Dual-chamber delivery device

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

Technology overview:

Dual-chamber delivery devices are a type of integrated reconstitution technology (including the delivery device) that can be used to deliver any vaccine that requires mixing of multiple components to simplify preparation. This innovation is typically used for injectable vaccines that require mixing of a liquid (diluent) and dry (vaccine) component. However, the innovation also applies to oral vaccines as well as other products that require mixing such as two incompatible liquid components that must be mixed at the point of use.

There are two subtypes of dual-chamber delivery devices included in this analysis:

- Syringe- or cartridge-based devices.
- Frangible seal-based devices.

Summary of vaccine and innovation compatibility:

This innovation could be applied to all dry vaccine presentations that require reconstitution with a diluent, or other multicomponent vaccines that require mixing. Vaccines where the components are currently stored separately (i.e. not co-packaged) typically benefit the most from this innovation compared to vaccines where the components are already stored together to prevent mismatching. This innovation could be particularly useful for lyophilized vaccines that are delivered through campaigns/outreach in order to task shift to lesser trained health workers, simplify logistics and training requirements, and increase coverage in remote areas. Examples of VIPS priority antigens that could be suitable include MR and yellow fever. Dual-chamber delivery devices are also well-suited for simplifying the preparation of vaccines with multiple components and complex preparation steps like ETEC to reduce preparation errors.

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

Problem statements addressed by innovation:

The problem statements applying to each vaccine that could potentially be addressed by dual-chamber delivery devices are presented in Table 1. The key properties of dual-chamber delivery devices that are relevant to these problem statements are:

- **Difficulties preparing and/or delivering the vaccine requiring trained personnel:** Dual-chamber delivery devices simplify vaccine preparation, which improves ease of use and training requirements.
- **Vaccine wastage or missed-opportunities due to multi-dose vials:** Dual-chamber delivery devices are a single-dose format. As such they avoid issues of missed opportunities for vaccination due to reluctance to open preservative-free multi-dose vials (MDVs).
- **Reconstitution related safety issues**: Dual-chamber deliver devices prevent errors associated with traditional reconstitution systems including use of the incorrect volume of diluent; reuse of reconstitution syringes, causing contamination; failure to discard reconstituted vaccine in multi-dose vials in the

allotted time frame (normally 6 hours) resulting in loss of vaccine potency and vaccine contamination; use of improperly stored diluent that can render a vaccine ineffective; use of an incorrect diluent; or worse, using a potentially deadly liquid drug as a diluent by mistake. Adverse events as a result of reconstitution errors can include local abscesses, toxic shock syndrome, or even death.

- **Contamination risk due to use of multi-dose vial:** Since dual-chamber delivery devices are a single-dose format, they will remove the risk of contamination associated with the use of liquid or lyophilized vaccines in multi-dose vial presentations.
- **Needle stick injuries:** Dual-chamber delivery devices do not require sharps for preparing the vaccine and require one sharp for administering the vaccine. Since the device is prefilled, drawing from a vial is also eliminated.
- **Negative impact on the environment due to waste disposal practices:** Dual-chamber delivery devices are expected to reduce the volume of medical waste (other than sharps) since the entire dual-chamber delivery device is disposed of in the sharps waste and a vial would not be disposed of with medical waste as with the comparator, which could improve disposal practices.

In the VIPS Phase II online survey of country stakeholders, vaccine wastage or missed opportunities due to provision of vaccines in multi-dose vials and reconstitution related safety issues were two of the top three challenges named for the lyophilized vaccines that were assessed including measles-containing, rabies, yellow fever. For meningitis A vaccine, these challenges were rated the second and fifth highest respectively. These results are reflected in Table 1 below for existing vaccines. Rationales are also stated for the inclusion of pipeline vaccines.

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[d]	Comparator dose(s) per container
Licensed vaccines							
Measles rubella (MR)	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)	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

[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] *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[d]	Comparator dose(s) per container
Rabies	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)
Yellow fever	Live-attenuated	Lyophilised	No	No	SC or IM	• **Vaccine wastage or missed opportunities due to multi-dose vial** • **Reconstitution related safety issues** • Vaccine ineffectiveness/wastage due to freeze exposure • **Needle-stick injuries** • Negative impact on the environment due to waste disposal practices	SDV or 5-dose vial
Pipeline vaccines[e]							
ETEC (ETVAX)	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized 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.

[e] *Vaccines included in the 'Pipeline vaccines' section were not approved as of the beginning of the Phase II analysis, therefore the Ebola vaccine although now licensed will be assessed as a pipeline vaccine. Barriers to vaccination for these vaccines were also not evaluated through the online vaccine problem statement survey.*

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[d]	Comparator dose(s) per container
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)[f]	Heterologous live attenuated recombinant viral vector + recombinant protein booster	**Lyophilized prime**; liquid booster (gp120) not assessed (see Table 2)	Yes (recombinant protein booster)	Not known	IM	• *Difficult preparation requiring trained personnel* • *Reconstitution-related safety issues*	As still in Phase 2b/3, assume SDV
Malaria (RTS,S)	Recombinant protein	Lyophilized vaccine; adjuvant in diluent	Yes (AS01E [QS21 + MPL] in diluent)	Not known	IM	• *Difficult preparation requiring trained personnel*	Dry (vaccine) SDV and liquid (adjuvant/diluent) SDV clipped together
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002)	Live attenuated	Lyophilised	No	No	ID	• *Difficult to deliver vaccine to the correct injection depth* • *Reconstitution-related safety issues* • *Difficult preparation requiring trained personnel*	SDV or 20-dose vial
RSV (pre-fusion F protein)	Subunit	Lyophilised	No	Not known	IM	• *Difficult preparation requiring trained personnel* • *Reconstitution-related safety issues*	SDV

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

** Must be discarded after 6 hours

[f] *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.*

Table 2: Vaccines not assessed due to technical feasibility

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Ebola (recombinant vesicular stomatitis virus, Zaire Ebola virus) (rVSV-ZEBOV)	Live vector	Liquid, frozen	No	No	IM	Liquid vaccine; no reconstitution required
Pentavalent (DT-containing)	Inactivated subunit plus PS-PCV	Liquid	Yes	Yes	IM	Liquid vaccine; no reconstitution required. (Pentavalent vaccines with lyophilised Hib component are not considered in this analysis).
Hepatitis B (birth dose)	Subunit	Liquid	Yes (Aluminium-salt based)	Yes	IM	Liquid vaccine; no reconstitution required
Human papillomavirus (HPV)	Subunit	Liquid	Yes (Aluminium - salt based)	No	IM	Liquid vaccine; no reconstitution required
Inactivated poliovirus (IPV)	Whole-inactivated	Liquid	No	Yes	IM or ID	Liquid vaccine; no reconstitution required
Rotavirus	Live attenuated virus	Liquid	No	No	Oral	Liquid vaccine; no reconstitution required
Typhoid (conjugate)	PS-PCV	Liquid	No	Yes**	IM	Liquid vaccine; no reconstitution required
HIV (ALVAC-HIV + bivalent Subtype C gp120)	Heterologous live attenuated recombinant viral vector + recombinant protein booster	**Liquid booster (gp120)**, Lyophilized prime is assessed (Table 1)	Yes (recombinant protein booster)	Not known	IM	Liquid vaccine (gp120 component only); no mixing required

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Influenza (pandemic, VAL-506440)	Nucleic acid	Liquid	No	Not known	IM	Liquid vaccine; no reconstitution required

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

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

Vaccines	*Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?*	Overall score
All vaccines assessed	Vaccine efficacy has not been evaluated for the vaccines being assessed with this innovation. As a primary container, the innovation is expected to have the same vaccine efficacy as the comparator assuming the device enables adequate mixing of the components.	**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

Vaccines	Parameter assessment	
	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 vaccines assessed	No effectiveness data available for any vaccine assessed.	**No data**

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

Note:

The assessments in table 5 have been made assuming that the innovation is used with current lyophilised formulations of each vaccine. If any of the vaccines were to be re-formulated and shown to have improved heat stability that supported controlled temperature chain (CTC) use, then the score would be **'better'** in each case.

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.

[g] *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)?* [h]	*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?*	Overall score
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 pairing has no impact on improving heat stability. **Neutral**	**Neutral**
Men 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).[i]	Yes. For initial campaign use.[j]	The pairing has no impact on improving heat stability. **Neutral**	**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.[k]	The pairing has no impact on improving heat stability. **Neutral**	**Neutral**

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

[i] 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.

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

[k] *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)?* [h]	*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?*	Overall score
Yellow Fever (Lyophilized SDV or 5-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 pairing has no impact on improving heat stability. **Neutral**	**Neutral**
ETEC (ETVAX) (Liquid SDV; lyo adjuvant; lyo buffer)	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 pairing has no impact on improving heat stability. **Neutral**	**Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: Lyophilized. 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 pairing has no impact on improving heat stability. **Neutral**	**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)?* [h]	*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?*	Overall score
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	Routine and Campaign use in areas of high endemicity.[l]	No data	No data.	Yes. For campaign use.[m]	The pairing has no impact on improving heat stability. **Neutral**	**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.	CTC use could be beneficial for birth-dose outreach to homes, storage at remote health facilities without cold chain, or outreach to adolescents.[n]	The pairing has no impact on improving heat stability. **Neutral**	**Neutral**
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 pairing has no impact on improving heat stability. **Neutral**	**Neutral**

[l] https://apps.who.int/iris/bitstream/handle/10665/149822/WHO_IVB_14.09_eng.pdf?sequence=1

[m] 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

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

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 improve freeze exposure?***	**Overall score**
All vaccines assessed	Dual-chamber delivery devices are not expected to impact the freeze sensitivity of the vaccines.	**Neutral**

1.2 Criteria on coverage and equity

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

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

Table 7

Parameter assessment		
Vaccines	***Does the innovation improve the overall coverage for the vaccine within a target population for one or all doses?***	**Overall score**
All vaccines assessed:	No data are available on the ability of a dual-chamber delivery device to improve overall coverage for all applicable vaccines.	**No data**

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

*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

Vaccines	*Does the innovation avoid reconstitution and is that an improvement?*	*Does the innovation require fewer vaccine product components?*	*Does the innovation require fewer preparation steps and less complex preparation steps?*	*Does the innovation improve dose control?*	*Does the innovation improve targeting the right route of administration (accuracy in terms of route and/or depth of injection)?*	Overall score
All applicable vaccines (injectable): • MR • Men A • Rabies • Yellow fever • HIV – lyophilized prime • Malaria • M.tb (VPM1002) • RSV	Dual-chamber delivery devices do not avoid reconstitution but simplify the process.	Dual-chamber delivery devices generally require one component (prefilled dual-chamber device alone), although some have a separate needle. The comparator requires four components (dry vaccine in a vial, diluent vial, reconstitution syringe, delivery syringe).	Dual-chamber devices simplify and reduce the number of steps involved in reconstitution, delivery, and disposal. Depending on the device design and the formulation being reconstituted, additional time and agitation steps by the user might be needed to ensure complete reconstitution.	Dual-chamber delivery devices are prefilled and therefore offer better dose control than use of an AD N&S to withdraw and deliver vaccine from a vial. This assumes however, that the design of the device enables adequate and complete mixing of the two components prior to delivery.	For an injectable vaccine, similar to the comparator these innovations would likely not impact targeting the right route of administration.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Neutral**	

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
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	Dual-chamber delivery devices do not avoid reconstitution but simplify the process.	Dual-chamber delivery devices generally require one component (prefilled dual-chamber device alone). The comparator requires six components (liquid vaccine, dry buffer, dry adjuvant, water; oral dropper, cup).	Dual-chamber devices simplify and reduce the number of steps involved in the reconstitution, delivery, and disposal. Depending on the device design and the formulation being reconstituted, additional time and agitation steps by the user might be needed to ensure complete reconstitution.	Dual-chamber delivery devices are prefilled and therefore offer better dose control than use of an oral dropper to withdraw and deliver vaccine from a cup. This assumes however, that the design of the device enables adequate and complete mixing of the multiple components prior to delivery.	Oral vaccines requiring reconstitution can be delivered parenterally in error if a reconstitution syringe is required, resulting in serious adverse reactions. A dual-chamber delivery device intended for oral delivery could reduce this risk, providing a needle could not be fitted onto the device.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	

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

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
Measles rubella (MR) (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.	Yes. The innovation simplifies preparation and reconstitution, which could enable delivery by lesser trained personnel. These devices are still in development but could potentially be similar in complexity of use and risk as compact prefilled autodisable (CPAD) devices such as Uniject. **Better**	Self-administration might be appropriate for older vaccine recipients for MR. However, dual-chamber devices have the potential to be easy to use similar to a CPAD device, which has been shown to enable self-administration of hormonal contraception (2)(3)(4), but only after training and practice injections. Therefore, dual chamber devices are unlikely to be suitable for self-administration. **Neutral**	**Better**
Men A (MenAfriVac) **(**Lyophilized 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.	Yes. Same assessment as for MR vaccine. **Better**	See assessment for MR **Neutral**	**Better**

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
Rabies (IM: Lyophilized SDV) (ID: Lyophilized 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 (5). 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 (5). Rabies vaccine can also be given via outreach to at-risk populations for pre-exposure prophylaxis (5).	Yes. Same assessment as for MR vaccine. **Better**	See assessment for MR **Neutral**	**Better**
Yellow Fever (Lyophilised SDV or 5-dose)	Routine Campaigns Outbreak response	Yes, for campaign and outbreak response.	Yes. Same assessment as for MR vaccine. **Better**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Better**
ETEC (ETVAX) (Liquid SDV; lyo adjuvant; lyo buffer)	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.[o]	Yes. Same assessment as for MR vaccine.	Not applicable as self-administration is not suitable for the intended target population for ETEC vaccine.	**Better**

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

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
			Better	**N/A**	
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV.)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	Yes. For outreach and campaigns	Yes. Same assessment as for MR vaccine.	See assessment for MR	**Better**
			Better	**Neutral**	
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	Routine and Campaign use in areas of high endemicity.[p]	Yes. For campaign use.	Yes. Same assessment as for MR vaccine.	Not applicable as self-administration is not suitable for the intended target population for malaria vaccine.	**Better**
			Better	**N/A**	
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. particularly if both vaccines are in formats that facilitate ease of use.[q]	Yes. For the birth dose it would be useful if the vaccine could be administered (ID) by midwives or traditional birth attendants. Delivery by lesser trained personnel (or self-administration) could be an advantage for routine vaccination of adolescents	Yes. Same assessment as for MR vaccine.	Not applicable as self-administration is not suitable for the primary intended target indication (birth dose) for this vaccine.	**Better**
			Better	**N/A**	

[p] 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*

[q] World Health Organization. *WHO Preferred Product Characteristics for New Tuberculosis Vaccines*. Geneva: World Health Organization; 2018. https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1.

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
RSV (pre-fusion F protein) (Lyophilized SDV)	Expected to be a routine maternal vaccine, and possibly administered on a seasonal basis.	Yes	Yes. Same assessment as for MR vaccine. **Better**	See assessment for MR **Neutral**	**Better**

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

Vaccines	*Does the innovation improve dose sparing of the vaccine?*	Overall score
All vaccines assessed:	Because they do not involve a change in the route of delivery, dual-chamber delivery devices will have no impact on the ability to facilitate dose sparing of vaccines.	**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**
Measles rubella (Lyophilized SDV or 10-dose)	The comparator is a single- or 10-dose presentation without preservative. A dual-chamber delivery device is a single-dose presentation and reluctance to open a MDV would be improved compared to the 10-dose vial comparator.	**Better (MDV)**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	The comparator is a single- or 10-dose presentation with preservative. A dual-chamber delivery device is a single-dose presentation and reluctance to open a MDV would be improved compared to the 10-dose vial comparator.	**Better (MDV)**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	A dual-chamber delivery device and the comparator are both a single-dose presentation. The rabies vaccine does not contain a preservative.	**Better (ID)** **Neutral (IM)**
Yellow Fever (Lyophilized SDV or 5-dose)	The comparator is a single- or 5-dose presentation without preservative. A dual-chamber delivery device is a single-dose presentation.	**Better (MDV)**
ETEC (ETVAX) (Liquid SDV; lyo adjuvant; lyo buffer)	A dual-chamber delivery device and the comparator are both a single-dose presentation. It is unknown whether this vaccine is expected to contain a preservative.	**Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV.)	A dual-chamber delivery device and the comparator are both a single-dose presentation. It is unknown whether this vaccine is expected to contain a preservative.	**Neutral**

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**
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	The comparator is a single- or 2-dose presentation without preservative. A dual-chamber delivery device is a single-dose presentation and reluctance to open a MDV would be improved compared to the 2-dose vial comparator.	**Better (MDV)**
M.tb (Next generation BCG: VPM1002) (Lyophilized SDV or 20-dose)	The comparator is a single- or 20-dose presentation. A dual-chamber delivery device is a single-dose presentation and reluctance to open a MDV would be improved compared to the 20-dose vial comparator. It is unknown whether this vaccine is expected to contain a preservative.	**Better (MDV)**
RSV (pre-fusion F protein) (Lyophilized SDV)	A dual-chamber delivery device and the comparator are both a single-dose presentation. It is unknown whether this vaccine is expected to contain a preservative.	**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 vaccines assessed	Pain is expected to be similar to the comparators. Dual-chamber delivery devices for parenteral vaccines still require an injection if used for parenteral vaccines and are not anticipated to impact pain associated with administration.	Dual-chamber delivery devices are not expected to impact the perception of ease of administration for vaccinees/caregivers as they would not interact with the innovation and delivery would still be by the same method.	A PATH acceptability study in India found this type of device was generally acceptable and useful for overcoming reconstitution challenges. Preference varied between devices and was dependent on the number of steps involved[r].	**Neutral**
	Neutral	**Neutral**	**Neutral**	

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.*

[r] *PATH. Integrated Vaccine Reconstitution: A user-centered approach to developing safe and cost-effective technologies that eliminate challenges with traditional reconstitution. Seattle: PATH, 2008.*

Table 13

Vaccines	*Does the innovation require fewer components?*	*Or does the innovation include labelling that facilitates product?*	Overall score
All <u>parenteral</u> vaccines assessed where the components are packaged and stored separately: • MR • Men A • Rabies • Yellow fever • HIV – lyophilized prime • M,tb (VPM1002) • RSV	Dual-chamber delivery devices reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber delivery devices generally require one (prefilled dual-chamber delivery device alone) or two (device plus separate needle) components. The comparator requires four components (dry vaccine in a vial; diluent; reconstitution syringe; delivery syringe).	The innovation has no impact on product labelling.	**Better**
	Better	**N/A**	
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent containing adjuvant)	Dual-chamber delivery devices reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber delivery devices generally require one (prefilled dual-chamber delivery device alone) or two (device plus separate needle) components. The comparator for RTS,S requires three components (dry vaccine clipped to diluent containing adjuvant; reconstitution syringe; delivery syringe).	The innovation has no impact on product labelling.	**Better**
	Better	**N/A**	
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	Dual-chamber delivery devices reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber delivery devices for oral vaccines generally require one (prefilled dual-chamber delivery device alone) component. The comparator for ETEC requires six components (liquid vaccine, dry buffer, dry adjuvant, water; oral dropper; cup).	The innovation has no impact on product labelling.	**Better**
	Better	**N/A**	

1.3 Criteria on safety

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

*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		
Vaccine	***Does the innovation reduce the frequency of serious AEFIs ?***	**Overall score**
All vaccines assessed	While the safety features of dual chamber delivery devices are likely to decrease the incidence of serious AEFIs, no AEFI data are available for the applicable vaccines in dual-chamber delivery devices.	**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.*

[s] *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

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?*[t]	*Overall score*
All <u>parenteral</u> vaccines assessed where the components are packaged and stored separately: • MR • Men A • Rabies • Yellow fever • HIV • M,tb (VPM1002) • RSV	Yes. Dual-chamber delivery devices reduce the risk of contamination while reconstituting since reconstitution takes place within the primary container which is a sterile environment.	Dual-chamber delivery devices are expected to have an autodisable feature so the risk of reuse would be similar to an AD N&S.	Yes. Since reconstitution is integrated into the device, dual-chamber delivery devices eliminate the potential risk of reuse of the reconstitution needle and syringe which is used for conventional reconstitution. Although some reconstitution syringes have a reuse prevention feature, they could theoretically be reused.	Yes. Dual-chamber delivery devices are ready to use and do not require filling a delivery device unlike the comparator.	Yes. Dual-chamber delivery devices have fewer and simpler steps, which reduce preparation errors including using the wrong volume of diluent.	Yes. Since the diluent is prefilled in the innovation with the other vaccine component it reduces the likelihood of using the incorrect diluent during reconstitution. Diluents are often shipped and stored at ambient temperature while vaccines are shipped and stored separately in the cold chain. Use of the incorrect diluent is a serious issue. For instance, in 2014 in Syria, 15 children died after a muscle relaxant was accidentally administered instead of the proper diluent (6).	**Better**
	Better	**Neutral**	**Better**	**Better**	**Better**	**Better**	

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

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?*[t]	*Overall score*
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent)	Yes. Same assessment as for parenteral vaccines.	Same assessment as for parenteral vaccines.	Yes. Same assessment as for parenteral vaccines.	Yes. Same assessment as for parenteral vaccines.	Dual-chamber delivery devices have fewer and simpler steps, which reduce preparation errors including using the wrong volume of diluent.	Since the liquid and dry vaccine components are clipped together for RTS,S which reduces the likelihood of using the incorrect diluent during reconstitution, the innovation would not further reduce this risk.	**Better**
	Better	**Neutral**	**Better**	**Better**	**Better**	**Neutral**	
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	Yes. Same assessment as for parenteral vaccines.	Yes. Oral delivery devices are not required to be autodisable. A dual-chamber delivery device for oral delivery which is prefilled, can therefore reduce the risk of reuse that might occur with a separate oral delivery device.	Since reconstitution is integrated into the device, dual-chamber delivery devices eliminate the potential risk of reuse of the reconstitution needle and syringe which is used for conventional reconstitution. However, oral vaccine devices are not required to be sterile, so overall risk to the patient is unchanged.	Dual-chamber delivery devices are ready to use and do not require filling a delivery device reducing the likelihood of contamination. However, oral vaccine devices are not required to be sterile, so overall risk to the patient is unchanged.	Yes. Dual-chamber delivery devices have fewer and simpler steps, which reduce preparation errors including using the wrong volume of diluent.	Yes. Same assessment as for parenteral vaccines.	**Better**
	Better	**Better**	**Neutral**	**Neutral**	**Better**	**Better**	

Indicator: Likelihood of needle stick injury

*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 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?*	*Does the innovation reduce the risk of injury after vaccine administration?*	Overall score
All parenteral vaccines assessed: • MR • Men A • Rabies • Yellow fever • HIV – lyophilized prime • Malaria • M,tb (VPM1002) • RSV	Yes. Dual-chamber delivery devices for parenteral delivery require one sharp compared to two sharps for the comparator (AD N&S + reconstitution syringe).	Yes. Dual-chamber delivery devices do not require sharps for preparing the vaccine and require one sharp for administering the vaccine. Since the device is prefilled, drawing from a vial is also eliminated. Some of the devices involve a separate needle that would need to be assembled with the primary container, which could have an impact on the risk of sharps injury, depending on the design.	Dual-chamber delivery devices are expected to have an autodisable feature similar to an AD N&S, though this has yet to be developed for many of the designs.	Current dual-chamber delivery devices do not include sharps injury prevention features, similar to an AD N&S.	Dual-chamber delivery devices have no impact on the risk of injury.	**Better**
	Better	**Better**	**Neutral**	**Neutral**	**Neutral**	

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
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	Delivery from a dual-chamber delivery device for oral delivery requires no sharps similar to the comparator.	The innovation and comparator do not require sharps to prepare and/or administer the vaccine.	For oral vaccines, AD features are not required for delivery. An oral dual-chamber delivery device is not AD, and neither is the comparator	The innovation does not include sharps and would not include a sharps injury prevention feature.	Dual-chamber delivery devices have no impact on the risk of injury	**Neutral**
	Neutral	**Neutral**	**Neutral**	**Neutral**	**Neutral**	

1.4 Criteria on economic costs

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

Note for Table 17

The assessments in Table 17 are high-level assessments of costs. For combination products such as dual-chamber delivery devices, the purchase cost of the vaccine includes the price of the administration device. The purchase cost of the delivery devices are the prices for any additional devices needed for vaccine administration (excluding the device with the vaccine) that would be required to be purchased separately. If no additional administration devices are needed, then this is a benefit of the innovation compared to the comparator. For the cost components included in Table 17, it should be noted that we do not have data on the vaccine prices or estimated cost of goods sold (COGS), especially those that are in early stages of development. However, previous costing studies have shown that for the comparators (SDV and MDV), between the three cost categories accounted for here (purchase cost of vaccine, purchase cost of delivery devices, safety box costs), the purchase cost of vaccines will be largest share of the costs compared to the purchase cost of delivery devices and safety box costs. Given that an AD N&S costs ~$0.04, a reconstitution syringe costs ~$0.04 but can be shared across multiple doses when used with a MDV, and the safety box costs are estimated at $0.005 per AD N&S, the magnitude of difference increases the higher the vaccine price.

*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?*	*Score*
All <u>parenteral</u> vaccines assessed • MR • Men A • Rabies • Yellow fever • HIV – lyophilized prime • Malaria • M,tb (VPM1002) • RSV **(SDV and MDV)**	[SDV assessment] There are no publicly available data on the COGs or potential price of a vaccine in a dual-chamber delivery device and there are many unknowns that will impact the COGs or price of this device. However, the wastage rate for a dual-chamber delivery device would likely be the same as for a SDV. Therefore, because of lack of information on the price or COGs estimates, this parameter is scored as 'No data'.	[SDV assessment] Yes. Dual-chamber delivery devices incorporate the delivery device and reconstitution would also be done in the same device, so no separate AD syringe or reconstitution syringe would be required. An AD syringe is priced at about $0.04 and a reconstitution syringe is priced at about the same.[u] The total cost would be $0.08 per dose. A dual chamber delivery device would eliminate the purchase costs of delivery devices.	[SDV assessment] The measured volume of dual-chamber chamber delivery device prototypes ranges from 21-86 cm^3. The volume of an AD N&S used for vaccine administration is 42 cm^3 and the volume of an RUP syringe used for reconstitution is 43 cm^3 for a total volume disposed of in a safety box of 85cm^3. The safety box costs would be `$0.01 per dose for both the AD N&S and reconstitution syringe. So depending on the final volume of the dual chamber delivery device, the safety box costs may remain the same or be decreased. This is scored as neutral because the final volumes of dual chamber delivery devices are unknown.	Overall score: **No data** • No data on the COGS or purchase price of dual-chamber delivery devices. • However, for combination product innovations like dual-chamber delivery devices, the vaccine price in this presentation is likely greater than for SDV. • There are no separate delivery devices needed and so delivery device costs decrease and so do safety box costs. Previous costing studies shown that for SDV and MDV, the vaccine price is larger than the combined cost of delivery devices and safety boxes and so the increase in vaccine price will outweigh the savings in other commodity costs components. • In summary, the overall score for dual-chamber delivery devices is likely to be worse but we score it as no data because of the unknown vaccine price data.
	No data	**Better**	**Neutral**	

[u] UNICEF. Auto-Disable (AD) and Re-Use Prevention (RUP) Syringes and Safety Boxes - current price data. Available at: https://www.unicef.org/supply/files/Auto-Disable_and_Re-Use_Prevention_Syringes_and_Safety_Boxes_-_current_price_data.pdf.

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Score*
	[MDV assessment] Same as for the SDV assessment, there are no publicly available data on the COGs or potential price of a vaccine in a dual chamber delivery device. Wastage rates for dual chamber devices, which are single dose devices, would be expected to be lower than for MDV. Therefore, because of lack of information on the price or COGs estimates, this parameter is scored as 'No data'.	[MDV assessment] Dual-chamber delivery devices incorporate the delivery device and reconstitution would also be done in the same device, so no separate AD syringe or reconstitution syringe would be required. An AD syringe is priced at about $0.04 and a reconstitution syringe is priced at about the same.[vu] With one reconstitution syringe shared among multiple doses for MDVs, the total cost is ~$0.05 per dose A dual- chamber delivery device would eliminate the purchase costs of delivery devices.	[MDV assessment] The measured volume of dual-chamber chamber delivery device prototypes ranges from 21-86 cm^3. The volume of an AD N&S used for vaccine administration is 42 cm^3 and the volume of an RUP syringe used for reconstitution is 43 cm^3. For a 10-dose vial, the total volume disposed of in a safety box would be approximately 46cm^3 per dose. The safety box costs would be <$0.01 per dose for both the AD N&S and reconstitution syringe. Depending on the final volume of the dual-chamber delivery device, the safety box costs may remain the same or be lower, or increase. This is scored as neutral because the final volume of a dual chamber delivery device is unknown.	Overall score: **No data** Same overall score rationale as for SDV.
	No data	**Better**	**Neutral**	

[v] UNICEF. Auto-Disable (AD) and Re-Use Prevention (RUP) Syringes and Safety Boxes - current price data. Available at: https://www.unicef.org/supply/files/Auto-Disable_and_Re-Use_Prevention_Syringes_and_Safety_Boxes_-_current_price_data.pdf.

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Score*
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	[SDV assessment] There are no publicly available data on the COGs or potential price of a vaccine in a dual chamber delivery device and so this indicator is scored as "No data".	[SDV assessment] Dual-chamber delivery devices incorporate the delivery function and no separate reconstitution device is required. For the comparator, the components needed for reconstitution would be co-packed with the vaccine and the vaccine price could include the price of these components. No separate reconstitution components would need to be purchased.	[SDV assessment] The innovation and comparator would not generate any sharps waste and so there would be no change in safety box purchase costs.	Overall score: **No data** • No data on the COGS or purchase price of dual-chamber delivery devices. • No change in delivery device or safety box costs.
	No data	**Neutral**	**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**; Yellow:** Mixed**:** Increases some economic/delivery costs and decreases others or has unknown impact on other costs. N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Note:
PATH VTIA model analysis have shown than the cold chain storage and transport costs per cm^3 are much higher than the costs of storage and transport out of the cold chain.

Table 18

Vaccines	*Does the innovation reduce the economic costs of cold chain storage and transport for a vaccine regimen?*	*Does the innovation reduce the economic costs of out of cold chain storage and transport for a vaccine regimen including delivery technology(ies)?*	*Does the innovation reduce the economic costs of time spent by the vaccinators when preparing and administering the vaccine?*	*Does the innovation reduce the economic costs of time spent by staff involved in stock management*	Overall score
All <u>parenteral</u> vaccines assessed: • MR • Men A • Rabies • Yellow fever • HIV – lyophilized prime • Malaria • M,tb (VPM1002) • RSV **(SDV and MDV)**	[SDV assessment] The estimated volume stored and transported in the cold chain for a dual chamber delivery device ranges from 21-86 cm^3 based on measured prototypes. A SDV for a lyophilized vaccine can have a cold chain storage and transportation volume that varies by vaccine type and manufacturer. For example, the cold chain volume can be 9.7cm^3 (meningococcal conjugate vaccine)[w], 21.09 cm^3 (measles containing vaccine)[x], 30cm^3 (rabies vaccine from Serum)[y] and 50.5 cm^3 (rabies vaccine from Sanofi).[z] Depending on the volume of a dual chamber delivery device which can range from 21 to 86 cm^3, a dual-chamber delivery device therefore reduces,	[SDV assessment] Yes. A dual-chamber delivery device does not have any volume per dose stored and transported out of the cold chain since the diluent, reconstitution device and delivery device are integrated and all are stored and transported in the cold chain. For the SDV, the AD N&S and reconstitution syringe would be stored and transported out of the cold chain. As reference point for the magnitude of these costs, out of cold chain storage and transport costs for delivery devices would be ~$0.01 for	[SDV assessment] Yes. It is expected that dual-chamber delivery devices would save time for the vaccinator in preparing and administering the vaccine because of simplifying and reducing the number of steps. However, data are not available comparing preparation and delivery time for a vaccine in a dual chamber device. A time and motion study estimated that it takes an average of 48.3 seconds for a health worker to prepare and administer a lyophilized vaccine in a SDV.[aa] As a reference point for the magnitude of these costs, average human resource costs per minute were estimated at ~$0.03 per minute by PATH's VTIA model, and using the assumption of 48 seconds to	[SDV assessment] There are no attributes on dual-chamber delivery devices that would impact the time spent by staff involved in stock management.	Overall score: **No data** • No data on cold chain storage and transport costs due to no volume data. • The costs of storage and transport out of the cold chain and the costs of vaccinator time would decrease. • Overall score is no data because of the unknown relative magnitude of the cold chain storage and transport costs versus other delivery cost components.

[w] *World Health Organization website. WHO Prequalified Vaccines page. Type: Meningococcal ACYW-135 (conjugate vaccine). Commercial Name: Nimenrix. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301.*
[x] *World Health Organization website. WHO Prequalified Vaccines page. Type: Measles. Commercial Name: Measles Vaccine, Live, Attenuated. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=145.*
[y] *World Health Organization website. WHO Prequalified Vaccines page. Type: Rabies. Commercial Name: Rabies Vaccine Inactivated (Freeze Dried) (RABIVAX-S). https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=322.*
[z] *World Health Organization website. WHO Prequalified Vaccines page. Type: Rabies. Commercial Name: VERORAB. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=111.*
[aa] *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.*

	maintains or increases the volume per dose stored and transported in the cold chain compared to a SDV. Given the unknowns, we score it as no data.	per syringe or ~$0.02 for the two syringes.	prepare and administer a lyophilized vaccine in a SDV, the human resource costs for the SDV vaccinator time would be ~$0.03 per dose. Given our assumption of a reduction in the time required for preparation and administration time with a dual chamber device, we score this as better		
	No Data	**Better**	**Better**	**Neutral**	
	[MDV assessment] No. MDV have a much smaller cold chain volume that SDV. The estimated volume stored and transported in the cold chain for a dual chamber delivery device ranges from 21-86 cm^3 based on measured prototypes. Each dose in a MDV for a lyophilized vaccine can have a cold chain storage and transportation volume of 4.2 cm^3 (measles containing vaccine in 5-dose vials)[bb] or 2.1 cm^3 (meningococcal conjugate vaccine in 10-dose vials).[cc] Compared to a MDV, a dual-chamber delivery device therefore increases the volume per dose stored and transported in the cold chain. As a reference point for the magnitude of these costs, using	[MDV assessment] Yes. As above, a dual-chamber delivery device does not have any volume per dose stored and transported out of the cold chain since the diluent, reconstitution device and delivery device are integrated, and all are stored and transported in the cold chain. As reference point for the magnitude of these costs, out of cold chain storage and transport costs for delivery devices would be ~$0.01 for per syringe and total costs would be $0.01 since the reconstitution syringe is shared across multiple doses.	[MDV assessment] A dual-chamber delivery device would save time for the vaccinator in preparing and administering the vaccine because of simplifying and reducing the number of steps for vaccine preparation. However, it would also require that the reconstitution be done for every vial / dose and so the efficiency gains for reconstitution steps from using MDV would be lost. A time and motion study estimated that it takes an average of 20.9 seconds for a health worker to prepare and administer a lyophilized vaccine in a 10-dose vial.[dd] However, because data are not available comparing preparation and delivery time for the dual chamber device and there is uncertainty with the impact on	[MDV assessment] There are no attributes on dual-chamber delivery devices that would impact the time spent by staff involved in stock management.	Overall score: **No data** • The costs for storage and transport in the cold chain will increase for the dual chamber delivery device compared to MDV. • The costs of storage and transport out of the cold chain would decrease. • No data on the costs for vaccinator time with this innovation. • Overall score is no data because of the unknown relative magnitude of health worker time costs but

[bb] *World Health Organization website. WHO Prequalified Vaccines page. Type: Measles and Rubella. Commercial Name: Measles and Rubella Vaccine, Live, Attenuated.* https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=139.

[cc] *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.

[dd] *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.

	PATH's VTIA model estimates, the cold chain storage costs for 20cm^3 of cold chain pace would be ~$0.04.		time of having to reconstitute each dose, we score this as no data.		previous costing studies show that cold chain costs are a larger share than out of cold chain and vaccinator time costs combined.
	Worse	**Better**	**No data**	**Neutral**	
ETEC (ETVAX), oral vaccine (Liquid SDV; lyo adjuvant; lyo buffer)	[SDV assessment] Measurement of prototypes of dual chamber delivery devices for oral vaccines were estimated to also range from 21 to 86cm^3 as for the one used with parenteral vaccines. The volume of the comparator can range by vaccine type. For ETEC, the estimated volume of the vaccine components (cells in single dose glass vial, buffer, LCTBA, and dmLT in foil sachet) was estimated at approximately 21cm^3 per dose. Note this was for a vaccine under development and so the final volume may change. Because of the many unknowns, we score it as no data.	[SDV assessment] For the dual chamber device and the comparator, all the vaccine components and supplies needed to deliver the vaccine would be stored and transported in the cold chain. Therefore, there would be no change in the volume stored and transported out of the cold chain.	[SDV assessment] There is no publicly available data on the time it could take to administer an oral vaccine in a dual chamber delivery device compared to the comparator.	[SDV assessment] There are no attributes on dual-chamber delivery devices that would impact the time spent by staff involved in stock management.	**Overall score: No data** • No data on cold chain storage and transport costs and on vaccinator time costs. • No change in out of cold chain storage and transport costs and time costs for staff involved in stock management.
	No data	**Neutral**	**No data**	**Neutral**	

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

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 vaccines assessed	Training costs: Training of vaccinators would be required to introduce dual-chamber delivery devices.	**Overall score: Worse** • Vaccinators would need to be trained on how to use dual-chamber delivery devices. • However, there are no other upfront or recurrent costs with dual chamber delivery devices.
	Worse	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs with dual chamber deliver devices.	
	Neutral	

1.5 Criteria on environmental impact

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

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

Table 20

Vaccine	*Does the innovation reduce the volume of medical (biohazard) disposal waste?*	*Does the innovation reduce sharps waste disposal?*	*Is the innovation, and its packaging, composed of more sustainable materials that improves waste disposal?*	Overall score
All vaccines assessed	Yes. The volume of medical waste (other than sharps) is expected to be reduced since the entire dual-chamber delivery device is disposed of in the sharps waste and a vial would not be disposed of with medical waste as with the comparator. **Better**	Although dual-chamber delivery devices eliminate RUP syringes for reconstitution and the overall number of sharps will be lower, since the entire device is disposed as sharps waste the overall volume may be similar to the comparator. **Neutral**	Frangible seal-based devices are generally made from a foil, polypropylene, polyester-based polymer, or a laminate. Syringe- or cartridge-based devices are typically glass. Glass, including vials used with standard needles and syringes do not burn easily and can explode and shatter. However, pit burning of plastic containers is easier and could result in a more complete burn though there is concern regarding the pollution created from burning plastic. Due to the wide range of estimated volumes of dual-chamber delivery devices, the volume of plastic burned for a dual-chamber delivery device may vary compared to an AD N&S and RUP syringe used for the comparator. Therefore, it is unclear how the innovation would impact waste disposal for this parameter and has been scored as 'no data'.	**Better**

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity

Note for Table 21:

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

- These are based on published data and input from regulatory consultants.
- Only endpoints related to efficacy have been considered. The safety issues related to vaccine-dual-chamber delivery device combinations and the clinical studies required to demonstrate safety of any given combination have not been considered.
- For pipeline vaccines, we have assumed that the vaccine will NOT be licensed using needle and syringe (or other standard delivery device) first. The complexity rating assumes that the vaccine is used with the innovation for initial licensure.

Use the legend to assess and score the indicator in an absolute manner stating the level of complexity (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.*

Table 21

Vaccines	*Is the clinical development pathway complex?*	Overall score
Measles rubella (Lyophilised SDV or 10-dose)	Immunogenicity assays have been used as endpoints for non-inferiority trials of MMR vaccines of different potencies (7). It is assumed that similar endpoints could be used to assess dual-chamber delivery devices.	**Low complexity**
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial)	Serum bactericidal antibody titres are regarded as the best correlate of protection for meningococcal vaccines (excluding serogroup B) (8), and SBA titres were used for the approval of MenAfriVac (9). It is assumed that similar endpoints could be used to assess dual-chamber delivery devices.	**Low complexity**

Vaccines	*Is the clinical development pathway complex?*	Overall score
Rabies (IM: Lyophilized SDV), (ID: Lyophilized SDV)	Immunogenicity (seroconversion to a neutralizing antibody titre ≥0.5 IU/) has been used as an endpoint in many studies to evaluate alternative immunization regimens (10)(11) and it assumed similar endpoints could be used for dual-chamber delivery devices. A strategy to guide the clinical evaluation of new rabies vaccines has recently been proposed (12).	**Low complexity**
Yellow Fever (Liquid SDV or 5-dose)	Neutralizing antibody titres are used as a correlate of protection in YF vaccine studies (protection is associated with a log neutralization index > 0.7) (13). It is assumed that similar endpoints could be used to assess dual-chamber delivery devices.	**Low complexity**
ETEC (ETVAX) (Liquid SDV; lyo adjuvant; lyo buffer)	Licensure of ETEC vaccines for use in paediatric populations in LMICs will require efficacy studies with clinical endpoints in this population.[ee] There is however, ongoing discussion of which clinical endpoints are the most relevant or useful (14). Trials assessing the effectiveness of the vaccine against traveller's diarrhea and controlled human infection models (CHIMs) might also aid clinical development (14).	**High complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Ongoing phase III clinical trials of HIV vaccines have prevention of HIV acquisition as the primary endpoint,[ff] and it seems likely that this will be the case for other new HIV vaccines. Attempts to define immunological correlates of protection based on data from earlier phase III trials are ongoing (15).	**High complexity**
Malaria (RTS,S), components clipped together (Lyophilized SDV or 2-dose vial, recon with diluent)	Key considerations for clinical trial design for different types of malaria vaccine have been summarized.[gg] RTS,S vaccine (Mosquirix) has EMEA approval.[hh] Currently there are no accepted correlates of protection and next-generation vaccines will require non-inferiority or superiority RCTs with clinical endpoints.[ii]	**High complexity**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	There are no accepted immunological correlates of protection for vaccines against BCG (16). Therefore, clinical endpoints will be needed (prevention of infection or recurrence or disease)[jj] and large phase III trials of long duration.	**High complexity**

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

[ff] 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.

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

[hh] *European Medicines Agency. EPAR summary for the public: Mosquirix. EPA: London, UK; 2015. https://www.ema.europa.eu/en/documents/medicine-outside-eu/mosquirix-summary-public_en.pdf*

[ii] *WHO. Preferred product characteristics (PPC) for malaria vaccines. Geneva: WHO; 2014. Available at http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf?ua=1.*

[jj] World Health Organization. *WHO Preferred Product Characteristics for New Tuberculosis Vaccines*. Geneva: World Health Organization; 2018 *https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1.*

Vaccines	*Is the clinical development pathway complex?*	Overall score
RSV (pre-fusion F protein) (liquid SDV)	There are no accepted immunological correlates of protection for maternal immunization against RSV. A pathway for regulatory approval based on clinical endpoints has been proposed and agreed by experts (17).	**Moderate complexity**

Indicator: Technical development challenges

Note:

As a primary container, dual-chamber delivery devices may be compatible with current vaccine formulations without the need for reformulation. Some of the key technical hurdles are adding an autodisable feature, the reconstitution feature, ensuring adequate mixing of the multiple components prior to delivery, ensuring that the moisture barrier between liquid and dry components is sufficiently impermeable to ensure the stability of the lyophilized component.

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

- Alternative vaccine drying and powder filling processes (6/9)
- Reconstitution mechanism (5/9)
- In situ lyophilization (5/9)
- Moisture vapor/gas barrier properties of materials (5/9)
- Cost of goods (4/9)
- Adequate mixing of the two components (4/9)
- Access to filling equipment for pilot runs/stability testing (3/9)
- Cold chain volume including packaging (3/9)
- Compatibility of the device material (2/9)
- Transparency of device material (1/9)
- Flexibility/deformability properties of squeezable device (1/9)

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 dual-chamber delivery devices held on 30th and 31st October 2019.

Table 22

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
Syringe-and cartridge-based devices (all vaccines assessed)	Syringe-based devices are currently on the market for pharmaceuticals, which demonstrates their technical feasibility.	**Low complexity**
Frangible seal-based devices (parenteral vaccines assessed)	Frangible seal-based devices for parenteral delivery are at a very early stage of development. Several designs are currently being explored. However, technical feasibility has not been demonstrated and it is not certain if the concepts will be viable due to challenges in identifying materials that provide a sufficient moisture vapor barrier but also enable visualization of the contents to confirm complete reconstitution.	**High complexity**
Frangible seal-based devices (oral vaccines assessed)	Technical feasibility of frangible seal-based devices for oral delivery has been demonstrated by Hilleman Laboratories. Hilleman's Integrated Reconstitution and Administration Device (IRAD) was originally developed for delivery of heat-stable rotavirus vaccine with potential for CTC/outside cold chain use (9 months at 45°C). This product was evaluated in several user acceptability studies in-country have been conducted.[ll]	**Moderate complexity**

Indicator: Complexity of manufacturing the innovation

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 on dual-chamber delivery devices.[mm] Eleven member organizations responded to the survey and nine member organizations responded to the question on manufacturing challenges. The following challenges were identified as the most important manufacturing challenges facing the development of dual-chamber delivery devices (most frequently identified challenges first):

[ll] Ajit pal Singh. *Heat Stable Rotavirus Vaccine. A thermostable rotavirus vaccine approach*. Presentation at Twelfth International Rotavirus Symposium 2016. https://www.sabin.org/sites/sabin.org/files/ajit_pal_singh.pdf.

[mm] Survey carried out after DTWG telecons on dual-chamber delivery devices held on 30th and 31st October 2019.

- Lyophilization/drying (7/9)
- Filling and sealing (6/9)
- Aseptic production (4/9)
- Manufacturing process validation (4/9)
- Quality control and inspection (3/9)
- Quality control and inspection (3/9)
- Availability of CMOs for device filling (3/9)
- Filling line capacity (2/9)
- Manufacturing time per unit (1/9)
- Supply of components (1/9)
- Facility space requirements for filling/packaging equipment (1/9)

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

Vaccines	*How complex is the manufacturing process? (Specify if special materials are used)*	Overall score
Syringe-and cartridge-based devices (all vaccines assessed)	Commodity components and filling equipment for standard glass syringes or cartridges may be able to be leveraged for syringe-and cartridge-based devices, though the process requires additional stopper insertion and filling steps, as well as potential changes to lyophilization protocols. Dual-chamber syringe manufacturing processes have been established for other products but must be validated for each new vaccine. If vaccine manufacturers are using 'components of commercially available prefilled syringes or cartridges for their dual chamber syringes, they should ensure they have more than one supplier.	**Low complexity**
Frangible seal-based devices (all parenteral vaccines assessed)	Novel fill/finish equipment will need to be developed for frangible seal-based devices. Work is underway to understand feasibility of in-situ lyophilization in frangible seal devices, but alternative vaccine drying processes are likely to be needed to enable powder filling of devices. An example of such a process is spray-freeze-drying which has been evaluated with YF vaccine (18).	**Very high complexity**
Frangible seal-based devices (all oral vaccines assessed)	Novel fill/finish equipment will need to be developed for frangible seal-based devices. Work is underway to understand feasibility of in-situ lyophilization in frangible seal devices, but alternative vaccine drying processes are likely to be needed to enable powder filling of devices. A pilot-scale production process for the IRAD device has been established.	**Moderate complexity**

Indicator: Robustness of the innovation-vaccine pipeline

Notes:

In table 24 it has been assumed throughout that:

- There are at least 10 'developers of the technology' (i.e. dual-chamber for use with vaccines - see phase I TN for details), including: Credence MedSystems, Vetter, LyoGo, Duoject, AktiVax, Neopac, Hilleman Laboratories, PATH, Pharmapan, and Rohrer AG.
- The 'suppliers/manufacturers of the vaccine' parameter focuses on WHO prequalified products (see WHO Prequalified Vaccines Database for details).[nn]
- As a primary container, their device formats could potentially be applied to all lyophilized parenteral and oral reconstituted vaccines. Some aspects of the device/manufacturing process may need to be customized for each antigen of interest. Therefore, on a non-vaccine-specific basis, the number of developers would be assessed as 'highly robust'. However, the pipeline is less robust when considered at the vaccine-specific level.
- Dual-chamber delivery device 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 pre-clinical 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.

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 (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Measles rubella (Lyophilised SDV or 10-dose)	Multiple device developers are pursuing dual-chamber devices for MR including Credence MedSystems, Rohrer AG, and PATH.	There are multiple producers of measles vaccine and a single producer of stand-alone rubella. Two manufacturers have WHO PQ MR vaccines.
	Moderately robust	**Moderately robust**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	No known development programmes.	There is only one manufacturer of MenAfriVac (which is WHO PQ) and one manufacturer known to be developing a MenACWYX vaccine. There are two PQ manufacturers of lyophilized Men ACWY vaccines.
	No data	**Moderately robust**

[nn] World Health Organization website. WHO Prequalified Vaccines page. https://extranet.who.int/gavi/PQ_Web/Browse.aspx?nav=3. Accessed 21/10/2019.

Vaccines (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	No known development programmes.	There are several manufacturers of rabies vaccines. Four manufacturers have WHO PQ products.
	No data	**Moderately robust**
Yellow Fever (Lyophilized SDV or 5-dose)	No known development programmes.	There are several manufacturers of YF vaccines. Four manufacturers have WHO PQ products.
	No data	**Moderately robust**
ETEC (ETVAX) (Liquid SDV; lyo adjuvant; lyo buffer)	No known development programmes.	There is only one manufacturer of this particular candidate ETEC vaccine. Other ETEC vaccines have different characteristics.
	No data	**Not robust**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (**Prime: lyo. SDV.** Boost: liquid SDV)	No known development programmes.	There is only one manufacturer of this particular candidate HIV vaccine. However, a similar candidate vaccine using a different virus vector and recombinant protein in a heterologous prime-boost regimen is in late-stage trials.[oo]
	No data	**Not robust**
Malaria (RTS,S), components clipped together Lyophilized SDV or 2-dose vial, recon with diluent)	No known development programmes.	There is only a single developer of RTS,S vaccine. Many other malaria vaccines are in clinical development, but have different characteristics to RTS,S.[pp]
	No data	**Not robust**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	No known development programmes. The current devices are also likely not suitable with ID delivery.	There is only one developer of the VPM 1002 vaccine, although 20 – 30 different recombinant BCG vaccines have been tested in preclinical models (19). Other candidate Mtb vaccines have different characteristics.
	No data	**Not robust**

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

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

Vaccines (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
RSV (pre-fusion F protein) (Lyophilized SDV)	No known development programmes. The current devices are also likely not suitable with ID delivery.	The pre-fusion F protein RSV vaccine being considered is produced by GSK. Several other manufacturers, including Pfizer have similar vaccines in development.[qq]
	No data	**Moderately robust**

1.7 Criteria on commercial feasibility

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.[rr] Eleven member organizations responded to the survey and nine 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 dual-chamber delivery devices (most frequently identified challenges first):

- Investment in manufacturing scale up (7/9)
- Cost/willingness to pay (5/9)
- Establishing partnerships to support development and commercialization (4/9)
- Market potential and uptake (4/9)
- Interest from country stakeholders (4/9)
- Regulatory strategy (2/9)
- Product development funding (2/9)
- Interest from major partners who procure and support the procurement of vaccines: UNICEF Supply Division; Gavi; PAHO (1/9)

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

Summary feedback from country consultation:

- Dual chamber delivery devices were ranked #2 useful innovation.
- Immunisation staff ranked heat stable liquid vaccines/CTC qualified as 4th out of 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's challenges and decision-makers 3rd - based on weighted scores approach.

[qq] *R. Karron. Update on RSV vaccine pipeline. Presented at: WHO PDVAC June 27, 2019. https://www.who.int/immunization/research/meetings_workshops/3_Karron_RSV_vaccines_PDVAC_2019.pdf?ua=1. Accessed 10/10/2019.*

[rr] Survey carried out after DTWG telecons on dual-chamber delivery devices held on 30th and 31st October 2019.

[ss] *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.*

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

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

Table 25

Vaccines (current presentations)	*Have countries expressed interest to suggest demand for the vaccine-innovation pairing and potential country uptake?*	Overall score
All applicable vaccines	No data are available to suggest country demand for the vaccine-innovation pairings and potential country uptake.	**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-dual-chamber delivery device combination would be used in particular settings or in addition to the current market for the vaccine delivered by N&S. There would not necessarily be a complete switch from the N&S product to the dual-chamber delivery device product. These complexities have 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
Measles rubella (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%).[tt] Most HIC and MIC countries use MMR rather than MR vaccine. It is possible that a dual-chamber deliver device for MR would be used to target specific, hard-to-reach populations only, or be used only in campaigns (20).	**Large**
Men A (MenAfriVac) **(**Lyophilized 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 immunisation (21). 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 (21). HICs (such as USA, UK, Australia) are increasingly introducing vaccination of adolescents with polyvalent meningococcal vaccines, and they are a requirement for Hajj pilgrims (22). Demand for MenACWY conjugate vaccine outside China and the meningitis belt was estimated to be 16.7M doses.[uu]	**Moderate (MenA)** **Large (polyvalent)**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized 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 (23). Gavi estimates cumulative demand of 304M doses (20M/year) between 2021 and 2035.[vv]	**Small / moderate**
Yellow Fever (Lyophilized SDV or 5-dose)	Use of YF vaccine is predominantly in the YF belt in South America and Asia. Gavi estimates suggest global demand is expected to grow from 133 million doses in 2018 to approximately 140 md in 2021.[ww] To date YF is not endemic in Europe, N America or Asia, though it has been suggested that the risk that YF might spread to these areas is increasing (24).	**Moderate**

[tt] *Gavi. MR Vaccine Supply and Procurement Roadmap. UPDATE November 2017. Available at https://www.gavi.org/sites/default/files/document/measles-rubella-vaccine-roadmap--public-summarypdf.pdf. Accessed 11/10/2019.*

[uu] *World Health Organization Global Market Study. Meningococcal meningitis vaccines. 2019. https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_meningococcal_vaccines_global_market_update_May2019.pdf. Accessed 11/10/2019.*

[vv] *Gavi Vaccine Investment Strategy Programme and Policy Committee Meeting. 18-19 October 2018. 06a -Annex C: Rabies Investment Case. Available at https://www.gavi.org/sites/default/files/document/ppc-meeting-18-19-october-2018---vis-06a---annex-c--rabies-investment-casepdf.pdf. Accessed 11/10/2019.*

[ww] *Yellow Fever Supply and Procurement Roadmap. UPDATE 20th March 2017. Available at.* https://www.gavi.org/sites/default/files/document/yellow-fever-roadmap-public-summarypdf.pdfE. *Accessed 11/10/2019.*

Vaccines	*How broad is the potential target market?*	Overall score
ETEC (ETVAX) (Liquid SDV vaccine, lyo buffer, lyo adjuvant)	ETEC (and shigella) are among the top five pathogens that cause diarrheal mortality in children under five. However, disease-burden estimates vary (25) 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 (25).	**Moderate**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. 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 (26).	**Large**
Malaria (RTS,S), components are clipped together Lyophilized SDV or 2-dose vial, recon with diluent)	Wide, country-level introduction of RTS,S has not yet been recommended by the WHO (27). Use is likely to be country, setting and population-dependent. Demand forecasts for Gavi countries estimate 665M doses from 2023 – 2035 (peaking at approximately 75M doses per year at the end of this period.[xx] It is likely there will be a significant non-Gavi market too.	**Moderate**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	The WHO recommends BCG vaccination in countries or settings with a high incidence of tuberculosis and/or high leprosy burden. In these countries, a single dose of BCG vaccine should be given to all healthy neonates at birth (28). The estimated global demand for BCG vaccine is ~325 M doses in 2019.[yy]	**Large**
RSV (pre-fusion F protein) (lyophilized SDV)	Gavi has estimated the cumulative demand for RSV vaccine for maternal immunization for 2021-2035 to be 289M doses for Gavi supported countries. There is expected to be a large market in HICs, for example RSV is the leading cause of hospitalization in infants in the USA (29).	**Large**

[xx] *Gavi VIS 2018. Programme & Policy Committee Meeting. Appendix 3. Malaria. Available at file:///Users/Julian/Downloads/06a_Appendix%203_Malaria%20Vaccine%20Analysis_vPPC.pdf. Accessed 21/10/2019.*

[yy] *World Health Organization. Global market study. BCG vaccine. 2019. Available at https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_BCG_vaccine_global_market_update_Feb2019.pdf. Accessed 11/10/2019.*

Indicator: Existence of partnerships to support development and commercialisation

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

*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

Vaccines	*Is there current donor and/or 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
Measles rubella (lyo; MDV)	BMGF-funded programmes for preclinical development of dual-chamber delivery devices for three developers.	No established partnerships exist between a technology developer and vaccine manufacturer. Current container development work is being conducted with placebo MR vaccine. Expressed interest from some vaccine manufacturers.	**Mixed interest**
	Moderate interest	**No interest**	
All other vaccines assessed	No known donor/stakeholder support	No known partnerships exist between a technology developer and vaccine manufacturer.	**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.*

Table 28

Vaccines	Parameter assessment	Overall score
	Are there known barriers to Global Access to the innovation as applied to the vaccine?	
All vaccines assessed	The three device developers currently supported by BMGF are subject to global access. It is unknown whether there are known barriers to global access for other developers.	**Mixed**

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

Dual-chamber delivery devices have the potential to simplify vaccine preparation and delivery, which positively impacts ease of use and could enable delivery by lesser trained health care workers (or self-administration if appropriate for the intended delivery setting). The innovation also improves safety by reducing the number of sharps associated with vaccine preparation and reduces the risk of using the incorrect diluent. Since the innovation is a single-dose presentation, the innovation also eliminates issues associated with preservative-free multidose containers and helps prevent missed opportunities for immunization. In the VIPS Phase II online survey of country stakeholders, vaccine wastage or missed opportunities due to provision of vaccines in multi-dose vials and reconstitution related safety issues were two of the top three challenges named for the lyophilized vaccines that were assessed including measles-containing, rabies, and yellow fever.

SYNERGIES WITH OTHER VIPS INNOVATIONS

Dual-chamber delivery devices could be compatible with several other innovations under evaluation in VIPS:

- **Sharps injury protection** features could be added to the needles of these devices to protect health workers after injections are given.
- The use of **controlled temperature chain** (CTC)-qualified dry vaccines in these devices could lessen the cold chain requirements for storage and transport prior to administration.
- If the products are CTC qualified, they would also benefit from the application of a **vaccine vial monitor with threshold indicator** (VVM-TI) label to improve temperature monitoring during CTC use.
- If new dry formulations with **improved heat-stability** compared with current lyophilized formulations are used in these devices, they could reduce vaccine wastage due to damage caused by accidental exposure to high temperatures.

- If the liquid component of a dual-chamber delivery device is freeze-sensitive, then a **freeze-damage resistant formulation** could help to prevent freeze damage and wastage due to suspected freeze damage.
- Lastly, **barcodes** on these devices would improve patient record keeping and inventory once health systems have the requisite equipment to use them.

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