Heat stable/Controlled temperature chain (CTC) qualified liquid formulations

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

Technology overview:

Heat stable liquid formulations (such as those incorporating stabilizing agents) enable vaccines to be exposed to high temperatures (e.g., a minimum of 3 days at ≤40°C) without losing their potency and can thus be controlled temperature chain (CTC) qualified.[a] Some formulations require optimized properties (e.g. buffer, pH, salt concentrations and stabilizing excipients) to prevent denaturing of proteins and reduce the occurrence of damaging chemical reactions caused by increasing temperature. Heat-stabilized vaccines will differ in the length of time they can be stored in a CTC and the maximum temperature they can endure while remaining stable and potent, and some vaccines will not be able to be reformulated into heat-stable liquids.

Summary of vaccine and innovation compatibility:

This innovation applies to all vaccines in liquid formulations that are sufficiently heat-stable to enable licensing and World Health Organization (WHO) prequalification approvals for use in a CTC. By WHO's current definition of CTC, the vaccine must be sufficiently heat stable at the end of its shelf life to allow exposure at ambient temperatures not exceeding 40°C for a minimum of 3 days just prior to administration. The assessment of whether this innovation is technically feasible for a specific vaccine type relied on existing stability data. In general, vaccines for which a lyophilised format is the only format available were excluded as they are unlikely to be sufficiently heat-stable in liquid format. Some vaccines that are currently lyophilised were included where there was evidence available that the vaccine could be reformulated into a heat-stable liquid and/or ongoing efforts to do so. An optimistic perspective was taken with some pipeline vaccines that are currently lyophilised or frozen as their heat stability may not yet be optimized and opportunity may yet exist to formulate them as heat stable liquids. In particular:

- Measles-rubella (MR) vaccine is included. While all currently available MR vaccines are lyophilised, research efforts are ongoing to attempt to achieve a vaccine that is a stable liquid suspension (1).[b]
- Meningitis A vaccine is included. While the existing WHO prequalified MenAfriVac is lyophilised, meningitis vaccines are available in liquid format from other manufacturers.[c]

[a] World Health Organization (WHO). WHO website. WHO Controlled temperature chain (CTC): The Controlled Temperature Chain (CTC) Working Group page [publications and guidance]. https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/index1.html. Accessed February 29, 2020.
[b] Personal communication, Bill & Melinda Gates Foundation.
[c] WHO website. WHO prequalified vaccines page. https://extranet.who.int/gavi/PQ_Web/.

- Rabies vaccine is included. While all currently available WHO prequalified rabies vaccines are lyophilised, liquid formulations are available from other manufacturers.[d]
- Ebola vaccine is included. Although the current vaccine is a frozen liquid, the stability has not yet been optimized.
- ETEC vaccine candidate, ETVAX, is included. It may be possible to reformulate the current three component vaccine as a single-component liquid oral vaccine.[e]

WHO has prioritized vaccines used in campaigns and special strategies for CTC use. This is because the benefits of CTC cannot be fully realized for routine vaccines that are stored and transported together unless all these vaccines are qualified for CTC use. Table 1 includes background information on the vaccines being analysed for compatibility with the heat stable/CTC qualified liquid formulation innovation. It also includes information on both WHO's current priority vaccines for CTC qualification[f] and additional vaccines that were recently prioritized at a December 2019 meeting of the WHO-led CTC working group.

Problem statements addressed by the innovation:

This innovation can potentially address the following public health issues when applied to compatible vaccines:

- **Vaccine ineffectiveness/wastage due to heat exposure**: The innovation will improve heat stability and the ability of the vaccine to withstand accidental or intentional (i.e., CTC use) heat exposure. The degree of heat stability will be vaccine- and formulation-dependent.
- **Vaccine ineffectiveness/wastage due to freeze exposure:** By reducing the need to be stored in the cold chain, the use of vaccines in a CTC reduces the likelihood of freeze-sensitive vaccines being exposed to freezing temperatures.
- **Cold chain requirements during outreach**: CTC-qualified vaccines may decrease logistical requirements for health workers as they do not need to prepare, condition, or transport ice packs when vaccines are used in a CTC for outreach. Without the constraints of the cold chain, vaccines can be transported over longer distances. These benefits can be realized for vaccines that are used in campaigns or special strategies. They can only be realized for other routine vaccines if all vaccines being transported and stored together are also CTC-qualified.
- **Difficult preparation requiring trained personnel**: Heat stable liquid presentations offer benefits over those that currently require reconstitution as the vaccine requires no preparation in terms of the need to mix components.

[d] WHO. *Public Assessment Summary Report Rabies Vaccine (Liquid).* Geneva: WHO; 2014. https://www.who.int/immunization_standards/vaccine_quality/pq_273_VPSAR_Rabies_SIIL.pdf.

[e] PATH. *Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries. Summary of Workshop in Geneva from December 12 to 13, 2016.* Seattle: PATH; 2016.

[f] 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.

Table 1: Profile of VIPS priority vaccines[g] to be assessed for use with the innovation[h] and the comparators[i]

Note that this analysis is comparing the innovation (the vaccine in heat stable/CTC liquid format) with the comparators in the same vial size and delivered by the same route.

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[j]	Comparator dose(s) per container
Licensed vaccines							
Pentavalent (Diphtheria tetanus pertussis hepatitis B haemophilus inflluenzae type B inactivated poliovirus; DTP, HepB, Hib) Not currently a WHO priority for CTC	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) Existing WHO priority vaccine for CTC	Subunit	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	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S.

[g] *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.*

[h] *Vaccines to be assessed were selected on the basis of: 1) Technical applicability of the vaccine with the innovation, 2) Identification of vaccine-specific problem statements and 3) Ability of the innovation to solve vaccine-specific problem statements. The vaccines and problem statements are not listed in any priority order.*

[i] *All comparators chosen are a SDV regardless of whether the current presentation of the vaccine is available as single-dose or not, and if available the most commonly used MDV has been selected.*

[j] *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.*

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[i]	Comparator dose(s) per container
Human papillomavirus (HPV) Existing WHO priority vaccine for CTC	Subunit	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** • **Vaccine ineffectiveness/wastage due to heat exposure** • Difficult preparation requiring trained personnel	SDV or 2-dose vial and delivery by IM injection with an AD N&S.
Measles rubella (MR) CTC working group recommends consideration of this vaccine for CTC use in single dose, dry formats only	Live attenuated.	Lyophilised	No	No	SC	• **Vaccine ineffectiveness/wastage due to heat exposure** • Vaccine wastage or missed opportunities due to multi-dose vial • **Reconstitution related safety issues** • **Cold chain requirements during outreach** • Needle-stick injuries	SDV or 10-dose vial
Meningitis A (MenAfriVac) Legacy vaccine already CTC qualified	PS-PCV	Lyophilised	Yes, in diluent (Aluminium-salt based)	Yes**	IM	• Vaccine wastage or missed opportunities due to multi-dose vial • **Cold chain requirements during outreach** • **Vaccine ineffectiveness/wastage due to heat exposure** • **Reconstitution related safety issues** • Needle-stick injuries	SDV or 10-dose vial
Inactivated poliovirus (IPV)* Not currently a WHO priority for CTC	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).

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[j]	Comparator dose(s) per container
Rabies* CTC working group recommends consideration of this vaccine for CTC in single dose, dry formats only	Whole-inactivated.	Lyophilised	No	No	IM or ID	• **Difficult preparation requiring trained personnel** • **Vaccine ineffectiveness/wastage due to heat exposure** • Reduced acceptability due to painful administration • Vaccine wastage or missed opportunities due to multi-dose vial • Needle-stick injuries	• IM (0.5ml/dose): SDV • ID (0.1ml/dose): SDV (5 fractional doses)
Rotavirus Not currently a WHO priority for CTC	Live attenuated virus	Liquid	No	No	Oral	• **Vaccine ineffectiveness/wastage due to heat exposure** • **Vaccine ineffectiveness/wastage due to freeze exposure** • **Cold chain requirements during outreach** • Negative impact on the environment due to waste disposal practices • Vaccine wastage or missed opportunities due to multi-dose vial	• Liquid single-dose plastic squeeze tube.
Typhoid (conjugate) CTC working group recommends consideration of this vaccine for CTC use	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 or 5-dose vial
Pipeline vaccines[k]							
Ebola (recombinant vesicular stomatitis	Live vector	Liquid, frozen	Not known	Not known	IM	• ***Cold-chain requirements during outreach (vaccine needs to be kept frozen)***	Recently licensed as SDV vial

[k] *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.*

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[j]	Comparator dose(s) per container
virus, Zaire Ebola virus) (rVSV-ZEBOV) CTC working group recommends consideration of this vaccine for CTC use						• ***Vaccine ineffectiveness/ wastage due to heat exposure***	
Enterotoxigenic E. coli (ETEC) (ETVAX) Not currently a WHO priority for CTC	Whole inactivated organism	Liquid vac, lyophilised buffer, lyophilised adjuvant	Yes (dmLT, double-mutant heat labile toxin [of ETEC])	No	Oral	• ***Difficult preparation requiring trained personnel*** • ***Reconstitution-related safety issues***	Currently in phase 2 for travellers and infants: Liquid vaccine in SDV that requires mixing in a cup with buffer (powder), adjuvant (lyophilised) and water; and delivery by oral dropper.
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)[l] CTC working group has deferred a decision on the appropriateness of this vaccine for CTC use	Heterologous live attenuated recombinant viral vector + recombinant protein booster	Lyophilised prime and liquid booster (gp120). Only the liquid booster is considered to be technically feasible.	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

[l] *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.*

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[j]	Comparator dose(s) per container
Influenza (pandemic, VAL-506440) CTC working group recommends consideration of this vaccine for CTC use.	Nucleic acid	Liquid	No adjuvant	Not known	IM	• *Not known* • *Possibly: need to deliver the vaccine to the correct injection depth.*	As still in phase I, assume SDV

* 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[m]

Vaccine	Vaccine type	Formulation	Adjuvant	Preserv-ative	Route	Rationale for exclusion
Yellow fever	Live-attenuated	Lyophilised	No	No	SC or IM	Judged to be too technically difficult to develop a heat stable liquid product.
Malaria (RTS,S)	Recombinant protein	Lyophilised vaccine; adjuvant in diluent	Yes (AS01E [QS21 + MPL] in diluent)	Not known	IM	
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002)	Live attenuated	Lyophilised	No	No	ID	
Respiratory syncytial virus (RSV) (pre-fusion F protein)	Subunit	Lyophilised	No	Not known	IM	

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preserv-ative	Route	Rationale for exclusion
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)	Heterologous live attenuated recombinant viral vector + recombinant protein booster	Lyophilised prime and liquid booster (gp120). The lyophilised prime is not expected to be technically feasible.	Yes (MF59 [oil-in-water emulsion]) (recombinant protein booster)	Not known	IM	

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.

Table 3

Parameter assessment		
Vaccines	**Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?**	**Overall score**
HPV vaccine	The CTC-qualified Gardasil® quadrivalent HPV vaccine and the comparator (non-CTC qualified Gardasil) product are identical formulations. The data to qualify the product for CTC use are based on stability studies.	**Neutral**
All other vaccines assessed	No clinical data available for all other vaccines assessed Two studies in mice showed improved immunogenicity of two experimental thermostable hepatitis B vaccine formulations after storage at 37°C compared to commercially available products (2)(3). However, these data may not be predictive of clinical efficacy improvements	**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	**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**
Hepatitis B (birth dose)	Several studies comparing hepatitis B vaccines stored in the cold chain against the same vaccines stored at ambient temperature (out of cold chain) or high temperatures showed no significant differences in the reactogenicity and immunogenicity of the vaccines based on the temperature storage conditions (4)(5)(6)(7)(8). One study showed that out of cold chain use of the vaccine did increase timeliness of vaccination (9).	**Better**
All other applicable vaccines	No effectiveness data for all other vaccines assessed.	**No data**

Indicator: Ability of the vaccine presentation to withstand heat exposure[n]

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 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.

[n] *Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.*

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)?[o]	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)? [p]	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.	By definition, a heat-stable liquid formulation of pentavalent vaccine would improve heat stability. However, to date there are no known data showing this. **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.[q]	Yes. There is evidence based on the VVM designations for this vaccine type as well as confidential stability data from vaccine manufacturers that this vaccine type is sufficiently heat-stable for CTC qualification. **Better**
HPV (liquid SDV or two-dose vial)		No. VVM30	Quadrivalent HPV vaccine (Merck) is qualified for CTC use. (up to 3 days, below 42°C).[r]	Yes. For outreach to schools and communities.[s]	Yes. One HPV vaccine is already CTC qualified. There are no known data on novel heat-stable formulations of HPV vaccine. **Better**

[o] *This parameter is not used for scoring purposes, it is contextual/background information.*

[p] *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.*

[q] 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.

[r] 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.

[s] 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

MR (Lyophilised SDV or 10-dose)	Routine Special immunization campaigns Outbreaks	No. VVM 14	No data. Unlikely given the heat stability of current products.	Yes. For use in outbreak and campaigns (10).	There are limited data with monovalent measles vaccine showing improved thermostability through reformulation of reconstituted vaccine (1). In this early study, the stability required for CTC use was not achieved however. **Neutral**
Meningitis A (MenAfriVac) (Lyophilised SDV or 10-dose vial)	Campaign settings during initial introduction	No. VVM 30	Yes. MenAfriVac can be used under CTC conditions (up to four days at temperatures not exceeding 40°C).[t]	Yes. For initial campaign use.[u]	No data. Although there are liquid meningitis vaccine products,[v] the comparator is lyophilised and there is evidence that it may be difficult to formulate the vaccine, particularly the Men A component into a heat stable liquid (11). **No data**
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**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	Emergency basis for post-exposure prophylaxis	No. VVM 30	Yes. May be sufficiently heat stable in dry format.	Yes. For storage in remote communities without cold chain, and for emergency outreach for post-exposure prophylaxis.[w]	No data. Although there are liquid rabies vaccine products,[x] the comparator is lyophilised and it may be extremely difficult to apply the innovation to obtain a heat stable liquid **No data**

[t] WHO website. WHO prequalified vaccines page. Type: Meningococcal A Conjugate 10 µg. Commercial Name: Meningococcal A Conjugate MenAfriVac. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=196. Accessed February 29, 2020.

[u] WHO website. Meningococcal meningitis page. https://www.who.int/immunization/diseases/meningitis/en/. Accessed February 29, 2020.

[v] WHO website. WHO prequalified vaccines page. Type: Meningococcal ACYW-135 (conjugate vaccine). Commercial Name: Menactra. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=269. Accessed February 29, 2020.

[w] WHO. *WHO Expert Consultation on Rabies, Third Report.* Geneva: WHO; 2018. WHO Technical Report Series, No. 1012. https://apps.who.int/iris/handle/10665/272364.

[x] WHO. *Public Assessment Summary Report Rabies Vaccine (Liquid).* Geneva: WHO; 2014. https://www.who.int/immunization_standards/vaccine_quality/pq_273_VPSAR_Rabies_SIIL.pdf.

Rotavirus (Liquid SD plastic tube)	Routine	No. VVM 7	No data. Unlikely given the heat stability of current liquid products.	No, unless other routine vaccines that it is co-administered with are also qualified for CTC use.	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 (12).	No data. However, the possibility of CTC qualification is high based on the heat stability of the existing vaccine. **No data**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. Stored as frozen liquid at -80°C to -60°C for long term storage. Can be stored at 2-8°C for no more than two weeks or at room temperature for four hours after thawing.[y]	No data, but unlikely.	Yes. for both use case scenarios.[z]	No data. Although the current vaccine is a frozen liquid, the stability has not yet been optimized. **No data**
ETEC (ETVAX) (Liquid SDV, lyophilised buffer and lyophilised adjuvant))	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	No data.	No data.	Yes. For outreach and campaigns	No data.

[y] Merck. ERVEBO® (Ebola Zaire Vaccine, Live) suspension for intramuscular injection [package insert]. Silver Spring: MD: US Food and Drug Administration; 2019. https://www.fda.gov/media/133748/download.

[z] WHO website. Immunization, Vaccines and Biologicals: WHO Ebola vaccine target product profile page. https://www.who.int/immunization/research/target-product-profile/ebolavaccine/en/. Accessed February 29, 2020.

	susceptible populations				**No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data.	No data.	Yes, for both use case scenarios	Stability studies with an mRNA vaccine from a different manufacturer (Curevac) showed an mRNA vaccine to be stable as a liquid for 1 week at 40°C (13). **Better**

Indicator: Ability of the vaccine presentation to withstand freeze exposure

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**
Freeze-sensitive vaccines: Pentavalent Typhoid, Hepatitis B, HPV, IPV **Freeze-sensitive vaccine candidates:ETEC (ETVAX), HIV (prime and boost), Influenza (mRNA)**	Accidental freezing can result in potency loss for freeze sensitive vaccines such as diphtheria, tetanus, pertussis, liquid *Haemophilus influenza* type b (Hib), hepatitis B, human papillomavirus, and inactivated polio virus (14). The cold chain protects vaccines from heat damage, yet often exposes them to freezing temperatures – especially when vaccines are kept in vaccine carriers or cold boxes with ice or un-conditioned icepacks or in domestic refrigerators. By reducing the need to be stored in the cold chain, a CTC-qualified formulation reduces the likelihood of the vaccine being exposed to freezing temperatures.	**Better**
Non freeze-sensitive vaccines: MR, Meningitis A, Rabies, Rotavirus, Ebola	No data for all other vaccines assessed. While in some cases, the lyophilised or liquid comparator is known to be freeze resistant, it is not clear if the reformulation of the vaccine into a heat stable liquid would alter the freeze resistance of the vaccine.	**No data**

1.2 Criteria on coverage and equity

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

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**
Hepatitis B (birth dose)	There is evidence that storing hepatitis B birth dose vaccine outside of the cold chain increases immunization coverage in health facilities and home births in comparison to vaccine stored in the cold chain (9)(15)(16).	**Better**
All other applicable vaccines	No data for all vaccines assessed.	**No data**

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

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 8

[aa] *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*

[bb] *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.*

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**
Liquid vaccines assessed: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)) (VAL 506440)	No difference. The comparators and the heat stable/CTC vaccine are liquid vaccines that do not require reconstitution.	No difference. The comparators and the heat stable/CTC vaccine equivalent have the same number of components.	No difference. The preparation steps are identical for the comparators and the heat stable/CTC vaccine equivalent.	No difference as the innovation doesn't affect delivery of the vaccine.	No difference as the innovation doesn't affect delivery of the vaccine.	**Neutral**
	Neutral	**Neutral**	**Neutral**	**Neutral**	**Neutral**	

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**
Lyophilised vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Yes. The innovation avoids reconstitution as it is a liquid product while the comparators are lyophilised.	Yes. The innovation requires the liquid vaccine vial and N&S (2 components) while the comparators require a vaccine vial, diluent vial, reconstitution syringe, and N&S (4 components).	Yes. The innovation removes the reconstitution step required for the comparators.	No difference as the innovation doesn't affect delivery of the vaccine.	No difference as the innovation doesn't affect delivery of the vaccine.	**Better**
	Better	**Better**	**Better**	**Neutral**	**Neutral**	
ETEC (ETVAX) with 5 components (Liquid SDV, lyophilised buffer and lyophilised adjuvant)	Yes. The innovation avoids reconstitution as it is a liquid product while the comparator includes three components that must be reconstituted.	Yes. The innovation requires only the liquid vaccine in a primary container with an oral dropper (2 total components) while the comparator consists of 3 vaccine components, a cup, and an oral dropper (5 total components).	Yes. The innovation circumvents the need to mix the vaccine components	No difference as the innovation doesn't affect delivery of the vaccine.	No difference as the innovation doesn't affect delivery of the vaccine.	**Better**
	Better	**Better**	**Better**	**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	**Assumed use case**	**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. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?***	**Does the innovation enable self-administration?**	**Overall score**
Pentavalent (Liquid SDV or 10-dose vial)	Routine	No, as this is a routine vaccine.	No. It does not simplify the task of delivering an injection and therefore is no different than the comparators. **Neutral**	Not applicable. This is a childhood vaccine so self-administration is not a possibility. **Not applicable**	**Neutral**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Health facilities Outreach Home births	Yes. The birth dose is often provided by outreach to homes or health facilities lacking cold chain and could be provided by midwives or traditional birth attendants.	No. Same assessment as for pentavalent vaccine. **Neutral**	Not applicable. This is a birth dose vaccine so self-administration is not a possibility. **Not applicable**	**Neutral**
HPV (SDV or 2-dose vial)	Outreach to schools and communities	Yes. HPV vaccine is often provided by outreach to schools and communities and could potentially be delivered by lesser trained personnel in these settings.	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**
Measles rubella (Lyophilised SDV or 10-dose)	Routine Special immunization campaigns Outbreaks	Yes. Would be beneficial if lesser trained personnel could deliver the vaccine in campaign/outbreak settings.	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**
Men A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	Campaign settings during initial introduction	Yes. During initial introduction and it would be beneficial if lesser trained personnel could deliver the vaccine in these campaign settings.	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**

Vaccines	Parameter assessment				
	Assumed use case	**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. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?***	**Does the innovation enable self-administration?**	**Overall score**
Polio (IPV) (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No, in the case of routine vaccine. Can be delivered as a co-formulation with other routine IM vaccines.[cc] Yes, it would be beneficial if lesser trained personnel could deliver the vaccine in campaign/ outbreak settings	No. Same assessment as for pentavalent vaccine. **Neutral**	Not applicable. This is a childhood vaccine so self-administration is not a possibility. **Not applicable**	**Neutral**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	Emergency basis for post-exposure prophylaxis	Yes. Rabies vaccine is composed of multiple immunizations that are needed on a specific schedule on post-exposure (17). Self-administration or administration by lesser-trained HCWs could enable administration of post-exposure vaccination booster doses without the need to return to the health facility. Recent simplification of PEP ID regimens mean that booster doses are only required at day 7, with an optional boost at day 28 (18,19). Rabies vaccine can also be given via outreach to at-risk populations for pre-exposure prophylaxis (17).	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**
Rotavirus (Liquid SD plastic tube)	Routine	No, as this is a routine vaccine (20). Already in an easy to administer presentation that would facilitate administration by a lesser trained person.	No. However, both the innovation and comparator could potentially be delivered by lesser trained personnel as this is an oral vaccine. **Neutral**	Not applicable. This is a childhood vaccine so self-administration is not a possibility. **Not applicable**	**Neutral**

[cc] Polio Global Eradication Initiative website. IPV page.http://polioeradication.org/polio-today/polio-prevention/the-vaccines/ipv/. Accessed February 29, 2020.

	Parameter assessment				
Vaccines	**Assumed use case**	**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. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?***	**Does the innovation enable self-administration?**	**Overall score**
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	Yes. Delivery by lesser-trained personnel could facilitate catch-up vaccination and vaccination in response to confirmed outbreaks of typhoid fever and in humanitarian emergencies (21).	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. The ability to deliver the vaccine by lesser trained personnel could help facilitate outbreak response.[dd]	No. Same assessment as for pentavalent vaccine. **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**
ETEC (ETVAX) (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Routine vaccine that is likely to be delivered in areas of high endemicity	No, as this is a routine vaccine that is likely to be delivered with other routine vaccines.[ee]	No. However, both the innovation and comparator could potentially be delivered by lesser trained personnel as this is an oral vaccine, though the comparator does require mixing. **Neutral**	Not applicable. This is a childhood vaccine so self-administration is not a possibility. **Not applicable**	**Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	Yes. For outreach and campaigns	No. Same assessment as for pentavalent vaccine **Neutral**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Neutral**

[dd] Branigan B. Health Policy Watch website. Evidence shows ring vaccination strategy effective in limiting Ebola outbreak in DRC page. https://www.healthpolicy-watch.org/evidence-shows-ring-vaccination-strategy-effective-in-limiting-ebola-outbreak-in-drc/.

[ee] PATH. *Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries. Summary of Workshop in Geneva from December 12 to 13, 2016.* Seattle: PATH; 2016.

	Parameter assessment				
Vaccines	**Assumed use case**	**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. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?***	**Does the innovation enable self-administration?**	**Overall score**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	Yes, for both use case scenarios	No. Same assessment as for pentavalent vaccine. **Neutral**	No. Same assessment as for HIV vaccine. **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; Red: **Worse** than the comparator (The innovation does not improve dose sparing); 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 vaccines	The innovation is a change to the recommended temperature storage conditions for a vaccine and sometimes is also a formulation improvement to improve stability and/or alter the product from a lyophilised vaccine to a liquid. The innovation is not expected to have any impact on the ability to use dose sparing for a particular vaccine and is therefore similar to the comparators.	**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 vaccines	In cases where no reformulation is required for CTC qualification, the innovation can be applied to both single-dose or multi-dose presentations (with or without preservative) and therefore is similar to the comparator(s) in all cases. If a novel formulation is required, then its compatibility with preservatives will need to be demonstrated if they are to be included with the vaccine.	**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 vaccines	No. Pain is unlikely to be affected by the innovation, though vaccines can have different osmolalities according to their formulations, which is linked to the excipients used, and is a factor associated with pain at the injection site (22).	No. The vaccines incorporating the innovation will be delivered using the same method as the comparators.	Yes. Satisfaction with immunization services may be improved due to increased access to vaccines enabled by use in a CTC. Note that all vaccines provided in routine immunization settings would need to be CTC-qualified to enable CTC use in these settings.	**Better**
	Neutral	**Neutral**	**Better**	

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**
Liquid vaccines assessed: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV)	No. Both the innovation and the comparators are liquid vaccines that are delivered in the same manner and with the same number of components.	No. The innovation does not include a change to labelling that impacts product tracking.	**Neutral**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	**Neutral**	**N/A**	
Lyophilised vaccines assessed: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	For lyophilised vaccines or other multi-component vaccines, the innovation reduces the number of components to be tracked.	No. The innovation does not include a change to labelling that impacts product tracking.	**Better**
	Better	**N/A**	

1.3 Criteria on safety

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

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**

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

available to measure the indicator.

Table 14

Parameter assessment		
Vaccines	**Does the innovation reduce the frequency of serious AEFIs ?**	**Overall score**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	A study of out of cold chain use of hepatitis B vaccine in Laos showed no increase or decrease in adverse events compared to the same product stored in the cold chain (16).	**Neutral**
Meningitis A **(**Lyophilised SDV or 10-dose vial)	A study of CTC use of meningitis A vaccine in Benin showed that CTC use was not associated with an increased rate of adverse events in the five days following immunisation, either when compared to a concurrent non-CTC population or to previous studies (23).	**Neutral**
All other applicable vaccines	No data for all vaccines other 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.

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?** [gg]	**Overall score**
Liquid vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV)	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).						**Neutral**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	**Neutral**						

[gg] *Incorrect diluent – use of the wrong substance as opposed to the wrong volume of diluent.*

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?** [gg]	**Overall score**
Lyophilised vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Yes. The innovation is a liquid vaccine so removes the risk of contamination during reconstitution in comparison to the lyophilised or multi-component comparators.	No. The innovation does not impact the delivery technology. The vaccine is delivered the same whether in a liquid format or a reconstituted format.	Yes. By removing the reconstitution step, the innovation reduces the number of product components and the complexity of preparation steps thereby reducing the risk of use of nonsterile components.	No. The innovation does not impact the way the delivery device is filled. The vaccine is filled into the delivery device in the same manner whether in a liquid format or a reconstituted format.	Yes. By removing the reconstitution step, the innovation reduces the number of product components and the complexity of preparation steps.	Yes. By removing the reconstitution step, the innovation removes the need for diluent or use of an incorrect component and therefore reduces this risk.	**Better**
	Better	**Neutral**	**Better**	**Neutral**	**Better**	**Better**	

Indicator: Likelihood of needle stick injury[hh]

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.

[hh] *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?**	**Does the innovation reduce the risk of injury after vaccine administration?**	**Overall score**
Liquid injectable vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	The innovation does not impact the number or type of sharps for liquid injectable vaccines so is identical to the relevant comparator(s) for these parameters. **Neutral**					**Neutral**
Liquid oral vaccines: **Rotavirus** (Liquid SD plastic tube) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Neither the innovation nor the comparators contain sharps since these vaccines are delivered orally. Therefore, the innovation is identical to the comparators for these parameters. **Neutral**					**Neutral**

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?**	**Does the innovation reduce the risk of injury after vaccine administration?**	**Overall score**
Lyophilised injectable vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV)	Yes. The lyophilised comparators require an additional sharp (reconstitution syringe) that is not required by the liquid innovation.	Yes. The lyophilised comparators require an additional sharp (reconstitution syringe) that is not required by the liquid innovation.	No. The innovation does not impact the delivery devices and therefore is no different than the comparators.	The innovation does not impact the delivery devices and therefore is no different than the comparators.	The innovation does not impact the delivery devices and therefore is no different than the comparators.	**Better**
	Better	**Better**	**Neutral**	**Neutral**	**Neutral**	

1.4 Criteria on economic costs

Indicator: Commodity costs of a vaccine regimen[ii] (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.*

Table 17

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?	Overall score
HPV (SDV or 2-dose vial)	No. There was no change in the price with the prequalification of Merck's Gardasil® 4 quadrivalent human papillomavirus vaccine for use in a CTC. A study conducted in two districts in Uganda with CTC use of Gardasil vaccine found wastage rates of 2.1% in Adjumani district and 6.2% in Luwero district. However wastage rates from the comparator districts were not available.[jj] A study conducted in Togo with CTC use of MenAfriVac vaccine found that the programmatic wastage rate when the vaccine was used in a CTC was the same as use in a cold chain, and so use of vaccines in a CTC would not impact wastage when microplanning is properly done (24).	No. Separate threshold indicators (TI) need to be purchased and distributed to monitor vaccines used in a CTC. A separate TI is quoted to cost between $0.26 and $0.50 but is shared across several vials and is reusable if it has not reached endpoint. In the Uganda study,[kk] the majority of facilities used over 50 vials in a CTC and so the cost per vial for the TI would be <$0.01. This separate cost will be removed if vaccine vial monitors with integrated threshold indicators (VVM-TIs) are provided on CTC qualified vaccines in the future – though the VVM-TI will likely increase the price of the vaccine products.	No. There would be no change in the waste disposal volumes and / or types of sharps waste generated.	Overall score: **Worse** • No change in the price of the vaccine assuming a separate TI is used and no change in safety box costs. • Delivery costs increase by **<$0.01 per vial** if a separate threshold indicator is used, because this TI is shared across several vials and reusable if it has not reached endpoint.
	Neutral	**Worse**	**Neutral**	

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

[jj] WHO. *Using the HPV vaccine in a Controlled Temperature Chain (CTC) in Uganda—a Pilot Project*. Final Report. Geneva: WHO; 2018.

[kk] WHO. *Using the HPV vaccine in a Controlled Temperature Chain (CTC) in Uganda—a Pilot Project*. Final Report. Geneva: WHO; 2018.

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?	Overall score
Other liquid vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	No data. Some vaccines (e.g., hepatitis B and typhoid) are likely sufficiently heat stable for CTC qualification but further stability studies and/or regulatory approvals may be necessary that could impact the price. Other vaccines would require reformulation and use of new excipients might alter the cost of the vaccine. We also lack data on the potential impact of CTC qualification and use on vaccine wastage since these products are not yet available for CTC use.	No. Same assessment as HPV vaccine.	No. There would be no change in the waste disposal volumes and / or types of sharps waste generated.	Overall score: **No data** • No data on the vaccine price given that the cost implications of reformulation or stability studies and regulatory approvals are unknown. Impact on programmatic wastage is also unknown. • No change in safety box costs. • Delivery costs increase by <$0.01 per vial because of the need for a separate threshold indicator, but this TI is shared across several vials and reusable if it has not reached endpoint.
	No data	**Worse**	**Neutral**	

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?	Overall score
Lyophilised injectable vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV)	No data. Since the vaccine would need to be reformulated to a liquid vaccine, the purchase price may increase. For vaccines that are currently lyophilised, removal of this step could potentially reduce manufacturing costs. In addition, wastage may be impacted by the improved heat stability and change of format.	Yes. The change in the presentation to a liquid vaccine would eliminate the need for reconstitution syringes, a saving of $0.04 per vial. However, as in the HPV assessment, a separate TI is needed, but the additional cost would be <$0.01 per vial. Thus, the purchase costs of delivery devices would decline by ~$0.03 per vial.	Yes. The change in the presentation to a liquid vaccine would eliminate the need for reconstitution syringes and hence reduce the volume of sharps wastage used. The sharps volume would decrease by 38 cm^3 per vial but the savings are <$0.01 per vial.	Overall score: **No data** • No data on the vaccine price given that the cost implications of reformulation and regulatory approvals are unknown. Impact on programmatic wastage is also unknown. • Delivery device costs decrease by ~$0.03 per vial because of the elimination of the reconstitution syringe while accounting for the need for a separate threshold indicator that is shared across several vials. • Safety box costs also decline by <$0.01 per vial because of the elimination of the reconstitution syringe.
	No data	**Better**	**Better**	

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?	Overall score
Multi-component oral vaccine: **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	No data. However, wastage may be impacted by the improved heat stability and change of format.	Yes. If the vaccine is formulated as a liquid in a primary container, then a separate mixing cup would not be needed to combine the 3 vaccine components, but there is no data on the savings resulting from the elimination of the mixing cup.	No. Neither the comparator nor the innovation use sharps.	Overall score: **No data** • No data on the vaccine price given that it is still under development. Impact on programmatic wastage is also unknown. • Delivery device costs would decrease because of the elimination of the mixing cup but there is no data on the magnitude of this cost reduction. • No change in the safety box costs because similar to the comparator, there are no sharps.
	No data	**Better**	**Neutral**	

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

*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**
Liquid vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	Yes. Using a vaccine in a CTC reduces the economic cost of cold chain storage and transport since the vaccine can be stored out of the cold chain for at least three days prior to vaccine administration (24). Note that this benefit would be minimized for CTC qualified vaccines that are stored and/or transported with other vaccines that are not CTC qualified.	No. Using a vaccine in a CTC does not impact the economic costs of out of cold chain storage and transport. In addition, because the delivery devices used for vaccine administration would not change, there is no change in the economic costs of out of cold chain storage and transport.	Yes. Staff would save time because they no longer have to spend time freezing and conditioning icepacks before leaving for the vaccination session and don't need to return for icepacks during long outreach trips (24). However, staff would also have to spend more time monitoring the vaccines if a separate threshold indicator is used but this time increase is likely to be negligible compared to the time spent on freezing and conditioning icepacks. If this innovation is combined with the vaccine vial monitor-threshold indicator, then staff would not need to spend any extra time monitoring the vaccines.	No. This innovation has no features that impact stock management activities.	Overall score: **Better** • Economic costs of cold chain storage and transport and costs of time for vaccinators is reduced. • No change in the economic costs of out of cold chain storage and transportation and costs of time for stock management staff.
	Better	**Neutral**	**Better**	**Neutral**	

Lyophilised vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Yes. Using a vaccine in a CTC reduces the economic cost of cold chain storage and transport since the vaccine can be stored out of the cold chain for at least three days prior to vaccine administration (24).	Yes. There would be no need for storage of out of cold chain components (e.g., reconstitution syringes, diluents or other components, or mixing cups) and so the economic costs of out of cold chain storage and transport would be reduced.	Yes. With CTC use of vaccines, staff would save time because they no longer have to spend time freezing and conditioning icepacks before leaving for the vaccination session (24). Also, because the vaccine is now in liquid form, the staff save time previously spent on vaccine reconstitution. A time and motion study conducted by PATH showed that staff spent 19.3 seconds preparing and administering a liquid vaccine in a SDV and 15.2 seconds for a liquid vaccine in a 10-dose vial. This is compared to 48.3 seconds for a lyophilised vaccine in a SDV and 20.9 seconds when in 10-dose vials.[ll] With CTC use, staff would also spend more time monitoring the vaccines, but this is likely to be negligible compared to the time spent on freezing and conditioning icepacks and vaccine reconstitution.	No. This innovation has no features that impact stock management activities.	Overall score: **Better** • Economic costs of both cold chain and out of cold chain storage and transport is reduced • Time spent by vaccinators is also reduced. • No change in costs spent by stock management staff.
	Better	**Better**	**Better**	**Neutral**	

[ll] PATH. *Pentavalent Vaccine in the Uniject™ Injection System—A Time and Motion Study*. Seattle: PATH; 2014. https://path.azureedge.net/media/documents/TS_pentavalent_vac.pdf

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		
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 vaccines	Training costs: There are one time/upfront costs with CTC use as use it requires training of vaccinators on how to store, monitor and use vaccines in a CTC.	Overall score: **Worse** • There are training costs as vaccinators need to be trained on CTC use of vaccines. • There are no other upfront costs for hardware or recurrent costs.
	Worse	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for use of vaccines in a CTC.	
	Neutral	

1.5 Criteria on environmental impact

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

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

[mm] *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).*

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**
Liquid vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	No. The innovation does not impact the product volume for liquid vaccines as it is just a change to the temperature storage conditions on the vaccine label and may include a small formulation change that does not impact the product volume.	No. The innovation does not impact the number or type of sharps for liquid vaccines so is identical to the relevant comparators for these parameters.	No. The innovation does not impact product packaging.	**Neutral**
	Neutral	**Neutral**		
Lyophilised vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Yes. The comparators require a diluent vial (or other vaccine components as in the case of ETEC) and a reconstitution syringe (or mixing cup for ETEC). Vaccines incorporating the innovation do not require these as they are liquid.	The comparators require a diluent vial (or other vaccine components as in the case of ETEC) and a reconstitution syringe (or mixing cup for ETEC). Vaccines incorporating the innovation do not require these as they are liquid.	No. The innovation does not impact product packaging.	**Better**
	Better	**Better**		

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity[nn]

Notes:

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

The clinical development pathway complexity to obtain heat stable, CTC-qualified liquid vaccine formulations varies depending on the current status and format of the vaccine. In general:

- These are based on published data and input from regulatory consultants.
- Commercially available liquid vaccines that are already heat stable may only require stability studies to produce sufficient data for CTC qualification. Clinical studies may not be required.[oo]
- Commercially available vaccines requiring reformulation to achieve a liquid formulation with adequate heat stability would likely require a non-inferiority trial using available metrics of potency.
- 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. The assessments for pipeline vaccines assume that the first approvals are obtained with the heat-stable formulation.
- Only endpoints related to efficacy have been considered. The safety issues related to vaccine reformulation and the clinical studies required to demonstrate safety of any given heat stable, CTC qualified liquid vaccine have not been considered.

*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.*

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

[oo] WHO. *WHO Technical Report Series No. 999, 2016. Annex 5. Guidelines on the Stability Evaluation of Vaccines for Use Under Extended Controlled Temperature Conditions*. Geneva: WHO; 2016. https://www.who.int/biologicals/areas/vaccines/Annex_5_Guidelines_on_Stability_evaluation_vaccines_ECTC.pdf?ua=1.

Table 21

Vaccines	Is the clinical development pathway complex?	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	Will likely require a change to the liquid formulation to achieve adequate heat stability for CTC qualification. Immunological endpoints (serum antibody titres) have been used for non-inferiority trials and approval of pentavalent vaccine in new delivery devices in the past (25). It is assumed that similar endpoints could be used to assess heat stable/CTC qualified liquid formulations.	**Low complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Existing products are sufficiently heat-stable for CTC qualification. Stability studies should suffice and no clinical studies would be required to qualify hepatitis B vaccines for CTC use.	**No complexity**
HPV (SDV or 2-dose vial)	Existing products are sufficiently heat-stable for CTC qualification and one product is already WHO prequalified. Stability studies will suffice and no clinical studies are required to qualify other heat stable HPV vaccines for CTC use.	**No complexity**
MR (Lyophilised SDV or 10-dose)	The current products are lyophilised so reformulation would definitely be required to achieve a heat-stable liquid product. Immunogenicity assays have been used as endpoints for non-inferiority trials of MMR vaccines of different potencies (26). It is assumed that similar endpoints could be used to assess heat stable/CTC qualified liquid formulations.	**Low complexity**
Meningitis A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	Some liquid meningitis vaccines exist, but there is some evidence that the components are not heat stable as liquids so reformulation is likely required to achieve adequate heat stability as a liquid (27). Serum bactericidal antibody titres are regarded as the best correlate of protection for meningococcal vaccines (excluding serogroup B) (28), and SBA titres were used for the approval of MenAfriVac (29). It is assumed that similar endpoints could be used to assess heat stable/CTC qualified liquid formulations.	**Low complexity**
IPV (IM: Liquid SDV or 10-dose), (ID: Liquid SDV or 5-dose)	The current liquid products have a VVM7 and therefore would require reformulation to achieve CTC qualification. Immunological endpoints (serum antibodies) have been used for non-inferiority trials of IPV (30) or IPV containing hexavalent vaccine (31). It is assumed that similar endpoints could be used to assess heat stable/CTC qualified liquid formulations.	**Low complexity**
Rabies (IM: Lyophilised SDV), (ID: Lyophilised SDV)	The current comparator products are lyophilised, though some liquid products do exist. We are assuming that reformulation would be required to achieve a heat-stable liquid product. Immunogenicity (seroconversion to a neutralizing antibody titre ≥0.5 IU/) has been used as an endpoint in many studies to evaluate alternative immunization regimens (32)(33) and it assumed similar endpoints could be used for heat stable/CTC qualified liquid formulations. A strategy to guide the clinical evaluation of new rabies vaccines has recently been proposed (19).	**Low complexity**
Rotavirus (Liquid SD plastic tube)	The current products have a VVM7 and therefore would require reformulation to achieve CTC qualification. Serum IgA titres were used to demonstrate non-inferiority of a new liquid rotavirus formulation compared to the previous lyophililsed presentation of the same vaccine (34). It is assumed that a similar approach could be used for heat stable/CTC qualified liquid formulations.	**Low complexity**

Vaccines	Is the clinical development pathway complex?	Overall score
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 (35).[pp] It is assumed that similar endpoints could be used to assess heat stable/CTC qualified liquid formulations. Heat stability could be addressed during product development of pipeline candidates, further decreasing the level of effort required to achieve CTC qualification.	**Low complexity**
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	Immunological correlates of protection have not been established for Ebola virus (36)(37), and it has only been possible to demonstrate efficacy of the most advanced candidate rVSV-ZEBOV) using ring vaccination trials (38). Demonstration of efficacy of a heat stable/CTC qualified liquid formulation is likely to require reformulation and an efficacy trial and as such, only be possible during an outbreak. Efforts are underway to expedite the approval process for Ebola vaccines.[qq]	**High complexity**
ETEC (ETVAX) (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Licensure of heat stable/CTC qualified ETEC vaccines for use in paediatric populations in LMICs will require efficacy studies with clinical endpoints in this population.[rr] There is, however, ongoing discussion of which clinical endpoints are the most relevant or useful (39). Trials assessing the effectiveness of the vaccine against traveller's diarrhea and controlled human infection models (CHIMs) might also aid clinical development (39).	**High / very high complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	Ongoing phase III clinical trials of HIV vaccines have prevention of HIV acquisition as the primary endpoint,[ss] 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 (40).	**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.[tt] 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.[uu]	**Low complexity**

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

[qq] WHO Essential Medicines and Health Products website: African regulators' meeting looking to expedite approval of vaccines and therapies for Ebola page. https://www.who.int/medicines/news/AFR_reg_meet/en/. Accessed February 29, 2020.

[rr] 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.

[ss] 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.

[tt] 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.

[uu] 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.

Indicator: Technical development challenges

Members of the WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, were invited to complete a survey[vv] following a consultation on heat stable/CTC qualified liquid vaccines. Six member organizations responded to the survey and five member organizations responded to the question on technical challenges. The following challenges were identified (most frequently identified challenges first):

- The need to achieve sufficient heat stability through reformulation or higher initial potency. (5/5)
- For multidose vials, the need to assess preservative efficacy at elevated temperatures for multidose vials of preserved vaccines being submitted for CTC qualification. (5/5)
- The need to perform additional stability studies for CTC qualification. (4/5)
- The need for clarity on priority vaccines for CTC qualification. (2/5)

Table 22 highlights vaccine-specific 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.

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**
Pentavalent (Liquid SDV or 10-dose vial)	Pentavalent vaccines are multivalent and adjuvanted. The components of combination vaccines can interact differently with each other and also with excipients. Further stabilizing pentavalent vaccine would require identification of excipients capable of stabilizing all five components, while ensuring non-interference between the antigens.	**Moderate complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Hepatitis B vaccine is monovalent and adjuvanted. Sufficiently heat stable hepatitis B vaccines are already WHO prequalified and stability data exist that are likely sufficient for CTC qualification	**Low complexity**
HPV (SDV or 2-dose vial)	HPV vaccines are 4- or 9-valent virus-like particles (VLPs) and are adjuvanted. One heat stable/CTC qualified HPV vaccine is already available and WHO prequalified.[ww]	**Low complexity**

[vv] *Survey carried out after DTWG telecons on heat stable and CTC qualified liquid formulations held on December 9 and 10, 2019.*
[ww] WHO website. WHO prequalified vaccines page. Type: Human Papillomavirus (Quadrivalent). https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178. Accessed February 29, 2020.

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**
MR (Lyophilised SDV or 10-dose)	Measles rubella vaccines are live-attenuated. This vaccine is currently lyophilised and efforts to reformulate it in lyophilised format have not resulted in products that are likely to be sufficiently heat-stable for CTC qualification. Obtaining a heat stable liquid formulation would be even more difficult (41).	**High complexity**
Meningitis A (MenAfriVac) (Lyophilised SDV or 10-dose vial)	MenA, MenACWY and MenACWYX vaccines are polysaccharide-protein conjugate vaccines. MenAfrivac and MenACWYX contain aluminium phosphate adjuvant in the diluent; other MenACWY vaccines are not adjuvanted. While liquid meningitis vaccines are commercially available, there are some inherent stability issues with the group A component (11).	**Moderate complexity**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Current IPV products are not sufficiently heat-stable for CTC qualification and further research would be required to determine methods to improve their heat-stability.	**Moderate complexity**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	Liquid rabies vaccines are commercially available and further research would be required to determine methods to improve their heat-stability.	**Moderate complexity**
Rotavirus (Liquid SD plastic tube)	Current rotavirus vaccines are not sufficiently heat-stable for CTC qualification and further research would be required to determine methods to improve their heat-stability.	**Moderate complexity**
Typhoid conjugate (Liquid SDV or 5-dose)	Typhoid conjugate is a polysaccharide-protein conjugate vaccine with no adjuvant. Current typhoid vaccine products are likely to be sufficiently heat-stable for CTC qualification. Some manufacturers are already incorporating stability studies to qualify for CTC prior to regulatory approvals.	**Low complexity**

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**
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	rVSV-ZEBOV is a live virus-vectored vaccine. It is currently stored as a frozen liquid. The existing comparator vaccine must be stored as a frozen liquid at -80°C to -60°C for long term storage and can only be stored at 2-8°C for no more than two weeks.[xx] While the formulation hasn't been optimized for stability, immunological correlates of protection have not yet been developed for this vaccine making the task to obtain a stable liquid highly complex.	**High complexity**
ETEC (ETVAX) (Liquid SDV, lyophilised buffer, lyophilised adjuvat)	The existing comparator vaccine is a three-component product. Achieving a multicomponent vaccine will present assay challenges as current assays must be evaluated for their applicability to the combination vaccine. For example, it is currently not possible to quantify the dmLT adjuvant in ETVAX once mixed with the cellular components due to aggregation to the whole cells, highlighting the need for a dmLT quantification assay.[yy] In addition, the components interact with each other. Novel approaches such as combining lyophilised components in a medium chain triglyceride oil, which keeps the components inert and separated until they enter the aqueous environment of the host stomach, could be explored but are technically challenging.[zz]	**Moderate complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	Data are lacking on the heat stability of this vaccine, however, it is assumed that efforts to further stabilize this liquid vaccine could be made in course of vaccine development.	**Moderate complexity**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Several different types of vaccines against influenza pandemics are and have been developed. The VIPS assessment is using an mRNA vaccine as an exemplar. Studies with a mRNA vaccine from a different developer found the vaccine to be stable as a liquid for 7 days at 40°C (13).	**Moderate complexity**

Indicator: Complexity of manufacturing the innovation

Members of the WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, were invited to complete a survey[aaa] following a consultation on heat stable/CTC qualified liquid vaccines. Six member organizations responded to the survey and five member organizations responded to the question on manufacturing challenges. Vaccine manufacturers surveyed through the Delivery Technologies Working Group confirmed that this innovation does not increase the complexity of producing vaccines. The only issue identified that influences manufacturing was the need to change the product

[xx] Merck. ERVEBO® (Ebola Zaire Vaccine, Live) suspension for intramuscular injection [package insert]. Silver Spring: MD: US Food and Drug Administration; 2019. https://www.fda.gov/media/133748/download.

[yy] PATH. *Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries. Summary of Workshop in Geneva from December 12 to 13, 2016.* Seattle: PATH; 2016.

[zz] PATH. *Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries. Summary of Workshop in Geneva from December 12 to 13, 2016.* Seattle: PATH; 2016.

[aaa] Survey carried out after DTWG telecons on heat stable and CTC qualified liquid vaccines held on December 9 and 10, 2019.

insert to reflect the CTC temperature storage indication. This was mentioned by 4/5 respondents. Table 23 describes the differences in manufacturing complexity for liquid and lyophilised vaccine products.

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.

Table 23

Parameter assessment		
Vaccines	**How complex is the manufacturing process? (Specify if special materials are used)**	**Overall score**
Liquid vaccines: **Pentavalent** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Rotavirus** (Liquid SD plastic tube) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120)** (Boost: liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	The improved heat stability of an existing liquid vaccine would have no impact on the manufacturing process for the vaccine. For novel formulations, it is assumed that existing GRAS (generally regarded as safe) excipients that are readily available would be used if formulation changes are made to a vaccine. Changes in the composition of the vaccine formulation might affect pH, osmolarity, interaction with adjuvants and ability to combine different components. This might have an impact on the complexity of manufacturing.	**No complexity**

Parameter assessment		
Vaccines	**How complex is the manufacturing process? (Specify if special materials are used)**	**Overall score**
Lyophilised vaccines: **MR** (Lyophilised SDV or 10-dose) **Meningitis A (**Lyophilised SDV or 10-dose vial) **Rabies** (IM: Lyophilised SDV) (ID: Lyophilised SDV) **ETEC (ETVAX)** (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Nearly all vaccine producers have the capability to manufacture and fill liquid vaccines, so it is assumed that established manufacturing facilities are available at commercial scale. For novel formulations, it is assumed that existing GRAS (generally regarded as safe) excipients that are readily available would be used if formulation changes are made to a vaccine. Changes in the composition of the vaccine formulation might affect pH, osmolarity, interaction with adjuvants and ability to combine different components. This might have an impact on the complexity of manufacturing, although the lyophilization step would no longer be required.	**No complexity**

Indicator: Robustness of the innovation-vaccine pipeline

Note for Table 24:

Table 24 identifies the current status of application of the innovation to specific vaccines. In table 24 it has been assumed that:

- In instances where a liquid vaccine is sufficiently heat stable for CTC qualification, the vaccine manufacturers are the technology developers.
- The 'suppliers/manufacturers of the vaccine' parameter focuses on WHO prequalified products (see WHO Prequalified Vaccines Database for details).[bbb]
- For some vaccines, especially those that are currently lyophilised or have lyophilised components, novel formulation methods and excipients may be required and the applied technology is likely to be unique for each vaccine.
- Confidential data have been used below from vaccine manufacturers for those liquid vaccines for which CTC use has been recognized by WHO and other stakeholders as being programmatically beneficial, e.g., vaccines used in campaigns and special strategies.
- No data are available for those vaccines for which CTC use is not deemed as being a priority by WHO as they are used in routine immunization programs.
- When assessing the robustness of vaccine supply, we have focussed on suppliers that are WHO prequalified (PQ) or likely to be PQ. Comments regarding non-PQ supply or robustness of the pipeline (for new vaccines) have been included.

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

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.

Table 24

Vaccines	Are there multiple developers of the technology?	Are there multiple suppliers/manufacturers of the vaccine?
Pentavalent (Liquid SDV or 10-dose vial)	No data. It is unknown if any vaccine manufacturers or researchers are working on further heat-stabilization of pentavalent vaccine.	There are multiple producers of liquid pentavalent or other DTP-containing vaccines. There are six WHO PQ manufacturers of pentavalent vaccine.
	No data	**Highly robust**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There are at two manufacturers of hepatitis B vaccine working towards CTC qualification. Both vaccine products are highly heat stable.	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ hepatitis B vaccine.
	Moderately robust	**Highly robust**
HPV (SDV or 2-dose vial)	One manufacturer has an HPV vaccine that is WHO prequalified for CTC use and at least one other manufacturer is pursuing a CTC qualified vaccine. A third manufacturer's product is sufficiently stable to be CTC qualified.	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 prequalified before 2021.[ccc]
	Moderately robust	**Moderately robust**
MR (Lyophilised SDV or 10-dose)	There is one known technology developer working on formulation of a liquid suspension of MR vaccine.[ddd]	There are multiple producers of measles vaccine and a single producer of stand-alone rubella. Two manufacturers have WHO PQ MR vaccines.
	Not robust	**Moderately robust**

[ccc] 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.

[ddd] Personal communication. Bill & Melinda Gates Foundation.

Vaccines	Are there multiple developers of the technology?	Are there multiple suppliers/manufacturers of the vaccine?
Meningitis A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	There are no known efforts to formulate a liquid, heat stable meningitis vaccine for CTC qualification.	There is only one manufacturer of MenAfriVac (which is WHO PQ) and one manufacturer known to be developing a MenACWYX vaccine.[eee] There are two PQ manufacturers of lyophilized Men ACWY vaccines.[fff]
	No data	**Moderately robust**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	There are no known efforts to heat-stabilize IPV for CTC qualification.	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV. There are however supply constraints[ggg] and only two suppliers to UNICEF (42) New manufacturers of PQ IPV are expected to enter the market from 2020.[hhh]
	No data	**Not robust**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	There are no known efforts to formulate a liquid, heat stable rabies vaccine for CTC qualification.	There are several manufacturers of rabies vaccines. Four manufacturers have WHO PQ products.
	No data	**Moderately robust**
Rotavirus (Liquid SD plastic tube)	There are no known efforts to stabilize liquid rotavirus vaccines for CTC qualification.	There are three WHO PQ suppliers of liquid rotavirus vaccines.
	No data	**Moderately robust**
Typhoid conjugate (Liquid SDV or 5-dose)	There are at least two vaccine manufacturers developing heat stable liquid typhoid vaccines suitable for CTC qualification.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ.
	Moderately robust	**Not robust**

[eee] Serum Institute of India PVt. LTD. website. Product pipeline: Pentavalent meningococcal conjugate vaccine (A, C, Y, W-135, X) page. https://www.seruminstitute.com/product_horizon.php. Accessed February 29, 2020.

[fff] WHO website. WHO prequalified vaccines page. Type: Meningococcal ACYW-135 (conjugate vaccine). Commercial Name: Menveo. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=267. Accessed February 29, 2020.

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

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

Vaccines	Are there multiple developers of the technology?	Are there multiple suppliers/manufacturers of the vaccine?
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	While efforts are likely underway to stabilize the current vaccine that must be kept at -80°C, there are no known efforts to further stabilize liquid Ebola vaccines for CTC qualification.	There is only one manufacturer of this particular candidate Ebola vaccine. Other Ebola vaccines have different characteristics.
	No data	**Not robust**
ETEC (ETVAX) (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	There are no known efforts to formulate ETEC vaccine as a single component liquid qualified for CTC use.	There is only one manufacturer of this particular candidate ETEC vaccine. Other ETEC vaccines have different characteristics.
	No data	**Not robust**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	There are no known efforts to stabilize the HIV liquid boost vaccine for CTC qualification.	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.[iii]
	No data	**Not robust**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	There are no known efforts to stabilize the pandemic influenza vaccine for CTC qualification.	There are a few developers of mRNA vaccines against pandemic flu: Moderna;[jjj] Curevac (universal flu vaccine)[kkk] and Vir (universal flu vaccine).[lll] Other pandemic influenza vaccines have different characteristics.
	No data	**Moderately robust**

1.7 Criteria on commercial feasibility[mmm]

In a survey of members of the WHO Delivery Technologies Working group, six member organisations responded to the survey and five responded to the questions on commercial feasibility of the technology. The following challenges to commercialisation of heat stable/CTC qualified liquid formulations were identified (most frequently identified challenges first):

- Regulatory approval for CTC qualified vaccines (4/5)

[iii] 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.

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

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

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

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

- Pricing strategy (4/5)
- Market potential and uptake (3/5)
- Country stakeholder interest (2/5)

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

Notes:

The assessment in Table 25 summarizes country stakeholder interest in the innovation as applied to specific vaccines. It draws upon a country survey conducted by UNICEF in 2017 as part of their annual forecasting activity[ooo] as well as past and planned country participation in vaccine/CTC introductions. In the 2017 UNICEF survey, 9 out of 94 countries expressed interest in using vaccines approved for CTC use in 2018.

Summary feedback from country consultation: In addition to the data in Table 25, the following feedback was received from country stakeholders during the VIPS Phase II country consultation interviews:

- 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.

[nnn] *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.*

[ooo] UNICEF Supply Division. Country Feedback to CTC Questions in Annual Forecasting Activity. At: Controlled Temperature Chain Working Group Meeting; December 3 to 5, 2019.

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.

Table 25

Parameter assessment		
Vaccines	**Have countries expressed interest to suggest demand for the vaccine-innovation pairing and potential country uptake?**	**Overall score**
Pentavalent (Liquid SDV or 10-dose vial)	No data. This vaccine is not prioritized by WHO for CTC use given that it is a routine vaccine that is transported and stored with other routine vaccines.	**No data**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	A WHO survey among countries in the African and Western Pacific Regions in which 25 countries responded (8/11 or 73% in WPRO and 17/46 or 37% in AFRO, with an overall response rate of 44%), produced the following results: 70% of participating countries think that CTC would facilitate the provision of the HepB-BD; most countries see potential advantages in integrating CTC in immunization programs, especially at health facility level and to a lesser extent for birth dose provision in homes. Countries with high percentages of home births were clearly interested in a CTC-licensed vaccine. In the recent UNICEF survey, 4 countries specified interest in CTC use of hepatitis B birth dose vaccine. In addition, many countries have and are currently using hepatitis B vaccine out of the cold chain for birth dose delivery (6)(7)(8)(43).	**Demonstrated country interest**
HPV (SDV or 2-dose vial)	In the UNICEF survey, one country specified interest in CTC use of HPV vaccine. Uganda has already introduced HPV vaccine in a CTC in two districts but has not yet proceeded with broader implementation due to competing priorities and changes in immunization program leadership.[ppp]	**Mixed country interest**
MR (Lyophilised SDV or 10-dose)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
Meningitis A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	As of 2017, approximately 4 million doses of MenAfriVac meningitis A vaccine have been used in a CTC in 6 countries. [qqq]	**Demonstrated country interest.**

[ppp] WHO. *Using the HPV vaccine in a Controlled Temperature Chain (CTC) in Uganda—a Pilot Project*. Final Report. Geneva: WHO; 2018.

[qqq] 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.

Parameter assessment		
Vaccines	**Have countries expressed interest to suggest demand for the vaccine-innovation pairing and potential country uptake?**	**Overall score**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
Rotavirus (Liquid SD plastic tube)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
Typhoid conjugate (Liquid SDV or 5-dose)	No data. A CTC qualified vaccine is not currently available.	**No data.**
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
ETEC (ETVAX) (Liquid SDV)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: Boost: liquid SDV)	No data. This vaccine is not currently available as a heat stable liquid.	**No data.**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No data. This vaccine is not currently available as a heat stable liquid.	**No data**

Indicator: Potential breadth of the target market

Note:

- 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.[rrr] 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 (44). Adoption of birth dose by national immunization programmes has not matched the implementation of 3-dose hepatitis B vaccination starting later in infancy (44).	**Large**
HPV (SDV or 2-dose vial)	The WHO recommends that all countries should introduce HPV vaccination into national immunization programmes (45). 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).[sss] 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.[ttt]	**Large**

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

[sss] WHO. *HPV: Global Market Study HPV*. Geneva: WHO; 2018. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary.pdf.

[ttt] WHO. *HPV: Global Market Study HPV*. Geneva: WHO; 2018. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary.pdf.

Vaccines	How broad is the potential target market?	Overall score
MR (Lyophilised SDV or 10-dose)	The average forecasted global MR demand through 2021 is approximately 400 million doses per year, split between the Gavi 71 countries (approx. 37%), India (39%), Indonesia (10%) and other non-Gavi-countries (14%).[uuu] Most HIC and MIC countries use MMR rather than MR vaccine. It is possible that a MR-MAP would be used to target specific, hard-to-reach populations only, or be used only in campaigns (46).	**Large**
Meningitis A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	For Men A conjugate vaccines, WHO recommends mass vaccination campaigns in countries in the African meningitis belt, followed by introduction into routine childhood immunization (47). For quadrivalent meningococcal vaccines, WHO recommends that countries with high or intermediate endemic rates (of invasive meningococcal disease and countries with frequent epidemics should introduce appropriate large- scale meningococcal vaccination programmes (routine, SIAs or private vaccination services). In countries where the disease occurs less frequently meningococcal vaccination is recommended for defined risk groups, such as children and young adults residing in closed communities (48). HICs (such as USA, UK, Australia) are increasingly introducing vaccination of adolescents with polyvalent meningococcal vaccines, and they are a requirement for Hajj pilgrims (49). Demand for MenACWY conjugate vaccine outside China and the meningitis belt was estimated to be 16.7M doses.[vvv]	**Moderate (MenA)** **Large (polyvalent)**
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.[www]	**Moderate**
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	Rabies vaccines are not included in national immunization schedules but are recommended for special at-risk groups in HICs and for post-exposure prophylaxis following a bite or exposure to a rabies-infected animal. Over 15 million people receive PEP treatments each year (50). Gavi estimates cumulative demand of 304M doses (20M/year) between 2021 and 2035.[xxx]	**Small / moderate**

[uuu] Gavi. *MR Vaccine Supply and Procurement Roadmap Update November 2017.* Geneva: Gavi; 2017. https://www.gavi.org/sites/default/files/document/measles-rubella-vaccine-roadmap--public-summarypdf.pdf.

[vvv] WHO. *Global Market Study: Meningococcal Meningitis Vaccines.* Working document. Geneva: WHO; 2019. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_meningococcal_vaccines_global_market_update_May2019.pdf .

[www] WHO. *Polio Post-Certification Strategy: A Risk Mitigation Strategy for a Polio Free World*. Geneva: WHO; 2018. http://polioeradication.org/wp-content/uploads/2018/04/polio-post-certification-strategy-20180424-2.pdf.

[xxx] Gavi. *Vaccine Investment Strategy Programme and Policy Committee Meeting: Annex C—Rabies Investment Case*. Geneva: Gavi; 2018. https://www.gavi.org/sites/default/files/document/ppc-meeting-18-19-october-2018---vis-06a---annex-c--rabies-investment-casepdf.pdf.

Vaccines	How broad is the potential target market?	Overall score
Rotavirus (Liquid SD plastic tube)	The WHO recommends that rotavirus vaccines should be included in all national immunization programmes and considered a priority in countries with high rotavirus gastroenteritis fatality rates (51). Currently At 47% of countries in the world have introduced rotavirus vaccine, but only 30% of non-Gavi, non-PAHO MICs. High income countries (HICs) account for 59% of the value of the market whereas Gavi countries accounts for 78% of the volume of the market.[yyy] Global rotavirus vaccine market is projected to grow 136%, reaching approximately 107 million courses by 2025. The growth will be driven mostly by demand for Gavi. 73 countries projected to peak in 2025 with approximately 85 million courses, of which 24 million courses is for India.[zzz]	**Large**
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.[aaaa] 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 (52).	**Small / moderate**
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	The future demand for Ebola vaccines is unknown and it is likely that the commercial market will be limited. Governments and non-governmental organizations will be the only likely buyers.[bbbb] Presumably primarily for stockpiling to control outbreaks, e.g., by ring vaccination with rVSV-ZEBOV.	**Small**
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 (53) 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 (53).	**Moderate**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (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 (54).	**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 (55). 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**

[yyy] WHO. V3P key findings for rota [rotavirus vaccine factsheet]. Working document. Geneva: WHO; 2018. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/rota_fact_sheet.pdf?ua=1.

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

[aaaa] 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.

[bbbb] Gavi. *Ebola Vaccine Supply and Procurement Roadmap.* Geneva: Gavi; 2018. https://www.gavi.org/sites/default/files/document/ebola-roadmap---public-summarypdf.pdf.

Indicator: Existence of partnerships to support development and commercialisation

*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	**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**
Pentavalent (Liquid SDV or 10-dose vial)	No known support.	No known partnerships or expressions of interest from vaccine manufacturers.	**No interest**
	No interest	**No interest**	
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Funding support has been provided by the Bill & Melinda Gates Foundation to both WHO and PATH to advance CTC use of this priority vaccine and multiple stakeholders have expressed interest in the innovation applied to this vaccine.	At least two vaccine manufacturers are working to WHO prequalify products for CTC use.	**Significant interest**
	Significant interest	**Significant interest**	
HPV (SDV or 2-dose vial)	Funding support has been provided by the Bill & Melinda Gates Foundation to both WHO and PATH to advance CTC use of this priority vaccine.	One HPV vaccine is already WHO prequalified for CTC use and at least one other manufacturer is working towards CTC qualification.	**Significant interest**
	Significant interest	**Significant interest**	

Parameter assessment			
Vaccines	**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**
MR (Lyophilised SDV or 10-dose)	A small study is currently being funded to support formulation of MR vaccine as a liquid suspension.[cccc]	No known partnerships or expressions of interest from vaccine manufacturers.	**Mixed interest**
	Significant interest	**No interest**	
Meningitis A (MenAfriVac) **(**Lyophilised SDV or 10-dose vial)	No known support to pursue a liquid, heat stable product. The current lyophilised vaccine is CTC qualified.	No known partnerships or expressions of interest from vaccine manufacturers.	**No interest**
	No interest	**No interest**	
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No known support to pursue a heat stable product	No known partnerships or expressions of interest from vaccine manufacturers	**No interest**
	No interest	**No interest**	
Rabies (IM: Lyophilised SDV) (ID: Lyophilised SDV)	No known support to pursue a liquid, heat stable product.	No known partnerships or expressions of interest from vaccine manufacturers	**No interest**
	No interest	**No interest**	
Rotavirus (Liquid SD plastic tube)	No known support to pursue a heat stable product	No known partnerships or expressions of interest from vaccine manufacturers	**No interest**
	No interest	**No interest**	
Typhoid conjugate (Liquid; MDV)	The programmatic benefits of future CTC use of this vaccine are obvious to stakeholders and WHO has identified vaccines used in campaigns and special strategies as a priority for CTC qualification. In addition, the CTC Working Group recently identified this vaccine as a high priority for CTC qualification and use.	At least one vaccine manufacturer is working to qualify their heat stable liquid typhoid conjugate vaccine for CTC use.	**Significant interest**

[cccc] Personal communication. Bill & Melinda Gates Foundation.

Parameter assessment			
Vaccines	**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**
	Significant interest	**Significant interest**	
Ebola (rVSV-ZEBOV) (Liquid SDV)	No known partnerships	No known partnerships or expressions of interest from vaccine manufacturers	**No interest**
	No interest	**No interest**	
ETEC (ETVAX) (Liquid SDV, lyophilised buffer, lyophilised adjuvant)	Candidates are in development, with support from multiple funders.	Optimization of thermostability should be encouraged through the WHO preferred product characteristics guidance[dddd] and candidate specific target product profiles.	**No interest**
	No interest	**No interest**	
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	Candidates are in development, with support from multiple partners.	Optimization of thermostability should be encouraged through the WHO preferred product characteristics guidance[eeee] and candidate specific target product profiles.	**No interest**
	No interest	**No interest**	
Influenza (pandemic) (VAL 506440) (Liquid; presentation unknown)	Candidates are in development	Optimization of thermostability should be encouraged through the WHO preferred product characteristics guidance[ffff] and candidate specific target product profiles.	**No interest**
	No interest	**No interest**	

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.*

[dddd] WHO website. WHO preferred product characteristics (PPCs) page. https://www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/. Accessed February 29, 2020.
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[ffff] WHO website. WHO preferred product characteristics (PPCs) page. https://www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/. Accessed February 29, 2020.

Table 28

Parameter assessment		
Vaccines	**Are there known barriers to Global Access to the innovation as applied to the vaccine ?**	**Overall score**
• **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) • **HPV** (SDV or 2-dose vial) • **Typhoid conjugate** (Liquid SDV or 5-dose)	No known barriers to access for these vaccines given that products from existing manufacturers are sufficiently heat stable for CTC qualification in their current formats.	**No known barriers to global access**
All other applicable vaccines	**No data.**	**No data**

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

This innovation can potentially address the following public health issues when applied to compatible vaccines: vaccine ineffectiveness/wastage due to freeze exposure, vaccine ineffectiveness/wastage due to heat exposure, cold chain requirements during outreach, and difficult preparation requiring trained personnel.

Application to existing liquid vaccines: Of the existing liquid vaccines analysed under VIPS that are deemed potentially technically feasible for application of this innovation, the following are also priority vaccines for CTC use as determined by WHO's CTC working group:

- Hepatitis B vaccine – The innovation addresses the top 3 priority problems for country stakeholders as identified in the VIPS Phase II online surveys: #1) vaccine ineffectiveness/wastage due to freeze exposure, #2) cold chain requirements during outreach, and #3) vaccine ineffectiveness/wastage due to heat exposure.
- HPV vaccine – The innovation addresses the 3/5 priority problems for country stakeholders: #2) vaccine ineffectiveness/wastage due to freeze exposure, #3) cold chain requirements during outreach, and #4) vaccine ineffectiveness/wastage due to heat exposure. This vaccine was identified as the highest priority vaccine for CTC use by country stakeholders participating in the VIPS Phase II online survey.
- Typhoid vaccine – The innovation addresses 1/5 priority problems for country stakeholders: #1) vaccine ineffectiveness/wastage due to freeze exposure.
- It should be noted that oral cholera vaccine is a CTC working group priority and one product is already WHO prequalified and several countries have begun introducing OCV in a CTC to facilitate rapid response to cholera outbreaks. However, this vaccine is not included as part of the VIPS evaluation.

Application to pipeline liquid vaccines: Development of heat stable liquid vaccine formulations for all pipeline vaccines should be encouraged, particularly for vaccines that are not envisaged to be delivered only though routine delivery strategies.

- Ebola and pandemic influenza vaccines – While not evaluated in the country consultations, there are likely strong benefits to CTC use of these vaccines for outbreak response if they can be sufficiently heat stabilized.
- HIV liquid booster – The CTC working group has deferred a decision on the appropriateness of this vaccine for CTC use given the unknowns around the context of use.

Application to lyophilised or heat labile vaccines: Not all vaccines can be sufficiently heat-stabilized for CTC qualification and presented as liquid formulations. This is especially true of vaccines that are currently lyophilised or need to be stored as frozen liquids. While MR and rabies vaccine have been included in this evaluation, they may be better suited to CTC qualification as dry products – ideally in single dose and ready-to-use formats to prevent safety and vaccine wastage issues associated with reconstitution. Note that Meningitis A vaccine is already WHO prequalified for CTC use as a lyophilised product. For this vaccine, the CTC use applies only to initial campaigns.

Exceptions: A number of vaccines included in this evaluation are not currently WHO priorities for CTC use including pentavalent, IPV, rotavirus and ETEC candidates.

SYNERGIES WITH OTHER VIPS INNOVATIONS:

Compact prefilled autodisable devices (CPADs): Heat stable and CTC qualified liquid vaccine formulations could offer additional benefits in terms of timely and increased immunization coverage if packaged in compact prefilled autodisable devices (CPADs) based on the history of successful out of the cold chain use of hepatitis B and tetanus toxoid vaccines in Uniject CPADs and the delivery of these vaccines by lesser trained health workers (7).[gggg]

Vaccine vial monitors with threshold indicators (VVM-TIs): At present, vaccines used in a CTC must be monitored for heat exposure with both VVMs and separate TIs. This presents a barrier to CTC introduction of vaccines given the additional training and logistics required to properly distribute, store, and use the TIs. The introduction of a combined VVM-TI that is read identically to the existing VVM would remove these obstacles and provide a more accurate indicator of heat exposure to vaccines.

Autodisable sharps injury prevention syringes (AD SIPs): As with all parenterally delivered vaccines, safety improvements could be realized with the use of AD SIPs with heat stable/CTC liquid vaccines.

Freeze-resistant liquid vaccine formulations: Many liquid vaccines that could qualify for CTC use are also freeze-sensitive, so the combination of a heat-stable and freeze-resistant formulation could prevent decreases in vaccine effectiveness due to freeze exposure.

Barcodes: As with all vaccine products, barcodes applied to the primary containers of heat stable/CTC qualified liquid vaccines would serve to improve vaccine availability, immunization coverage and equity, and save health worker time when used for inventory management and record-keeping.

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