been considered.
- For pipeline vaccines, the complexity of clinical development might be independent of whether or not the innovation is used. If the innovation is applied early-enough in the development pathway it should not increase complexity

*Score legend: **High complexity:** Lacks a clear licensure pathway; **Moderate complexity**: Will likely require a phase III efficacy study and it should be possible to run a trial with a clinical endpoint (as case definitions and clinical endpoints have been agreed upon, there is sufficient disease burden to evaluate the effect of the vaccine, and trial sites and capacity are available); **Low complexity**: Will likely require a non-inferiority trial (as there is an available metric of potency (surrogate or correlate of protection (CoP)) to compare with the existing vaccine); **No complexity:** Will likely not require a phase III efficacy study or non-inferiority trial (as there is no change in formulation, route of administration, or delivery mechanism); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 21

Vaccines	*Is the clinical development pathway complex?*	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	Immunological endpoints (serum antibody titres) have been used for non-inferiority trials and approval of pentavalent vaccine in new delivery devices in the past (8). It is assumed that similar endpoints could be used to assess freeze resistant formulations.	**Low complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Seroprotection against hepatitis B is defined as having anti-HBs concentration of ≥ 10 mIU/ml (9). Therefore it should be possible to conduct non-inferiority trials with and immunological endpoint, as was done for approval of new liquid formulations of pentavalent vaccine (which includes a HepB component) (8) and also initial studies of HepB vaccine in Uniject (9). It is assumed that similar endpoints could be used to assess freeze resistant formulations.	**Low complexity**
HPV (SDV or 2-dose vial)	Non-inferiority trials using immunological endpoints (anti-HPV GMTs) have been used to compared 2 vs 3-dose schedules (10). It is assumed that similar endpoints could be used to assess freeze resistant formulations.	**Low complexity**

[cc] *This indicator will be evaluated in an absolute manner, not relative to a comparator*

Vaccines	*Is the clinical development pathway complex?*	Overall score
IPV (IM: Liquid SDV or 10-dose), (ID: Liquid SDV or 5-dose)	Immunological endpoints (serum antibodies) have been used for non-inferiority trials of IPV vaccine (11) or IPV containing hexavalent vaccine (12). It is assumed that similar endpoints could be used to assess freeze resistant formulations.	**Low complexity**
Typhoid conjugate (Liquid SDV or 5-dose)	According to WHO guidelines, immunogenicity endpoints (antibody titres) can and have been used for approval of typhoid conjugate vaccines (13).[dd] It is assumed that similar endpoints could be used to assess freeze resistant formulations.	**Low complexity**
ETEC (ETVAX) (Liquid SDV, lyophilized buffer, lyophilized adjuvant)	Licensure of ETEC vaccines for use in paediatric populations in LMICs will require efficacy studies with clinical endpoints in this population.[ee] There is however, ongoing discussion of which clinical endpoints are the most relevant or useful (14). Trials assessing the effectiveness of the vaccine against traveller's diarrhea and controlled human infection models (CHIMs) might support clinical development of vaccines for licensure in LMICs, and CHIM may be useful in immunobridging between candidates licensed on efficacy data and next generation vaccines with modified formulations (14).	**High complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Ongoing phase III clinical trials of HIV vaccines have prevention of HIV acquisition as the primary endpoint,[ff] and it seems likely that this will be the case for other new HIV vaccines. Attempts to define immunological correlates of protection based on data from earlier phase III trials are ongoing (15).	**High complexity**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	WHO guidelines refer to three different types of pandemic vaccines: vaccines against novel inter-pandemic influenza strains; vaccines for stockpiling; vaccines developed following the outbreak of a pandemic.[gg] The approach for licensure of each of these, particularly the post-pandemic vaccines will differ, but is likely to involve immunological endpoints similar to those used for seasonal influenza vaccines.[gg]	**Low complexity**

[dd] WHO. *Guidelines on the Quality, Safety and Efficacy of Typhoid Conjugate Vaccines.* Geneva: World Health Organization; 2013. https://www.who.int/biologicals/areas/vaccines/TYPHOID_BS2215_doc_v1.14_WEB_VERSION.pdf.

[ee] Bourgeouis L, Center for Vaccine Innovation and Access, PATH. *Status of Vaccine Development for ETEC.* Presented at: WHO Product Development for Vaccine Advisory Committee (PDVAC). June 27, 2018; Geneva, Switzerland. 2018. https://www.who.int/immunization/research/meetings_workshops/24_Bourgeois_ETEC.pdf?ua=1.

[ff] Chinyenze K. HIV Vaccines and monoclonal antibodies—Preparation for success. Policy & access considerations. Presented at: WHO PDVAC, June 26, 2018; Geneva, Switzerland. https://www.who.int/immunization/research/meetings_workshops/15_Chinyenze_HIV_vaccines.pdf?ua=1.

[gg] WHO. Proposed Guidelines: Regulatory Preparedness for Human Pandemic Influenza Vaccines. Presented at: Expert Committee on Biological Standardization, October 8 to 12, 2007; Geneva, Switzerland. https://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf.

Vaccines	*Is the clinical development pathway complex?*	Overall score
Malaria (RTS,S) (Lyophilized SDV or 2-dose vial, recon with diluent)	Key considerations for clinical trial design for different types of malaria vaccine have been summarized.[hh] Currently there are no accepted correlates of protection and next-generation vaccines will require non-inferiority or superiority RCTs with clinical endpoints.[hh]	**High complexity**

Indicator: Technical development challenges

Members of the WHO Delivery Technologies Working group, which is comprised of industry representatives and global health stakeholders, were invited to complete a survey[ii] following a consultation on freeze damage resistant liquid formulations. Ten member organizations responded to the survey and 6 member organizations responded to the question on technical challenges. The following challenges were identified as the most important technical challenges facing the development of freeze damage resistant liquid formulations (most frequently identified challenges first):

- Performing the studies required to determine that the formulations are indeed 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 (5/6)
- The potential impact of the additional excipient(s) on other vaccine components (5/6)
- Obtaining and qualifying excipient(s) for use (4/6)

Additional challenges highlighted by the DTWG:

- Other freeze sensitive vaccines may have yet undiscovered technical challenges.

Score legend: ***High complexity*** *of technical development challenges that are unlikely to be overcome;* ***Moderate complexity*** *of technical development challenges that might be overcome with longer development time and/or more funding;* ***Low complexity*** *of technical development challenges, e.g. applying an existing barcode; N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

[hh] WHO. *WHO Preferred Product Characteristics (PPC) for Malaria Vaccines*. WHO/IVB/14.09. Geneva: WHO; 2014. https://apps.who.int/iris/bitstream/handle/10665/149822/WHO_IVB_14.09_eng.pdf?sequence=1

[ii] *Survey carried out after DTWG telecons on freeze damage resistant liquid formulations held on 14th and 15th January 2020*

Table 22

Parameter assessment		
Vaccines	***How complex are the technical challenges to overcome for successful product development (i.e. difficulties applying the innovation to a combination vaccine, reformulation requirements, vaccine not well characterized, etc)?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	Moderate complexity since applying the innovation affects the vaccine formulation and studies will be required to determine whether the addition of the excipient to render the vaccine freeze-resistant is effective in doing so. In addition, studies will be needed to determine whether the excipient has any negative effects on all relevant vaccine characteristics. This will be more complicated for multivalent vaccines.	**Moderate complexity**

Indicator: Complexity of manufacturing the innovation

The following challenges were identified by members of the WHO Delivery Technologies Working group as the most important manufacturing challenges facing the development of freeze damage resistant liquid formulations (most frequently identified challenges first)[ii]:

- Impact of adding the excipients on the manufacturing process (5/6)
- In the case of reformulation, changes to the product insert and/or label to identify new temperature storage conditions if required (3/6)

Additional challenges highlighted by the DTWG:

- Cost and disruption of re-licensing product

Score legend: ***Very high complexity:*** *Novel manufacturing processes not yet under development;* ***High complexity****: Novel manufacturing processes under development;* ***Moderate complexity****: Novel processes demonstrated at pilot scale ;* ***Low complexity****: Established manufacturing processes, but cannot leverage current capacity ;* ***No complexity:*** *Established manufacturing processes available at commercial scale and access to production facilities if relevant.*

[ii] *Survey carried out after DTWG telecons on freeze damage resistant liquid formulations held on 14th and 15th January 2020*

Table 23

Parameter assessment		
Vaccines	***How complex is the manufacturing process?*** ***(Specify if special materials are used)***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	No complexity as the innovation should not impact the manufacturing process or equipment (materials used are either glycerin, polyethylene glycol 300, or propylene glycol and all are readily available excipients) (1)(4)(6)(7).	**No complexity**

Indicator: Robustness of the innovation-vaccine pipeline

Notes:

In Table 24 it has been assumed throughout that:

- There is one 'developer of the technology' (i.e. freeze damage resistant formulation for use with vaccines – see phase I TN for details): PATH.
- Therefore, on a non-vaccine-specific basis, the number of developers would be assessed as 'not robust'. However, the pipeline is even less robust when considered at the vaccine-specific level.
- Developers have been assessed as to whether or not they have a programme on the specific vaccine in question.
    - Where possible only products that are in 'full' preclinical development (i.e. with a clear path and intention to enter clinical trials) or clinical development have been listed.
    - In cases where studies have been published, and it is possible, but not clear whether the programme will progress to clinical studies, the key publications have been listed.
    - Exploratory, preclinical studies, especially by academic groups have not been included.
- The 'suppliers/manufacturers of the vaccine' parameter focuses on WHO prequalified products (see WHO Prequalified Vaccines Database for details).[kk]

Score legend: ***Not robust:*** *There is only one single technology developer or one single vaccine supplier/manufacturer;* ***Moderately robust:*** *There are multiple technology developers, but each developer's product is unique or there are multiple vaccine manufacturers but each manufacturer product is unique;* ***Highly Robust:*** *There are multiple technology developers and they all use the same device format / manufacturing process or there are multiple vaccine manufacturers and they all produce a similar vaccine; N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

[kk] WHO website. WHO prequalified vaccines page. https://extranet.who.int/gavi/PQ_Web/Browse.aspx?nav=3. Accessed February 29, 2020.

Table 24

Vaccines (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Pentavalent (Liquid SDV or 10-dose vial)	One vaccine manufacturer applied the technology to pentavalent vaccine through preclinical studies, but later dropped the technology due to competing priorities.	There are multiple producers of liquid pentavalent or other DTP-containing vaccines. There are six WHO PQ manufacturers of pentavalent vaccine.
	Not robust	**Highly robust**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	While research has been done with hepatitis B vaccine, there are no vaccine manufacturers currently applying the technology to this vaccine.	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ hepatitis B vaccine.
	Not robust	**Highly robust**
HPV (SDV or 2-dose vial)	No known development programmes.	There are two manufacturers of three licensed HPV vaccines. Both have WHO PQ products. Several other manufacturers are developing HPV vaccines. UNICEF does not expect any new HPV vaccines to be WHO PQ'ed before 2021.[ll]
	No data	**Moderately robust**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No known development programmes.	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV. There are however supply constraints[mm] and only two suppliers to UNICEF (16) New manufacturers of PQ IPV are expected to enter the market from 2020.[nn]
	No data	**Not robust**
Typhoid conjugate (Liquid SDV or 5-dose)	No known development programmes.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ.
	No data	**Not robust**
ETEC (ETVAX) (Liquid SDV)	No known development programmes.	There is only one manufacturer of this particular candidate ETEC vaccine. Other ETEC vaccines have different characteristics.
	No data	**Not robust**

[ll] United Nations Children's Fund (UNICEF). *Human Papillomavirus Vaccine Supply and Demand Update.* Copenhagen: UNICEF; 2018. https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf.

[mm] UNICEF. *Inactivated Polio Vaccine: Supply Update.* Copenhagen: UNICEF; 2019. https://www.unicef.org/supply/files/ipv-inactivated-polio-vaccine-supply-update.pdf.

[nn] UNICEF. *Inactivated Polio Vaccine: Supply Update.* Copenhagen: UNICEF; 2019. https://www.unicef.org/supply/files/ipv-inactivated-polio-vaccine-supply-update.pdf.

Vaccines (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	No known development programmes.	There is only one manufacturer of this particular candidate HIV vaccine. However, a similar candidate vaccine using a different virus vector and recombinant protein in a heterologous prime-boost regimen is in late-stage trials.[oo]
	No data	**Not robust**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No known development programmes.	There are a few developers of mRNA vaccines against pandemic flu: Moderna[pp]; Curevac (universal flu vaccine)[qq] and Vir (universal flu vaccine)[rr]. Other pandemic influenza vaccines have different characteristics.
	No data	**Moderately robust**
Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent)	No known development programmes.	There is only a single developer of RTS,S vaccine. Many other malaria vaccines are in clinical development, but have different characteristics to RTS,S.[ss]
	No data	**Not robust**

1.7 Criteria on commercial feasibility[tt]

The following challenges were identified by members of the WHO Delivery Technologies Working group as the most important commercial challenges facing the development of freeze damage resistant liquid formulations (most frequently identified challenges first) [uu]:

[oo] Chinyenze K. HIV Vaccines and monoclonal antibodies—Preparation for success. Policy & access considerations. Presented at: WHO PDVAC, June 26, 2018; Geneva, Switzerland. https://www.who.int/immunization/research/meetings_workshops/15_Chinyenze_HIV_vaccines.pdf?ua=1.

[pp] Moderna website. Moderna's pipeline page. https://www.modernatx.com/pipeline. Accessed February 29, 2020.

[qq] Curevac website. Our pipeline page. https://www.curevac.com/our-pipeline. Accessed February 29, 2020.

[rr] VIR website. Our focus page. https://www.vir.bio/pipeline/#focus. Accessed February 29, 2020.

[ss] Ockenhouse C. Malari update: PDVAC. Presented at: WHO PDVAC, June 26, 2018; Geneva, Switzerland. https://www.who.int/immunization/research/meetings_workshops/14_Ockenhouse_Malaria.pdf?ua=1

[tt] *These indicators will be evaluated in an absolute manner, not relative to a comparator.*

[uu] *Survey carried out after DTWG telecons on freeze damage resistant liquid formulations held on 14th and 15th January 2020*

- Pricing strategy (5/6)
- Impact of additional excipients on perceived acceptability of vaccine (4/6)
- Market potential and uptake (4/6)
- Identification of priority vaccines to focus on for freeze-damage resistance (2/6)
- Interest from country stakeholders (2/6)

Additional challenges highlighted by the Delivery Technologies Working Group:

- COGS would be negligible, but the cost and disruption of re-licensing the product for a low margin market would likely prevent adoption by most manufacturers.

Indicator: Country interest based on evidence from existing data [vv]

Summary feedback from country consultation:

- Freeze damage resistant liquid vaccines were ranked as the #4 useful innovation.
- Immunisation staff ranked heat stable liquid vaccines/CTC qualified as 4th out of 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's challenges and decision-makers 3rd - based on weighted scores approach.
- Both groups mentioned the benefits of possibility to keep vaccines out of cold chain, reduced wastage due to heat exposure and freeze damage, ability to enable delivery outside health facility, potential of improving coverage, saved health worker time and improved timeliness of dose delivery.
- Both groups raised concerns about the overall cost, complexity of CTC protocol, potential of creating carelessness/confusion in vaccine management and risk of wastage due to heat damage/exceeding CTC duration limit.
- Immunisation staff reported need for community sensitisation, not enough CTC qualified vaccines and risk of reduced acceptability to community as possible challenges.
- Decision makers were also concerned about possible increase in price per dose and training requirements- though 21 out of 28 decision makers interviewed expressed interest in purchasing heat stable liquid vaccines/CTC qualified, 4 stated potential interest, 3 participants said they would not be interested.
- Decision makers provided feedback that number of days out of cold chain needs to be higher 2.
- Immunisation staff suggested to combine heat stable/CTC liquid vaccines with vaccine vial monitors/threshold indicators and that CTC minimum duration should be set at 7 days instead of 3 days. They also inquired whether the vaccine can be returned to the cold chain after CTC use to lengthen the time period before discard.

Score legend: ***No country interest:*** *There is interest from countries but unfavourable in LMIC contexts OR there is no interest;* ***Mixed country interest:*** *Yes there is some interest – but with concerns, e.g. with regards to implementation in LMICs, price/willingness to pay, etc.;* ***Demonstrated country interest:*** *Stakeholders demonstrated interest in LMICs; N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator*

[vv] *As part of VIPS phase II activities, in-depth country consultations were conducted in 6 countries (Ethiopia, Mozambique, Nepal, Senegal, Uganda, Nigeria) gathering information from X respondents representing immunisation staff and decision makers/purchasers on vaccine specific delivery challenges faced by immunization programme and which innovations they perceived could address these challenges and provide additional benefits. The interviews were conducted between November 2019 and February 2020 by PATH and CHAI using semi-structured and open-ended questions.*

Table 25

Parameter assessment		
Vaccines (current presentations)	***Have countries expressed interest to suggest demand for the vaccine-innovation pairing and potential country uptake?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	A 2011-2012 study with 158 immunization stakeholders in Brazil, China, India, Peru, the Philippines, and Tanzania (both mainland and Zanzibar) found that respondents were interested in vaccine products with improved freeze stability characteristics. The majority of those involved in vaccine purchasing indicated they would be willing to pay a US$0.05 premium per dose for a freeze-stable pentavalent vaccine (68%) (17).	**Demonstrated country interest**

Indicator: Potential breadth of the target market

Notes:

- Estimates of market size have been based mostly on information available from WHO, UNICEF or Gavi and are based on number of doses, not the US$ value of the market for the vaccine.
- It is possible that a vaccine-innovation combination would only be used in particular settings. This possibility has not been captured in the table, which is a high-level, superficial assessment of the market.

Scoring legend: ***Small:*** *Limited LMIC market (e.g. use case targeting sub-population or a specific setting)* ; ***Moderate:*** *No HIC market but broad use case scenario in LMIC market (e.g. vaccine available for all immunization settings);* ***Large:*** *Broad use case scenario in both HIC and LMIC markets (e.g. vaccine available for all immunization settings, as well as sub-populations and specific settings);* N/A*: the indicator measured is* ***not applicable*** *for the innovation;* Grey*:* ***no data*** *available to measure the indicator.*

Table 26

Vaccines	***How broad is the potential target market?***	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	Global demand for wP containing pentavalent vaccines has been estimated to be between 300 – 350 M doses per year between 2015 – 2035.[ww] Most HICs and upper-middle income countries use aP, rather than wP-containing vaccines. This should not impact the feasibility of use with the innovation however, but this would need to be confirmed.	**Large**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	WHO recommends a birth dose of hepatitis B. In 2015, 97 (49%) of countries had introduced HepB birth dose, but coverage rates vary and were approximately 35% globally in 2015 (18). Adoption of birth dose by national immunization programmes has not matched the implementation of 3-dose hepatitis B vaccination starting later in infancy (18).	**Large**

[ww] Gavi. *Pentavalent Vaccine Supply and Procurement Roadmap*. Geneva: Gavi; 2016. https://www.gavi.org/sites/default/files/document/penta-roadmap-public-summarypdf.pdf.

HPV (SDV or 2-dose vial)	The WHO recommends that all countries should introduce HPV vaccination into national immunization programmes (19). As of May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV into the national routine immunization schedule. But, despite carrying the greatest share of disease burden, LICs and MICs are lagging in the introduction of HPV vaccine. To date, the majority of the countries have self-procured HPV vaccines (74% in 2017).[xx] A global demand forecast for HPV vaccine has been developed; base demand is estimated to be 55M doses in 2019, reaching ~100M doses in 2025 and stabilizing at ~110M annual doses from 2028 onward.[yy]	**Large**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	The market for IPV is uncertain. IPV was introduced into all routine immunization schedules in 2016. However long-term future markets will depend on the timing of polio-eradication, post-certification polio-vaccination strategies and country preferences for stand-alone IPV vs. IPV in combination vaccines such as hexavalent vaccines. High-income and many middle-income countries have already introduced IPV either as a stand-alone antigen or, more commonly, in a combination vaccine. In 2016, 42 countries reported using the hexavalent (DTaP-Hib-HepB-IPV) combination vaccine and 39 reported using pentavalent (DTaP-Hib-IPV) vaccine in their routine immunization schedules.[zz]	**Moderate**
Typhoid conjugate (Liquid SDV or 5-dose)	Gavi TCV demand forecast for Gavi 73 supported countries has wide range of estimated demand from over 100 million doses per year to as low as 10 million doses per year.[aaa] Factors such as whether the vaccine is used for routine vaccination of infants or vaccination of high-risk infants impact forecast demand by approximately 4-fold (20).	**Small / moderate**
ETEC (ETVAX) (Liquid SDV)	ETEC (and shigella) are among the top five pathogens that cause diarrheal mortality in children under five. However, disease-burden estimates vary (21) and consequently the value proposition for, and therefore future demand and market size for ETEC vaccines is unknown. In addition to use in paediatric populations in LMICs, a vaccine might be used as a travellers' vaccine in HICs and for the military (21).	**Moderate**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	The estimated market size for an HIV vaccine will depend on whether it prevents infection only, or also decrease viral load in those who acquire infection. One model study estimated that demand for vaccines that would prevent infection only was 22–61 million annual doses. Depending on the model inputs, HICs represented ~30% of the market size, but 70% of the value, whereas LICs were ~45% of the market size (17M doses), but only 10% of the value (22).	**Large**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	In theory, in the event of a pandemic, there would be enough vaccine for the entire global population (approximately 7.4 bn). Current manufacturing capacity for influenza vaccines is ~6.3 bn doses, sufficient to immunize 43% of the population if two doses are required (23). However, this assumes production of a pandemic vaccine after the start of a pandemic and once the pandemic strain has been isolated. Other strategies, such as stockpiling vaccine are possible.	**Small**

[xx] *WHO. Global Market Study HPV. 2018. Available at https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary.pdf. Accessed 11/10/2019*

[yy] *WHO. Global Market Study HPV. 2018. Available at https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary.pdf. Accessed 11/10/2019*

[zz] *WHO. Polio post-certification strategy 2018. Available at http://polioeradication.org/wp-content/uploads/2018/04/polio-post-certification-strategy-20180424-2.pdf . Accessed 11/10/2019*

[aaa] Gavi. *Typhoid Conjugate Vaccine (TCV) Supply and Procurement Roadmap.* Geneva: Gavi; 2018. https://www.gavi.org/sites/default/files/document/typhoid-conjugate-vaccine-roadmap--public-summarypdf.pdf.

Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent)	Wide, country-level introduction of RTS,S has not yet been recommended by the WHO (24). Use is likely to be country, setting and population-dependent. Demand forecasts for Gavi countries estimate 665M doses from 2023 – 2035 (peaking at approximately 75M doses per year at the end of this period.[bbb] It is likely there will be a significant non-Gavi market too.	**Moderate**

Indicator: Existence of partnerships to support development and commercialisation[ccc]

*Score legend **for donor and/or stakeholder support column: No interest:** No known donor and/or stakeholder support; **Moderate interest**: Donors and/or stakeholders have expressed interest by funding or providing technical support to research; **Significant interest:** Support from donors and/or stakeholders with intent or mandates to bring the innovation to market; N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

*Score legend **for technology developer and vaccine manufacturer partnership column**: **No interest:** No known technology developer and vaccine manufacturer partnerships, even for early stage work; **Moderate interest**: Technology developer and vaccine manufacturer partnerships have expressed interest by funding, conducting, and/or collaborating on research (e.g., on preclinical or early stage clinical trials for combined vaccine/delivery products or on feasibility or pilot studies for labelling products); **Significant interest:** Technology developer and vaccine manufacturer partnerships are committed to commercialise the innovation-vaccine combination; N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

*Score legend **for overall score**: **No interest:** No known interest from donors/stakeholders AND technology developer/vaccine manufacturer partnerships; **Mixed interest:** Different levels of interest from donors/stakeholders and technology developers/vaccine manufacturer partnerships; **Moderate interest**: Moderate interest from donors/stakeholders AND technology developer/vaccine manufacturer partnerships; **Significant interest:** Significant interest from donors/stakeholders AND technology developer/vaccine manufacturer partnerships; N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 27

Parameter assessment			
Vaccines (current presentations)	***Is there current donor/stakeholder support for the vaccine-innovation pairing?***	***Do partnerships exist between at least one of the technology developers and a vaccine manufacturer or have vaccine manufacturers expressed interest?***	**Overall score**
All applicable vaccines	No. There has been donor support and manufacturers have undertaken laboratory and preclinical research in the past.	Partnerships existed in the past between the technology developer and multiple vaccine manufacturers. However, none exist at present due to perceived lack of demand.	**No interest**
	No interest	**No interest**	

[bbb] Gavi. *Vaccine Investment Strategy Programme and Policy Committee Meeting: Annex C—Malaria*. Geneva: Gavi; 2018. https://www.gavi.org/sites/default/files/document/ppc-meeting-18-19-october-2018---vis-appendix-3--malaria-vaccine-analysispdf.pdf.

[ccc] *If the innovation is a stand-alone device and does not require a partnership with a vaccine manufacturer for commercialization, this indicator is not applicable.*

Indicator: Known barriers to global access to the innovation

Use the legend to assess and score the indicator in an absolute manner (not against a comparator)

Score legend: ***Yes:*** *IP not accessible and no freedom to operate;* ***Mixed:*** *IP and freedom to operate accessible within 5-10 years;* ***No:*** *No known barriers to access and/or IP is in the public domain; N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

Table 28

Parameter assessment		
Vaccines	***Are there known barriers to Global Access to the innovation as applied to the vaccine ?***	**Overall score**
All applicable freeze-sensitive vaccines and diluents	No known barriers. The technology has been placed in the public domain and is freely available to all vaccine developers.	No

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

Inadvertent exposure of vaccines to freezing temperatures is a well-characterized problem in countries at all income levels. Use of freeze-sensitive vaccines in immunization programs is increasing and various studies and observations by cold chain experts have reported that vaccines are frequently exposed to freezing temperatures during storage and transport due to use of domestic refrigerators with poor temperature control, transport of vaccines with ice or unconditioned ice-packs, and/or transport in cold climates (5)(25)(26)(27).

The fact that vaccine immunogenicity can be reduced by freezing has been shown by studies in animals with a number of vaccines containing aluminum salt based adjuvants, including: hepatitis B vaccine (1) (4), acellular pertussis vaccine (in a diphtheria-tetanus-pertussis [DTP] combination) (28), and DTP vaccines (29). Epidemiological evidence of the clinical impact of the use of frozen vaccines is relatively limited due to the difficulties in conducting such studies; however, anecdotal or circumstantial evidence has been reported. Poor seroconversion rates to hepatitis B vaccine in rural versus urban areas of Mongolia (70% and 94%, respectively) have been attributed to inadvertent freezing of the vaccine during transportation, which occurs more frequently during transport to rural areas (30). An increased prevalence of hepatitis B infection has been reported in Mongolian infants vaccinated during the winter months in rural areas, and it has been suggested that this might be attributed to vaccine damage caused by the cold winter temperatures (-15 to -32°C) (31). A recent study in the United States suggests that the reported high incidence (24% of 54 vaccine refrigerators) of freezing in refrigerators throughout Harris County, Texas correlated to increased rates of pertussis (32).

In the VIPS Phase II online survey of country stakeholders, vaccine freeze sensitivity was rated as the top problem for hepatitis B, human papillomavirus, inactivated poliovirus, and pentavalent vaccines; and the fifth most important problem for typhoid conjugate vaccine. Health workers participating in the VIPS Phase II country consultations rated freeze resistant formulations of vaccines highly. While decision makers rated them less highly, the majority were interested in purchasing freeze resistant vaccine products if available.

The innovation offers a straightforward method to prevent damage to vaccines (particularly those with aluminum adjuvants) when freeze exposure occurs with the benefits of helping to ensure delivery of potent vaccines and decreasing vaccine wastage due to suspected freeze exposure (1)(5)(6). It should be noted that other methods to prevent freeze damage to freeze-sensitive vaccines do exist including temperature monitoring during storage and transport, improved cold chain equipment with better temperature control, new freeze-free vaccine carriers and cold boxes (which are becoming increasingly available), and training of health workers and logisticians regarding the need for ice pack conditioning.

SYNERGIES WITH OTHER VIPS INNOVATIONS

This innovation could be synergistically paired with other innovations under review by VIPS that are appropriate for use with liquid vaccines. These include compact filled auto disable devices (CPADs) and dual chamber delivery devices (if they contain a liquid component that would benefit from formulation to avoid freeze sensitivity). The innovation could also be combined with heat stable/controlled temperature chain-qualified formulations and delivered with auto disable sharps injury protection syringes. Lastly, primary containers of freeze resistant vaccines could be labelled with barcodes and combined vaccine vial monitor-threshold indicators.

References

(1) Braun LJ, Jezek J, Peterson S, et al. Characterization of a thermostable hepatitis B vaccine formulation. *Vaccine*. 2009 Jul 23;27(34):4609–4614. doi: 10.1016/j.vaccine.2009.05.069.

(2) Kristensen D, Chen D, Cummings R. Vaccine stabilization: research, commercialization, and potential impact. *Vaccine*. 2011 Sep 22;29(41):7122–7124. doi: 10.1016/j.vaccine.2011.05.070.

(3) Typhoid vaccines: WHO position paper – February 2008. *Weekly Epidemiological Record*. 2008;83(6):49-60. https://www.who.int/wer/2008/wer8306.pdf.

(4) Chen D, Tyagi A, Carpenter J, Perkins S, Sylvester D, Guy M, et al. Characterization of the freeze sensitivity of a hepatitis B vaccine. *Human Vaccines*. 2009;5(1):26–32.

(5) Chen D, Kristensen D. Opportunities and challenges of developing thermostable vaccines. *Expert Review of Vaccines*. 2009;8(5):547–557.

(6) Braun LJ, Tyagi A, Perkins S, et al. Development of a freeze-stable formulation for vaccines containing aluminum salt adjuvants. *Vaccine*. 2009 Jan 1;27(1):72–79. doi: 10.1016/j.vaccine.2008.10.027.

(7) Xue H, Yang B, Kristensen DD, Chen D. A freeze-stable formulation for DTwP and DTaP vaccines. *Human Vaccines and Immunotherapeutics*. 2014;10(12):3607–3610. doi: 10.4161/21645515.2014.980195.

(8) Schmid DA, Macura-Biegun A, Rauscher M. Development and introduction of a ready-to-use pediatric pentavalent vaccine to meet and sustain the needs of developing countries--Quinvaxem®: the first 5 years. Vaccine. 2012 Sep 28;30(44):6241–6248. doi: 10.1016/j.vaccine.2012.07.088.

(9) Otto BF, Suarnawa IM, Stewart T, Nelson C, Ruff TA, Widjaya A, Maynard JE. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. Vaccine. 1999 Oct 14;18(5–6):498–502.

(10) Neuzil KM, Canh DG, Thiem VD, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. *JAMA*. 2011 Apr 13;305(14):1424–1431. doi: 10.1001/jama.2011.407.

(11) Clarke E, Saidu Y, Adetifa JU, et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles-rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. *The Lancet Global Health*. 2016 Aug;4(8):e534–e547. doi: 10.1016/S2214-109X(16)30075-4.

(12) Vesikari T, Rivera L, Korhonen T, et al. Immunogenicity and safety of primary and booster vaccination with 2 investigational formulations of diphtheria, tetanus and Haemophilus influenzae type b antigens in a hexavalent DTPa-HBV-IPV/Hib combination vaccine in comparison with the licensed Infanrix hexa. *Human Vaccines and Immunotherapeutics*. 2017 Jul 3;13(7):1505–1515. doi: 10.1080/21645515.2017.1294294.

(13) Mohan VK, Varanasi V, Singh A, et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clinical Infectious Diseases*. 2015 Aug 1;61(3):393–402. doi: 10.1093/cid/civ295.

(14) Porter CK, Gutierrez RL, Kotloff KL. Clinical endpoints for efficacy studies. *Vaccine*. 2019 Aug 7;37(34):4814–4822. doi: 10.1016/j.vaccine.2019.03.051.

(15) Kim JH, Excler JL, Michael NL. Lessons from the RV144 Thai phase III HIV-1 vaccine trial and the search for correlates of protection. *Annual Review of Medicine*. 2015;66:423-37. doi: 10.1146/annurev-med-052912-123749.

(16) Sutter RW, Cochi SL. Inactivated Poliovirus Vaccine Supply Shortage: Is There Light at the End of the Tunnel? *Journal of Infectious Diseases*. 2019 Oct 8;220(10):1545–1546.

(17) Kristensen DD, Lorenson T, Bartholomew K, Villadiego S. Can thermostable vaccines help address cold-chain challenges? Results from stakeholder interviews in six low-and middle-income countries. *Vaccine*. 2016;34(7):899–904.

(18) Hepatitis B vaccines: WHO position paper—July 2017. *Weekly Epidemiological Record.* 2017;92:369–392.

(19) WHO. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. *Vaccine*. 2017 Oct 13;35(43):5753–5755. doi: 10.1016/j.vaccine.2017.05.069.

(20) Mogasale V, Ramani E, Park IY, Lee JS. A forecast of typhoid conjugate vaccine introduction and demand in typhoid endemic low- and middle-income countries to support vaccine introduction policy and decisions. *Human Vaccines and Immunotherapeutics*. 2017 Sep 2;13(9):2017–2024. doi: 10.1080/21645515.2017.1333681.

(21) Hosangadi D, Smith PG, Kaslow DC, Giersing BK; WHO ETEC & Shigella Vaccine Consultation Expert Group. WHO consultation on ETEC and Shigella burden of disease, Geneva, 6-7th April 2017: Meeting report. *Vaccine*. 2019 Nov 28;37(50):7381-7390. doi: 10.1016/j.vaccine.2017.10.011.

(22) Marzetta CA, Lee SS, Wrobel SJ, Singh KJ, Russell N, Esparza J. The potential global market size and public health value of an HIV-1 vaccine in a complex global market. *Vaccine*. 2010 Jul 5;28(30):4786–4797. doi: 10.1016/j.vaccine.2010.04.098.

(23) McLean KA, Goldin S, Nannei C, Sparrow E, Torelli G. The 2015 global production capacity of seasonal and pandemic influenza vaccine. *Vaccine*. 2016 Oct 26;34(45):5410-5413. doi: 10.1016/j.vaccine.2016.08.019.

(24) WHO. Malaria vaccine: WHO position paper, January 2016 Recommendations. *Vaccine*. 2018 Jun 14;36(25):3576–3577. doi: 10.1016/j.vaccine.2016.10.047.

(25) Kartoglu Ü, Özgüler NK, Wolfson LJ, Kurzatkowski W. Validation of the shake test for detecting freeze damage to adsorbed vaccines. *Bulletin of the World Health Organization*. 2010;88:624–631.

(26) Wirkas T, Toikilik S, Miller N, Morgan C, Clements CJ. A vaccine cold chain freezing study in PNG highlights technology needs for hot climate countries. *Vaccine*. 2007;25(4):691–697.

(27) Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. *Vaccine*. 2007 May;25(20):3980–3986.

(28) Boros CA, Hanlon M, Gold MS, Roberton DM. Storage at -3 degrees C for 24 h alters the immunogenicity of pertussis vaccines. *Vaccine*. 2001;19(25-26):3537–3542.

(29) WHO. The effect of freezing on the appearance, potency and toxicity of adsorbed and unadsorbed DPT vaccines. *Weekly Epidemiological Record.* 1980; 55:385–392.

(30) Edstam JS, Dulmaa N, Tsendjav O, Dambasuren B, Densmaa B. Exposure of hepatitis B vaccine to freezing temperatures during transport to rural health centers in Mongolia. *Preventive Medicine*. 2004;39(2):384–388.

(31) Davaalkham D, Ojima T, Wiersma S, et al. Administration of hepatitis B vaccine in winter as a significant predictor of the poor effectiveness of vaccination in rural Mongolia: evidence from a nationwide survey. *Journal of Epidemiology and Community Health*. 2007;61(7):578–584.

(32) McColloster P, Vallbona C. Graphic-output temperature data loggers for monitoring vaccine refrigeration: implications for pertussis. *American Journal of Public Health*. 2011;101(1):46–47.