Combined Vaccine Vial Monitor and Threshold Indicator

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

Technology overview

Vaccine vial monitors (VVMs) change gradually change colour in response to cumulative heat exposure, however their response is not rapid enough at higher temperatures (e.g. above 37°C or 40°C) for use with vaccines kept in a controlled temperature chain (CTC). Therefore, a separate threshold indicator (TI) must be used in addition to VVMs when vaccines are kept in a CTC. The TI reacts rapidly if exposed at or above a defined threshold temperature. Currently, VVMs and TIs are not integrated. VVMs on vaccine primary containers and standalone TIs are used when vaccines are kept in a CTC. These TIs must be purchased and distributed separately from the vaccine and kept at temperatures below their threshold. They are placed in vaccine carriers and cold boxes (without icepacks) during CTC storage and transport.

A combined VVM-TI on primary containers is a single indicator that undergoes gradual colour change up to a specified peak threshold temperature and rapidly reacts if exposed at or above the threshold temperature.

Summary of innovation applicability to vaccines:

It is technically feasible to apply this innovation to all vaccines. VVM-TIs are more accurate indicators of potential heat damage than existing VVMs as the integrated indicator allows for both cumulative monitoring of heat exposure as well as the additional rapid indication when vaccines are exposed to high temperatures. VVM-TIs are especially appropriate for vaccines intended for use in a CTC as these vaccines are intentionally exposed to ambient temperatures for a limited time period in order to facilitate vaccine outreach. The VVM-TI innovation is evaluated for all VIPS priority vaccines in this technical note with special consideration given to its applicability to vaccines that are currently used in a CTC or those vaccines that could potentially be used in a CTC in the future.

The vaccines considered or not considered for use with VVM-TIs in this Technical Note are summarised in Tables 1 and 2 respectively.

Problem statements to be addressed:

VVM-TIs provide benefits in terms of improved temperature monitoring and facilitation of CTC use of vaccines, but do not address vaccine specific problems identified by stakeholders.

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

Per World Health Organization guidelines, vaccines recommended for CTC use are those used in campaign or special strategy settings.[d] Existing and potential CTC vaccines are marked as such in the table below. For this technology the comparator for vaccines used in a CTC is the same vaccine and presentation with a VVM and a separate threshold indicator. For all other vaccines, the comparator is the same vaccine and presentation with a VVM.

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[e]	Comparator dose(s) per container[f,g]
Licensed vaccines							
Pentavalent (Diphtheria tetanus pertussis hepatitis B haemophilus inflluenzae type B inactivated poliovirus; DTP, HepB, Hib) Not a WHO priority for CTC	Inactivated subunit plus polysaccharide-protein conjugated vaccine (PS-PCV)	Liquid	Yes (Aluminium-salt based)	Yes	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S
Hepatitis B (birth dose) Potential CTC use	Subunit	Liquid	Yes (Aluminium-salt based)	Yes	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S.

[a] *From a long list of vaccines, 17 VIPS priority vaccines were selected based on covering a wide spectrum of different vaccine platforms, route of administration, vaccine presentations and delivery strategy to ensure they represent different family of vaccines, such that evaluating one antigen will be representative of the others and innovations for one family member would be applicable to all. The final list include 11 licensed vaccines that are WHO PQ'd, GAVI funded and UNICEF procured, as well as 6 pipeline candidate vaccines. Refer to the document 'Scope of vaccines' for the detailed explanation.*

[b] *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.*

[c] *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.*

[d] World Health Organization website. Immunization, Vaccines and Biologicals: Controlled temperature chain (CTC) page. https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/. Accessed 21/10/2019.

[e] *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 in vaccination strategies and existing vaccine products across 54 countries. Participants were provided with a standard list of problem statements for the 10 licensed vaccines analysed through VIPS and were asked to select the top 3 problem statements for all vaccines they had knowledge about. Table 1 presents the top 3 predominant problem statements selected by the respondents and ranked in order per vaccine.*

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[e]	Comparator dose(s) per container[f,g]
Human papillomavirus (HPV) Existing CTC use	Subunit	Liquid	Yes (Aluminium-salt based)	No	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 2-dose vial and delivery by IM injection with an AD N&S.
Measles rubella (MR) Potential CTC use	Live attenuated.	Lyophilised	No	No	SC	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 10-dose vial
Meningitis A (MenAfriVac) Existing CTC use	PS-PCV	Lyophilised	Yes, in diluent (Aluminium-salt based)	Yes**	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 10-dose vial
Inactivated poliovirus (IPV)* Not a WHO priority for CTC	Whole-inactivated	Liquid	No	Yes	IM or ID	VVM-TIs provide benefits, but do not address vaccine-specific problems.	• IM (0.5ml/dose): SDV or 10-dose vial • ID (0.1ml/dose): SDV (5 fractional doses) or 5-dose vial (25 fractional doses).
Rabies* Potential CTC use	Whole-inactivated.	Lyophilised	No	No	IM or ID	VVM-TIs provide benefits, but do not address vaccine-specific problems.	• IM (0.5ml/dose): SDV • ID (0.1ml/dose): SDV (5 fractional doses)
Rotavirus Not a WHO priority for CTC	Live attenuated virus	Liquid	No	No	Oral	VVM-TIs provide benefits, but do not address vaccine-specific problems.	Liquid single-dose plastic squeeze tube.

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[e]	Comparator dose(s) per container[f,g]
Typhoid (conjugate) Potential CTC use	PS-PCV	Liquid	No	Yes**	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 5-dose vial
Yellow fever Potential CTC use	Live-attenuated	Lyophilised	No	No	SC or IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 10-dose vial
Ebola (recombinant vesicular stomatitis virus, Zaire Ebola virus) (rVSV-ZEBOV) Potential CTC use	Live vector	Liquid, frozen	Not known	Not known	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	Recently licensed as SDV vial
Enterotoxigenic *E. coli* (ETEC) (ETVAX) Not a WHO priority for CTC	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized adjuvant	Yes (dmLT, double-mutant heat labile toxin [of ETEC])	No	Oral	VVM-TIs provide benefits, but do not address vaccine-specific problems.	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.

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[e]	Comparator dose(s) per container[f,g]
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)[h] Potential CTC use	Heterologous live attenuated recombinant viral vector + recombinant protein booster	Lyophilized prime and liquid booster (gp120)	Yes (MF59 [oil-in-water emulsion]) (recombinant protein booster)	Not known	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	As still in Phase 2b/3, assume SDV
Influenza (pandemic, VAL-506440) Potential CTC use	Nucleic acid	Liquid	Not known	Not known	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV
Malaria (RTS,S) Potential CTC use	Recombinant protein	Lyophilized vaccine; adjuvant in diluent	Yes (AS01E [QS21 + MPL] in diluent)	Not known	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	Dry (vaccine) SDV and liquid (adjuvant/diluent) SDV clipped together
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002) Potential CTC use	Live attenuated	Lyophilised	No	No	ID	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV or 20-dose vial
Respiratory syncytial virus (RSV) (pre-fusion F protein) Not a WHO priority for CTC	Subunit	Lyophilised	No	Not known	IM	VVM-TIs provide benefits, but do not address vaccine-specific problems.	SDV

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

[h] *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.*

** Must be discarded after 6 hours

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

Vaccine	Rationale for exclusion
None	There are no vaccines that are not technically feasible, as the innovation can be applied to all vaccine primary containers.

SECTION TWO: Assessment of vaccine-innovation product against a comparator

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

1.1 Criteria on health impact

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

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**
All applicable vaccines	The VVM-TI is a heat indicator label and has no impact on vaccine efficacy and therefore is no different than the comparator.	**Neutral**

[i] *Vaccines not assessed were excluded on the basis of lack of applicability of the vaccine with the innovation. Vaccines that scored 'maybe' in the pairing matrix have been excluded.*

Indicator: Vaccine effectiveness

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

Table 4

Parameter assessment		
Vaccines	**Parameter:** ***Does the innovation improve vaccine effectiveness as per the following parameters based on field or other evidence?*** ○ ***Cases averted*** ○ ***Outpatient visits averted*** ○ ***Hospitalisations averted*** ○ ***Deaths averted*** ○ ***Vaccine doses given within the recommended age range (timeliness of vaccination)***	**Overall score**
All applicable vaccines	The VVM-TI might improve vaccine effectiveness in comparison to vaccines with just VVMs by preventing use of vaccines that have been exposed to temperatures above the threshold temperature in the TI. However, there are no data to support this.	**No data**

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

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

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

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

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)?*	*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)?*	*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.	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
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.[l]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
HPV (liquid SDV or two-dose vial)	Outreach to schools and communities	No. VVM30	Quadrivalent HPV vaccine (Merck) is qualified for CTC use (up to 3 days, below 42°C). [m]	Yes. For outreach to schools and communities.[n]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

[l] World Health Organization, PATH. Controlled Temperature Chain: Strategic Roadmap for Priority Vaccines 2017-2020. Geneva: WHO; 2017. https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1.

[m] *World Health Organization 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 21/10/2019.

[n] Summary of the WHO Position Paper on Typhoid vaccines: WHO position paper – March 2018. https://www.who.int/immunization/policy/position_papers/PP_typhoid_2018_summary.pdf?ua=1.

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?*	*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)?*	*Does the innovation paired with the vaccine improve heat stability?*
MR (Lyophilized 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 (1).	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
Meningitis A (MenAfriVac) (Lyophilized 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).[o]	Yes. For initial campaign use.[p]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
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	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized 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.[q]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

[o] *World Health Organization 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 21/10/2019.

[p] *World Health Organization website. Meningococcal meningitis page.* https://www.who.int/immunization/diseases/meningitis/en/. Accessed 21/10/2019.

[q] *WHO Expert Consultation on Rabies, third report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1012).*

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)?*	*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)?*	*Does the innovation paired with the vaccine improve heat stability?*
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.	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
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 (2).	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
Yellow Fever (Lyophilized SDV or 10-dose)	Routine Campaigns Outbreak response	No VVM 14	No. A study to analyse CTC potential for YF in multidose vial format by one manufacturer did not support the CTC indication based on stability of the lyophilized product and stability of the reconstituted product at 40°C. New YF formulations may be more stable, however.	Yes, for both use case scenarios	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

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)?*	*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)?*	*Does the innovation paired with the vaccine improve heat stability?*
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. Stored as frozen liquid at -80°C for long term storage.[r] Can be stored at 2-8°C for no more than two weeks or at room temperature for four hours after thawing.[s]	No data, but unlikely.	Yes. for both use case scenarios.[t]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
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.	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	No data	No data.	Yes. For outreach and campaigns	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

[r] World Health Organization, Ebola vaccines – Background paper for SAGE deliberations. Overview of the Current Research, Development and Use, of Vaccines Against Ebola. WHO: Geneva; 2019. https://www.who.int/immunization/sage/meetings/2019/october/CICG_sitting_plan.pdf. Accessed 21/10/2019.

[s] Merck Sharp & Dohme Corp. ERVEBO® [package insert]. Whitehouse Station, NJ: Merck; 2019. Available at: https://www.fda.gov/media/133748/download

[t] World Health Organization 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 20, 2020.

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)?*	*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)?*	*Does the innovation paired with the vaccine improve heat stability?*
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data	No data.	Yes, for both use case scenarios	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	Routine and campaign use in areas of high endemicity.[u]	No data	No data	Yes. For campaign use.[v]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002) (Lyophilized SDV or 20-dose)	Routine-use in neonates and adolescents Could be co-administered with hepatitis B birth dose.	No: VVM 14 or 30 (based on BCG)	No data	Yes. Vaccine is likely to be for routine-use only. However, given that is administered at or close to birth, it could be co-administered with heat stable hepatitis B vaccine. CTC use could be beneficial for birth-dose outreach to homes, storage at remote health facilities without cold chain, or outreach to adolescents.[w]	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

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

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

[w] *WHO Preferred Product Characteristics for New Tuberculosis Vaccines. Geneva: World Health Organization; 2018.*

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)?*	*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)?*	*Does the innovation paired with the vaccine improve heat stability?*
Respiratory syncytial virus (RSV) (pre-fusion F protein) (Lyophilized SDV)	Expected to be a routine maternal vaccine, and possibly administered on a seasonal basis.	No data	No data	Not essential. Assumed to be delivered during an anti-natal visit.	The VVM-TI is a heat indicator label and has no impact on the heat stability of vaccines, which is no different than the comparator. **Neutral**

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**
All applicable vaccines	The VVM-TI is a heat indicator label and does not impact damage to a vaccine due to freeze exposure, which is no different than the comparator.	**Neutral**

1.2 Criteria on coverage and equity

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

*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**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	CTC use of vaccines can likely help to improve equitable coverage and use of combined VVM-TIs can likely help to facilitate CTC use better than the CTC comparator. However, there are no data on whether the combined VVM-TI can better facilitate CTC use than the comparator.	**No data**

[x] *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*

Parameter assessment		
Vaccines	***Does the innovation improve the overall coverage for the vaccine within a target population for one or all doses?***	**Overall Score**
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	Both the innovation and comparator monitor heat exposure of vaccines and do not impact coverage.	**Neutral**

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

*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.*

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

Table 8

Parameter assessment						
Vaccines	***Does the innovation avoid reconstitution and is that an improvement?***	***Does the innovation require fewer vaccine product components?***	***Does the innovation require fewer preparation steps and less complex preparation steps?***	***Does the innovation improve dose control?***	***Does the innovation improve targeting the right route of administration (accuracy in terms of route and/or depth of injection)?***	**Overall score**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on vaccine reconstitution.	The VVM-TI is a single indicator attached to primary packaging, while the comparator has 2 separate components (a VVM and a standalone TI).	The VVM-TI would replace the stand-alone TIs that are currently distributed with vaccines in a CTC. Health workers managing vaccines in a CTC would only have to interpret the VVM-TI instead of two indicators (the VVM and separate TI).	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on dose control.	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on targeting the right route of administration.	**Better**
	Neutral	**Better**	**Better**	**Neutral**	**Neutral**	
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on vaccine reconstitution.	The innovation is a label that would replace the existing VVM and therefore is no different than the comparator.	The innovation would simply be read instead of the existing VVM. The currently available VVM-TI is identical in appearance and interpretation to the existing VVM.	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on dose control.	The innovation, like the comparator, only indicates whether vaccines have been exposed to heat and therefore has no impact on targeting the right route of administration.	**Neutral**
	Neutral	**Neutral**	**Neutral**	**Neutral**	**Neutral**	

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

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

Table 9

Parameter assessment					
Vaccines	***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. caregivers/parents/lesser trained personnel) to administer the vaccine?***	***Does the innovation enable self-administration?***	**Overall score**
All applicable vaccines	The assumed use case varies by vaccines. However, the innovation has no impact on the intended use case and it would be the same as for the comparators.	The VVM-TI, like the comparators, only indicates whether vaccines have been exposed to heat and therefore does not impact the ability of a lesser trained person to prepare or administer a vaccine nor does it impact the ability to self-administer a vaccine.			**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 VVM-TI, like the comparators, only indicates whether vaccines have been exposed to heat and therefore does not impact the ability to use dose sparing for a vaccine.	**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	The VVM-TI, like the comparators, only indicates whether vaccines have been exposed to heat. The VVM-TI and comparators are applicable to both SDV and MDV and have no impact on the presence of preservatives.	**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**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	The VVM-TI, like the comparator, only indicates whether vaccines have been exposed to heat and therefore does not impact pain experienced by the vaccine recipient.	While health care workers may need slightly less time to refer to the VVM-TI than to the comparator (VVM and standalone TI), this is unlikely to impact the time taken by the health care worker to administer the vaccine or any other parameter affecting the vaccinees or caregivers.	CTC use of vaccines can likely make vaccination more convenient for vaccinees/caregivers and use of combined VVM-TIs can likely help to facilitate CTC use better than the comparator. However, there are no data on whether the combined VVM-TI can better facilitate CTC use than the comparator.	**Neutral**
	Neutral	**Neutral**	**No data**	
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	The VVM-TI, like the comparator, only indicates whether vaccines have been exposed to heat and therefore does not impact pain experienced by the vaccine recipient.	The VVM-TI is read similarly to the existing VVM comparator and therefore should not impact the time taken by the health care worker to deliver the vaccine or any other parameter affecting the vaccinees or caregivers.	The VVM-TI provides more accurate information than the existing VVM comparator when a vaccine is inadvertently exposed to higher temperatures. However, there are no data on whether or not vaccines/caregivers are aware of vaccine indicators or their accuracy.	**Neutral**
	Neutral	**Neutral**	**No data**	

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

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

Table 13

Parameter assessment			
Vaccines	***Does the innovation require fewer components?***	***Or does the innovation include labelling that facilitates product tracking?***	**Overall score**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	Yes. The VVM-TI (1 component) is used in comparison to having a VVM on the primary container and a separate TI (2 components) that must be stocked and distributed with CTC vaccines.	The VVM-TI and the comparator are heat indicator labels that are not used to track commodities in the supply chain.	**Better**
	Better	**N/A**	
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	No. The VVM-TI simply replaces the comparator (VVM on the primary container) so does not affect the number of components.	The VVM-TI and the comparator are heat indicator labels that are not used to track commodities in the supply chain.	**Neutral**
	Neutral	**N/A**	

1.3 Criteria on safety

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

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

Table 14

Parameter assessment		
Vaccines	***Does the innovation reduce the frequency of serious AEFIs ?***	**Overall score**
All applicable vaccines	The innovation, like the comparators, only indicates whether vaccines have been exposed to heat. Heat exposure can impact vaccine effectiveness, but is unlikely to impact the frequency of serious AEFIs.	**Neutral**

Indicator: Likelihood of contamination and reconstitution errors due to use of wrong diluent

(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.*

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

Table 15

Parameter assessment							
Vaccines	***Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?***	***Does the innovation reduce the potential risk of reuse of delivery technology?***	***Does the innovation reduce the risk of use of nonsterile components?***	***Does the innovation reduce the risk of contamination while filling the delivery device?***	***Does the innovation require fewer preparation steps and less complex preparation steps)?***	***Does the innovation reduce the likelihood of using an incorrect diluent during reconstitution?[aa]***	***Overall score***
All applicable vaccines	The innovation, like the comparators, only indicates whether vaccines have been exposed to heat and has no impact on risk of vaccine contamination during reconstitution or filling a delivery device, potential reuse of delivery technology, use of nonsterile components, preparation steps, or potential use of incorrect diluent.						**Neutral**

Indicator: Likelihood of needle stick injury[bb]

*Score l***egend: 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 16

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?[cc]***	***Does the innovation reduce the risk of injury after vaccine administration?***	**Overall score**
All applicable vaccines	The innovation, like the comparators, only indicates whether vaccines have been exposed to heat and has no impact on quantity of sharps, use of sharps, inclusion of auto disable features, sharps injury prevention, or risk of injury after vaccine administration.					**Neutral**

[aa] *Incorrect diluent – use of the wrong the substance as opposed to the wrong volume of diluent.*
[bb] *For all vaccines being assessed the assessment and score of this indicator remains the same as in Phase 1.*
[cc] *NOTE: In Phase I, sharps-free innovations were scored as N/A for this feature since SIP features are not applicable. Scoring methodology was revised to reflect the added value of a sharps-free innovation.*

1.4 Criteria on economic costs

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

*Score l*egend: 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*
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies	A VVM-TI costs more than a VVM. Pricing and availability of VVM-TIs in dot format was published in the Temptime's *2019 HEATmarker® VVM Worldwide Public Donor Market Price Guide*".[ee] Price quotations indicate a 75% maximum price premium for a VVM-TI over the same VVM type. The premium ranges from about $0.03 to $0.04 per unit. A decrease in premium is anticipated when sustained annual VVM-TI demand exceeds 50 million units, additional decreases in premium will likely be applied at higher volumes.[ff]	The innovation, like the comparator, would not have any impact on costs of delivery devices.	The innovation, like the comparator, would not have any impact on safety box costs.	Overall score: **Worse** • VVM-TI would result in a maximum of a 75% price premium (equivalent to a price increase of $0.03 – $0.04 per unit) compared to the same VVM type, though price reductions are possible when demand increases beyond 50 million units.

[dd] *Vaccine regimen cost refers to the vaccine product and innovation cost times number of doses for complete immunization.*
[ee] 2019 HEATmarker® VVM Worldwide Public Donor Market Price Guide. Temptime Corporation. November 2018 edition.
[ff] Personal communication, Temptime.

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*
• Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	A VVM-TI would also cost more than a VVM with a standalone TI card. Quotations from TI manufacturers showed that TI card prices range from $0.26 to $0.50 per card depending on production volumes. Since one TI card is used per vaccine carrier, this cost is shared across several doses and the TI card can be reused as long as it has not reached endpoint. An unpublished PATH study estimated that the purchase cost of vaccines would increase with a VVM-TI compared to a VVM with a separate TI. So the use of a VVM-TI would increase the purchase cost of vaccines. This is especially true for vaccines in single-dose containers where one dose bears the full cost of the VVM-TI (Note wastage rate is normally extremely low for SDV).			• A VVM-TI would cost more than use of a separate VVM and TI (estimated cost of separate a TI is $0.25 - $0.50 per vaccine carrier which can be <$0.01 per dose since it is shared among several doses and reusable if it has not reached endpoint). • No change in delivery device and safety box purchase costs.
	Worse	**Neutral**	**Neutral**	
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	As above, a VVM-TI costs more than a VVM so the use of a VVM-TI would increase the purchase cost of vaccines.	The innovation, like the comparator, would not have any impact on costs of delivery devices.	The innovation, like the comparator, would not have any impact on costs of delivery devices.	Overall score: **Worse** Same overall score rationale as for vaccines potentially used in a CTC.
	Worse	**Neutral**	**Neutral**	

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

*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**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	The use of this innovation would not impact the costs of the cold chain storage or transport. For the comparator (VVM with a separate TI card) one TI card is placed in each cold box or vaccine carrier and shared across several vaccine vials. The additional volume from the separate TI indicator is negligible given the TI is a flat card.	The use of this innovation would not impact the costs of out of cold chain storage and transport compared to the VVM with a separate TI card. For the comparator, the separate TI card would be stored in a cool dark place before use and this adds a very small and insignificant volume to the commodities that are stored and transported out of the cold chain.	When using vaccines in a CTC, having a VVM-TI would reduce the time vaccinators spend on monitoring vaccines during vaccination sessions since with a VVM-TI they would only check one indicator rather than checking two indicators when using a VVM and a separate TI card.[hh] However, this cost saving is very small since vaccinator time costs are low.	Neither the use of this innovation or the comparator would change the time spent by staff in stock management.	Overall score: **Better** • Reduction in time spent by vaccinators on monitoring vaccines since they will only have to monitor one indicator. But the cost savings are very small because vaccinator time costs are low. • No change in costs for cold chain and out of cold chain storage and transport. • No change in costs of time spent by staff in stock management.
	Neutral	**Neutral**	**Better**	**Neutral**	

[gg] *Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing.*
[hh] PATH. *Field Evaluation Report: Temptime Combined Vaccine Vial Monitor and Threshold Indicator*. Seattle: PATH; 2017.

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**
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	The use of this innovation would not impact the costs of the cold chain storage or transport. Both the VVM-TI and existing VVM comparator are small labels on the primary package that do not impact cold chain volumes.	Neither the innovation or the comparator are stored out of the cold chain so there is no impact on out of cold chain costs with either technology.	The time vaccinators spend reviewing the status of the VVM-TI versus the VVM is expected to be identical.	The VVM-TI and the existing VVM are both labels provided on vaccine primary containers and do not impact time spent by staff on stock management.	**Overall score: Neutral** • The innovation does not impact delivery costs for vaccines not used in a CTC.
	Neutral	**Neutral**	**Neutral**	**Neutral**	

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

*Score legend: Green: **Better than the comparator**: Reduces the introduction/recurrent costs of the vaccine regimen Green: 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?***	**Overall score**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	Training costs: Less training required for CTC implementation as training on separate TIs would not be required with use of VVM-TIs.	**Better**
	Better	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for VVM-TIs.	
	Neutral	
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	Training costs: There is no training required since a VVM-TI is interpreted identically to the existing VVM.	**Neutral**
	Neutral	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for VVM-TIs.	
	Neutral	

1.5 Criteria on environmental impact

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

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

Table 20

Parameter assessment				
Vaccine	***Does the innovation reduce the volume of medical (biohazard) disposal waste?***	***Does the innovation reduce sharps waste disposal?***	***Is the innovation, and its packaging, composed of more sustainable materials that improves waste disposal?***	**Overall score**
Vaccines potentially used in a CTC (including those currently qualified or prioritized for CTC use and those for which CTC use could provide benefits): • Hepatitis B (birth dose) • HPV • MR • Meningitis A • Rabies • Typhoid • YF • Ebola • HIV • Influenza • Malaria • MTb	Neither the innovation or the comparator impact the volume of medical disposal waste. **Neutral**	Neither the innovation or the comparator impact the presence of sharps or their disposal. **Neutral**	The VVM-TI innovation is a small label on the primary container that is identical in size to the existing VVM. The comparator is the existing VVM plus use of a separate standalone TI card that must be disposed of after it has been exposed to heat above the threshold temperature.	**Better**

[ii] *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).*

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**
Vaccines not used in a CTC: • Pentavalent • IPV • Rotavirus • ETEC • RSV	Neither the innovation or the comparator impact the volume of medical disposal waste. **Neutral**	Neither the innovation or the comparator impact the presence of sharps or their disposal. **Neutral**	The VVM-TI is a small label on the primary container that is identical in size to the comparator which is the existing VVM.	**Neutral**

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexityjj

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

*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.*

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

Table 21

Vaccines	*Is the clinical development pathway complex?*	Overall score
All applicable vaccines	No clinical development is required for application of a VVM-TI to a vaccine primary container. The application of the innovation to the vaccine will not require a phase III efficacy study or non-inferiority trial as there is no change in the formulation, route of administration, or delivery mechanism (needle and syringe). The replacement of existing VVMs to VVM-TIs on vaccine vials is a label change that would likely be driven by WHO and UNICEF procurement policies and/or vaccine manufacturer interest in providing an improved heat exposure indicator on their products. The label change would require identification of the correct VVM-TI for each vaccine followed by regulatory and WHO prequalification authorization.	**No complexity**

Indicator: Technical development challenges

A survey[kk] of the WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, were invited to complete a survey following a consultation VVM-TI. Six member organizations responded to the survey and five member organizations responded to the question on technical challenges. The following challenges were identified as the most important technical challenges facing the development of VVM-TIs (most frequently identified challenges first):

- Internal testing of new VVM-TIs (5/5).
- Identification of the appropriate VVM-TIs for specific vaccines (4/5)
- Write-in response: Develop a reliable & affordable TI solution (1/5)

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

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.*

[kk] *Survey carried out after DTWG telecons on VVM-TI held on 9th Dec and 10th Dec, 2019.*

Table 22

Parameter assessment		
Vaccines	***How complex are the technical challenges to overcome for successful product development (i.e. difficulties applying the innovation to a combination vaccine, reformulation requirements, vaccine not well characterized, etc)?***	**Overall score**
All applicable vaccines	One version of the technology (the VVM250-TI40)[ll] produced by Temptime/Zebra is WHO prequalified. The Temptime VVM-TI is based on the VVM indicators that have been used in immunization programs for decades and includes a TI chemical layer under the active VVM chemical layer. VVM30 with 40°C TI will be the next version for prequalification. Versions with different TI temperature thresholds are possible but proliferation of the range of offerings will likely impact the pricing grid. Many of these versions are specifically being developed for vaccines that are or will be used in a CTC.[mm] Other temperature indicator manufacturers have developed different VVM technologies and could also conceivably produce VVM-TIs in the future. Vaccine manufacturers surveyed through the Delivery Technologies Working Group[nn] verified that there are minimal technical challenges associated with labelling products with VVM-TIs other than the need to conduct internal testing of the label and to identify the appropriate VVM-TI for each vaccine. The labelling equipment used to place VVM-TIs on vaccine products is the same as that used for existing VVMs.	**Low complexity**

Indicator: Complexity of manufacturing the innovation

A survey[oo] of the WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, were invited to complete a survey following a consultation VVM-TI. Six member organizations responded to the survey and five member organizations responded to the question on manufacturings challenges. The following challenge was identified as the most important technical challenge facing the development of VVM-TIs:

- Labelling issues (assume the label attachment method is the same as the existing VVM) (2/5)

Of the five respondents, three selected 'do not know'.

[ll] *WHO. Temperature monitoring devices: E006 [Product Information Sheet]. Geneva: WHO; 2019-2020. http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/LinkPDF.aspx?UniqueID=62f37a16-e2cd-4dd3-9ed5-973fcbef2ba5&TipoDoc=DataSheet&ID=0.*

[mm] *Personal communication, Temptime.*

[nn] *Survey carried out after DTWG telecons on VVM-TI held on 9th Dec and 10th Dec, 2019.*

[oo] *Survey carried out after DTWG telecons on VVM-TI held on 9th Dec and 10th Dec, 2019.*

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

*Score l*egend: **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**
All applicable vaccines	The manufacturing process for Temptime VVM-TIs is well suited for large scale production of VVM-TI dots. Capacity can be increased beyond the current single shift (5 days a week) to meet any anticipated demand. At least a two-year supply of VVM active monomer is maintained as part of Temptime's Business Continuity Plan. Components for TI are readily available[pp].	**No complexity**

Indicator: Robustness of the innovation-vaccine pipeline

In table 24, it has been assumed throughout that:

- There is one VVM-TI device developer (i.e.Temptime/Zebra – see phase I TN for details).
- The 'suppliers/manufacturers of the vaccine' parameter focuses on WHO prequalified products (see WHO Prequalified Vaccines Database for details).[qq]
- Therefore, on a non-vaccine-specific basis, the number of developers would be assessed as 'not robust'. However, the pipeline is even less robust when considered at the vaccine-specific level.
- While VVMs are broadly used for all WHO prequalified vaccines supplied through UNICEF and Gavi, only one vaccine manufacturer is preparing to label one lyophilized rotavirus vaccine product (not a VIPS priority vaccine) with a VVM250-TI40 – though their vaccine is not intended for CTC use.
- Developers have been assessed as to whether or not they have a programme on the specific vaccine in question.
    - Where possible only products that are in 'full' preclinical development (i.e. with a clear path and intention to enter clinical trials) or clinical development have been listed.
    - In cases where studies have been published, and it is possible, but not clear whether the programme will progress to clinical studies, the key publications have been listed.
    - Exploratory, preclinical studies, especially by academic groups have not been included.

[pp] Personal communication, Temptime.

[qq] 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 development programmes.	There are multiple producers of liquid pentavalent or other DTP-containing vaccines. There are six WHO PQ manufacturers of pentavalent vaccine.
	Not robust	**Highly robust**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	No development programmes.	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ hepatitis B vaccine.
	Not robust	**Highly robust**
HPV (SDV or 2-dose vial)	No development programmes.	There are two manufacturers of three licensed HPV vaccines. Both have WHO PQ products. Several other manufacturers are developing HPV vaccines. UNICEF does not expect any new HPV vaccines to be WHO PQ'ed before 2021.[rr]
	Not robust	**Moderately robust**
MR (Lyophilised SDV or 10-dose)	No development programmes.	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**
Meningitis A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	No development programmes.	There is only one manufacturer of MenAfriVac (which is WHO PQ) and one manufacturer known to be developing a MenACWYX vaccine.[ss]
	Not robust	**Not robust**

[rr] *UNICEF 2018. HPV vaccine supply and demand update. https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf. Accessed 21/10/2019.*

[ss] Serum Institute of India PVt. LTD. Website. Product Pipeline page. Accessed 21/10/2019. https://www.seruminstitute.com/product_horizon.php.

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No development programmes.	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV. There are however supply constraints[tt] and only two suppliers to UNICEF (3). New manufacturers of PQ IPV are expected to enter the market from 2020.[uu]
	Not robust	**Not robust**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	No development programmes.	There are several manufacturers of rabies vaccines. Four manufacturers have WHO PQ products.
	Not robust	**Moderately robust**
Rotavirus (Liquid SD plastic tube)	No development programmes.	There are three WHO PQ suppliers of liquid rotavirus vaccines.
	Not robust	**Moderately robust**
Typhoid conjugate (Liquid SDV or 5-dose)	No development programmes.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ.
	Not robust	**Not robust**
Yellow Fever (Lyophilised SDV or 10-dose)	No development programmes.	There are several manufacturers of YF vaccines. Four manufacturers have WHO PQ products.
	Not robust	**Moderately robust**
Ebola (rVSV-ZEBOV) (Liquid SDV or 10-dose)	No development programmes.	There is only one manufacturer of this particular Ebola vaccine candidate. Other Ebola vaccines have different characteristics.
	Not robust	**Not robust**
ETEC (ETVAX) (Liquid SDV)	No development programmes.	There is only one manufacturer of this particular candidate ETEC vaccine. Other ETEC vaccines have different characteristics.
	Not robust	**Not robust**

[tt] UNICEF 2019. IPV vaccine supply update. Available at https://www.unicef.org/supply/files/ipv-inactivated-polio-vaccine-supply-update.pdf. Accessed 21/10/2019.

[uu] UNICEF 2019. IPV vaccine supply update. Available at https://www.unicef.org/supply/files/ipv-inactivated-polio-vaccine-supply-update.pdf. Accessed 21/10/2019.

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	No development programmes.	There is only one manufacturer of this particular candidate HIV vaccine. However, a similar candidate vaccine using a different virus vector and recombinant protein in a heterologous prime-boost regimen is in late-stage trials. [vv]
	Not robust	**Not robust**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No development programmes.	There are a few developers of mRNA vaccines against pandemic flu: Moderna [ww]; Curevac (universal flu vaccine)[xx] and Vir (universal flu vaccine)[yy]. Other pandemic influenza vaccines have different characteristics.
	Not robust	**Moderately robust**
Malaria (RTS,S) Lyophilized SDV or 2-dose vial, recon with diluent)	No development programmes.	There is only a single developer of RTS,S vaccine. Many other malaria vaccines are in clinical development, but have different characteristics to RTS,S.[zz]
	Not robust	**Moderately robust**
M. Tb (next generation, VPM 1002) (Lyophilized SDV or 20-dose)	No development programmes.	There is only one developer of the VPM 1002 vaccine, although 20 – 30 different recombinant BCG vaccines have been tested in preclinical models (4). Other candidate Mtb vaccines have different characteristics.
	Not robust	**Not robust**
RSV (pre-fusion F protein) (lyophilized SDV)	No development programmes.	The pre-fusion F protein RSV vaccine being considered is produced by GSK. Several other manufacturers, including Pfizer have similar vaccines in development.[aaa]
	Not robust	**Moderately robust**

[vv] Kundai Chinyenze.. *HIV Vaccines and monoclonal Antibodies - Preparation for success. Policy & access considerations.* Presented at: WHO PDVAC 2018. https://www.who.int/immunization/research/meetings_workshops/15_Chinyenze_HIV_vaccines.pdf?ua=1.

[ww] Moderna website. Moderna's Pipeline page. *https://www.modernatx.com/pipeline. Accessed 10/10/2019.*

[xx] Curevac website. Our Pipeline page. *https://www.curevac.com/our-pipeline Accessed 10/10/2019.*

[yy] VIR website. Our Focus page. *https://www.vir.bio/pipeline/#focus Accessed 10/10/2019.*

[zz] *Chris Ockenhouse 2018. Presentation at WHO PDVAC 2018. https://www.who.int/immunization/research/meetings_workshops/14_Ockenhouse_Malaria.pdf?ua=1.*

[aaa] *R*. Karron. *Update on RSV vaccine pipeline.* Presented at: WHO PDVAC 2019. *https://www.who.int/immunization/research/meetings_workshops/3_Karron_RSV_vaccines_PDVAC_2019.pdf?ua=1 Accessed 10/10/2019.*

1.7 Criteria on commercial feasibility[bbb]

The WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, was invited to complete a survey following a consultation of dual-chamber delivery technologies.[ccc] Six member organizations responded to the survey and five member organizations responded to the question on commercial feasibility challenges. The following challenges were identified as the most important commercial feasibility challenges facing the development of VVM-TIs (most frequently identified challenges first):

- Pricing strategy (5/5)
- Interest from country stakeholders (4/5)
- Regulatory approval (2/5)
- Market potential and uptake (1/5)

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

Summary feedback from country consultation:

- VVM-TIs were ranked #8 useful innovation
- Immunisation staff ranked VVM-TIs as 7th out of 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's challenges and decision-makers 9th - based on weighted scores approach.
- Both groups mentioned the benefits of reduced vaccine wastage due to heat damage/suspected heat damage, possibility to keep vaccines out of cold chain, saved health care worker time, increased ability to deliver vaccines outside of a health facility and assuring quality of vaccines that are administered, and improved ease of use since VVM-TIs ensure both VVM and TI are combined monitored.
- Immunisation staff mentioned other benefits such improved ability to monitor vaccines for heat exposure and reduced worry/stress for health care workers.
- Both groups raised concerns about the overall cost.
- Immunisation staff reported risk of vaccine wastage as possible challenge.
- Decision makers were also concerned about the price per dose and training requirements - though 20 out of 28 decision makers interviewed expressed interest in purchasing VVM-TIs, 3 stated potential interest, 5 participant said they would not be interested.
- Decision makers who do not support CTC were not positive about VVM-TIs.
- A few immunisation staff respondents reacted positively to the clarity of the TI indicator, as compared to the gradual change of the VVM.

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bbb These indicators will be evaluated in an absolute manner, not relative to a comparator.

[ccc] Survey carried out after DTWG telecons on VVM-TI held on 9th Dec and 10th Dec, 2019.

[ddd] 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 84 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.

- Some Immunisation staff respondents indicated confusion: one person said, “Helps reduce stock outs because we sometimes throw vaccines that have changed VVM but are still potent because we don't have TI on the VVM.”

Additional information on country:

While the VVM-TI was one of the lowest ranked innovations by stakeholders participating in the VIPS Phase II country consultations, this is thought to be largely due to the fact that very few respondents have experience with CTC use of vaccines with heat exposure monitoring by both VVMs and separate TIs. However, these same stakeholders did identify heat stable liquid CTC qualified vaccines as one of the highest priority innovations with health workers ranking it in fourth place and procurement decision makers/influencers ranking it in first place out of the nine innovations. The VVM-TI is a technology with a primary purpose of facilitating another VIPS innovation – CTC use of vaccines.

*Score l*egend: **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**
All applicable vaccines	No data	**No data**

Indicator: Potential breadth of the target market

Notes:

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

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

Table 26

Parameter assessment		
Vaccines	***How broad is the potential target market?***	**Overall score**
CTC qualified vaccines only	If the VVM-TI is only supplied on CTC-qualified vaccines (which could occur due to a WHO recommendation), then its near term use will be limited to those vaccines that are CTC-qualified (i.e. HPV, meningitis A, and oral cholera). Currently only one brand of each vaccine is CTC-qualified but others are anticipated. The target market for the VVM-TI will increase with additional CTC-qualified vaccines in the future such as hepatitis B birth dose, polyvalent meningitis (A,C,W,Y,X), and typhoid. An optimistic forecast by PATH estimated the market for VVM-TIs to be 38 million units/year in 2021 if the VVM-TIs were mandated for use on all HPV vaccine, OCV, tetanus-containing, and hepatitis B vaccines.[eee]	**Small**
All applicable vaccines (non-CTC vaccines)	While use of the VVM-TI could be considered for all vaccines as a substitute for the current VVM, it is unlikely that the LMIC markets will be willing to pay the cost premium for non-CTC vaccines and there is no known HIC market or alternate LMIC market (beyond vaccines) for the technology at present. In the unlikely scenario that VVM-TIs were mandated for use on all vaccines purchased by UNICEF then the quantity purchased in 2021 is estimated to be 362 million units.[fff]	**Moderate**

[eee] PATH. Vaccine Vial Monitor Analysis, Version 1. Seattle: PATH; 2018.

[fff] PATH. Vaccine Vial Monitor Analysis, Version 1. Seattle: PATH; 2018.

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

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

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

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

Table 27

Parameter assessment			
Vaccines (current presentations)	***Is there current donor/stakeholder support for the vaccine-innovation pairing?***	***Do partnerships exist between at least one of the technology developers and a vaccine manufacturer or have vaccine manufacturers expressed interest?***	**Overall score**
All applicable vaccines	Yes. The Bill & Melinda Gates Foundation supported the early development of the VVM-TI by Temptime and separately supported work by PATH to assess the acceptability of the VVM-TI in two countries.[hhh] The WHO prequalification team has also finalized specifications and verification protocols for VVM-TI products.	No. While one manufacturer is in the process of adopting the VVM250-TI40 for use on their thermostable lyophilized rotavirus vaccine, this is not one of the vaccines being analysed under VIPS. Vaccine manufacturers surveyed by the Delivery Technologies Working Group[iii] identified pricing strategies and need to understand country interest and the potential market as barriers to VVM-TI adoption.	**Mixed Interest**
	Moderate Interest	**No Interest**	

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

[hhh] PATH. *Field Evaluation Report: Temptime Combined Vaccine Vial Monitor and Threshold Indicator*. Seattle: PATH; 2017.

[iii] *Survey carried out after DTWG telecons on VVM-TI held on 9th Dec and 10th Dec, 2019.*

Indicator: Known barriers to global access to the innovation

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

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

Table 28

Parameter assessment		
Vaccines	***Are there known barriers to Global Access to the innovation as applied to the vaccine?***	**Overall score**
All applicable vaccines	No known barriers. Temptime owns all relevant patents for their VVM-TI technology and there are no known Global Access issues, e.g. 3rd parties holding IP on VVM-TI technology. As with the Temptime VVM, Temptime intends to make VVM-TIs available to any interested vaccine manufacturer.	**No**

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

This innovation differs from other VIPS innovations in that its primary purpose is to facilitate another VIPS innovation – heat stable and CTC qualified vaccines. While the VVM-TI was ranked near the bottom of the nine innovations in the VIPS Phase II country consultations, heat stable liquid CTC qualified vaccines were ranked as one of the highest priority innovations. In the VIPS Phase II online survey, vaccine ineffectiveness and/or wastage due to heat exposure was identified as one of the highest priority problems by country stakeholders. The VVM-TI provides a more accurate heat exposure reading for individual vaccine primary containers and therefore can help to improve vaccine effectiveness and potentially decrease vaccine wastage – especially for vaccines exposed to ambient temperatures during CTC use. The innovation also decreases logistics for CTC implementation. CTC use of vaccines is a priority for the World Health Organization for vaccines that are used in campaigns and special strategies. The need for countries to purchase, stock, store, and provide training on a separate TI for CTC implementation is a barrier to CTC use of vaccines. The VVM-TI removes that barrier by virtue of simply replacing the existing VVM label on primary containers and negating the need for special training on the standalone TI.

SYNERGIES WITH OTHER VIPS INNOVATIONS

While the most relevant use of the VVM-TI is application to CTC qualified vaccines, it can also be used as a more accurate heat exposure indicator on all primary containers of vaccines. For liquid vaccines, these include compact prefilled auto disable delivery devices and freeze-resistant formulations of vaccines. For dry vaccines, these include dual chamber delivery devices, microarray patches, and solid dose implants. The

application of VVM-TIs would be especially appropriate if these vaccines were CTC qualified – whether in liquid or dry format. Lastly, the VVM-TI innovation could be used with any product with a barcode on a primary container.

References

(1) Measles vaccines: WHO position paper – April 2017. *Weekly Epidemiological Record*. 2017 28 April;92(17):205-208. https://apps.who.int/iris/bitstream/handle/10665/255149/WER9217.pdf;jsessionid=19C907B061A1C194F9A711BF8F327BED?sequence=1.

(2) Typhoid vaccines: WHO position paper – March 2018. *Weekly Epidemiological Record*. 2018;93(13):153-172. https://www.who.int/immunization/policy/position_papers/typhoid/en/.

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

(4) Nieuwenhuizen NE, Kaufmann SHE. Next-Generation Vaccines Based on Bacille Calmette-Guérin. *Frontiers in Immunology*. 2018;9:121.