Solid dose implants (SDIs)

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

Technology overview:

SDIs consist of vaccines (including antigens, adjuvants and excipients) that have been reformulated into a solid single-dose format, typically needle-shaped, that is sharp and strong enough to be implanted below the skin. After injection, the dose either dissolves immediately or is released slowly depending on the formulation. Some SDIs are contained in a cartridge or cassette for easy handling prior to administration with an applicator to propel the SDI into the skin using a spring or compressed gas. The applicator might be separate and re-usable, or integrated and single use.

Summary of innovation applicability to vaccines:

Solid dose implants (SDIs) could **potentially be used to deliver any vaccine that is currently administered by injection with needle and syringe** (N&S). The technology does have some features that might however preclude its use with some vaccines, as the product is developed, in particular:

1. **Adjuvants:** The need to dry the vaccine for incorporation into the SDI might preclude the use of some adjuvants, including those based on aluminium salts (such as alum).
   We have assumed that manufacturing processes will be developed that are compatible with aluminium salt based adjuvants, or that it might prove to be technically feasible to remove the adjuvant from the formulation of some vaccines such as HPV and HepB whilst maintaining immunogenicity. For some vaccines however (RTS,S and HIV) we have assumed the adjuvant will not be suitable for SDIs, nor will there be interest in removing the adjuvant.[a]

2. **Payload.** Antigens need to be available at a sufficiently high concentration (which might be higher than standard bulk harvests) to enable a full dose to be loaded into a SDI.
   The amount of vaccine required to be loaded onto a SDI relative to the yields of the manufacturing process has NOT been considered in this analysis, and no vaccines have been excluded on this basis.

3. **Route of delivery**. SDIs will not be suitable for use with vaccines that are currently delivered orally.
   Live-attenuated rotavirus vaccines, and ETVAX, the candidate vaccine selected as the exemplar for Enterotoxigenic E. coli (ETEC) have therefore not been considered for use with SDIs. The candidate M.tb vaccine VPM1002 is a recombinant BCG so will need to be delivered intradermally (ID) thus SDIs will not be suitable for administration of this vaccine.

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

[a] *Alumimium-salt based adjuvants and saponins might be compatible with SDIs, but oil-in-water adjuvants are unlikely to be suitable. [No data provided] EnesiPharma communication, 19 November 2019.*

Problem statements addressed by innovation:

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

- **Vaccine ineffectiveness/wastage due to freeze exposure:** It is possible, but not yet demonstrated, that resistance to damage by freezing might also be improved.
- **Vaccine ineffectiveness/wastage due to heat exposure:** Vaccines need to be reformulated into a dry format for administration by SDIs. A dry presentation doesn't guarantee thermostability per se, but the requirement to develop a new formulation provides an opportunity to improve the thermostability of the vaccine. Data obtained to date suggest that for some vaccines at least improved heat stability can be obtained with different SDI formats [1,2].
- **Cold chain requirements during outreach.** If formulations developed for SDIs have improved stability compared with current vaccines, then it is possible that they will not require the cold-chain for distribution
- **Reconstitution-related safety issues:** SDIs remove the need for reconstitution and associated risks of using the incorrect diluent and contamination when administering lyophilized vaccines.
- **Contamination risks with multi-dose vials**. Because SDIs will be single-dose format, they will remove the risk of contamination associated with the use of liquid or lyophilized vaccines in multi-dose vial presentations.
- **Difficult preparation requiring trained personnel:** SDIs are intended to be easy to use. They also remove the need for reconstitution and associated extra steps involved in administration and therefore could be appropriate for administration by lesser trained personnel.
- **Needle-stick injuries:** SDIs eliminate the risk of needle-stick injury (NSI).
- **Vaccine wastage or missed opportunities due to multi dose-vials:** SDIs 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).
- **Difficult to deliver vaccine to the correct injection depth:** The implants are delivered to a fixed depth depending on the design and parameters of the applicator, allowing reproducible, accurate targeting of the correct route (SC) of delivery.
- **Administration of the vaccine is painful, which reduces acceptability.** It is possible, but not yet demonstrated that administration of SDIs might be less painful than injection by needle and syringe.
- **Need for dose-sparing.** SDIs might facilitate dose-sparing in terms of amount of antigen per dose or number of doses required, due to slow-release of vaccine from the injection site. There are no clinical data on this point, however.
- **Negative impact on the environment due to waste-disposal practices.** Depending on the design of the SDI device, they might be more favourable for disposal than current vials and needles and syringe.

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

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

[b] *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.*

[c] *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.*

[d] *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.*

[e] *An online survey was conducted to collect information on key vaccine-specific delivery challenges faced by countries that can be addressed by innovations in the scope of VIPS. The survey was completed by 168 global and country level experts 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[e]	Comparator dose(s) per container
						• **Cold chain requirements during outreach** • **Vaccine ineffectiveness/wastage due to heat exposure** • **Difficult preparation requiring trained personnel**	injection with an AD N&S.
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	In diluent	Yes**	IM	• **Vaccine wastage or missed opportunities due to multi-dose vial** • **Cold chain requirements during outreach** • **Vaccine ineffectiveness/wastage due to heat exposure** • **Reconstitution related safety issues** • **Needle-stick injuries**	SDV or 10-dose vial
Inactivated poliovirus (IPV)*	Whole-inactivated	Liquid	No	Yes	IM or ID	• Vaccine ineffectiveness/wastage due to freeze exposure • **Vaccine ineffectiveness/wastage due to heat exposure** • **Cold chain requirements during outreach** • Reduced acceptability due to painful administration • Negative impact on the environment due to waste disposal practices	• IM (0.5ml/dose): SDV or 10-dose vial • ID (0.1ml/dose): SDV (5 fractional doses) or 5-dose vial (25 fractional doses).
Rabies*	Whole-inactivated.	Lyophilised	No	No	IM or ID	• **Difficult preparation requiring trained personnel** • **Vaccine ineffectiveness/wastage due to heat exposure**	• IM (0.5ml/dose): SDV • ID (0.1ml/dose): SDV (5 fractional doses)

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[e]	Comparator dose(s) per container
						• Reduced acceptability due to painful administration • **Vaccine wastage or missed opportunities due to multi-dose vial** • **Needle-stick injuries**	
Typhoid (conjugate)	PS-PCV	Liquid	No	Yes**	IM	• **Vaccine ineffectiveness/wastage due to heat exposure** • **Vaccine wastage or missed opportunities due to multi-dose vial** • **Difficult to deliver vaccine to correct injection depth** • **Difficult preparation requiring trained personnel** • Vaccine ineffectiveness/wastage due to freeze exposure	SDV or 5-dose vial
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. [f] • **Needle-stick injuries** • Negative impact on the environment due to waste disposal practices	SDV or 5-dose vial
Pipeline vaccines[g]							
Ebola (recombinant vesicular stomatitis virus, Zaire Ebola virus) (rVSV-ZEBOV)	Live vector	Liquid, FROZEN	No	No	IM	• ***Cold-chain requirements during outreach (vaccine needs to be kept frozen)*** • Vaccine ineffectiveness/ wastage due to heat exposure	Recently licensed as SDV vial

[f] *Vaccine ineffectiveness/wastage due to freeze exposure of YF vaccine was identified as a problem in the online survey. However it is the view of the VIPS WG that this is probably not a significant issue as YF is a lyophilised vaccine and as such is unlikely to be freeze-sensitive.*

[g] *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[e]	Comparator dose(s) per container
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only[h]	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	• *Heterologous prime-boost regimen with different vaccine types and presentations.* • *Priming vaccine is lyophilised.*	As still in Phase 2b/3, assume SDV
Influenza (pandemic, VAL-506440)	Nucleic acid	Liquid	Not known	Not known	IM	• *Not known* • *Possibly: need to deliver the vaccine to the correct injection depth.*	As still in phase I, assume SDV
Respiratory syncytial virus (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

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Rotavirus	Live-attenuated	Liquid	No	No	Oral	Live oral vaccine, not suitable for parenteral delivery.
Enterotoxigenic *E. coli* (ETEC) (ETVAX)	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized adjuvant	Yes	No	Oral	Oral vaccine, unlikely to be suitable for parenteral delivery.

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

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

Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120) gp120 boost only	Heterologous prime-boost. Live-attenuated recombinant viral vector + recombinant protein booster	Lyophilized prime and liquid booster (gp120)	Yes (boost)	Not known	IM	Boost contains MF59 oil-in-water adjuvant which is unlikely to be compatible with SDIs. We have assumed that there will be reluctance to remove the adjuvant from this vaccine.
Malaria (RTS,S)	Subunit	Lyophilized vaccine; liquid adjuvant	Yes (in diluent)	Not known	IM	Vaccines contains AS01 adjuvant which is unlikely to be compatible with SDIs. We have assumed that there will be reluctance to remove the adjuvant from this vaccine.
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002)	Live attenuated	Lyophilised	No	No	ID	SDIs deliver the vaccine SC (not ID), which is not appropriate for a BCG-based vaccine.

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

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

1.1 Criteria on health impact

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 applicable vaccines	No clinical data for any of the vaccine assessed[j]	**No data**

[j] *The assessment and scoring for this and other indicators is based on clinical data. However for some indicators, relevant pre-clinical data from non-human primates (but not small rodent) models, or laboratory studies) have been summarised for additional information*

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 per the following parameters based on field or other evidence?*** ○ ***Cases averted*** ○ ***Outpatient visits averted*** ○ ***Hospitalisations averted*** ○ ***Deaths averted*** ○ ***Vaccine doses given within the recommended age range (timeliness of vaccination)***	**Overall score**
All applicable vaccines	There are no data on effectiveness of administration by SDIs for any of the vaccines assessed	**No data**

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

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.

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

[l] *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. being kept frozen)?*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	Routine	No. VVM 14	No data. Unlikely given the heat stability of current products.	No, unless other routine vaccines that it is co-administered with are also qualified for CTC use.	Not known. Improved heat-stability is likely based on product attributes. **No data**
Hepatitis B (birth dose) (Liquid SDV or 10-dose vial)	Health facilities Outreach Home births	No. VVM30	Yes. CTC qualification in process for one or more vaccines.	Yes. For birth-dose outreach to homes and for storage at remote health facilities without cold chain.[m]	Yes. Bioneedles formulated with Hep B (no adjuvant) were significantly more stable (and immunogenic) at 37°C, 50°C and 60°C than the standard, adjuvanted, liquid formulation stored under the same conditions [3]. **Better**
HPV (Liquid SDV or two-dose vial)	Outreach to schools and communities *The initial MAC (typically 5 or 6 age cohorts rather than 1 may be special circumstance for CTC*	No. VVM30	Quadrivalent HPV vaccine (Merck) is qualified for CTC use (up to 3 days, below 42°C). [n]	Yes. For outreach to schools and communities.[o]	Not known. Improved heat-stability is likely based on product attributes. **No data**

[m] https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1
[n] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178
[o] https://www.who.int/immunization/policy/position_papers/PP_typhoid_2018_summary.pdf?ua=1

Vaccines	Assumed use case	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. being kept frozen)?*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
MR (Lyophilised SDV or 10-dose)	Routine Special immunization campaigns Outbreaks	No. VVM 14	No data. Unlikely given the heat stability of current products.	Yes. For use in outbreak and campaigns.[p]	Not known. Improved heat-stability is likely based on product attributes. **No data**
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial)	Campaign settings during initial introduction	No. VVM 30	MenAfriVac can be used under CTC conditions (up to four days at temperatures not exceeding 40°C). [q]	Yes. For initial campaign use.[r]	Not known. Improved heat-stability is likely based on product attributes. **No data**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No. VVM 7	No data. Unlikely given the heat stability of current products.	Yes, for use in campaigns	Yes: In one stability study IPV-containing Bioneedles retained 60%, 100% and 50% of potency for IPV1, 2 and 3 respectively after 1 week at 45°C. The potencies of IPV1,2 and 3 in liquid formulations were 0%, 20% and 20% respectively [1]. **Better**
Rabies (IM: 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	Not known. Improved heat-stability is likely based on product attributes.

[p] https://apps.who.int/iris/bitstream/handle/10665/255149/WER9217.pdf;jsessionid=19C907B061A1C194F9A711BF8F327BED?sequence=1

[q] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=196

[r] https://www.who.int/immunization/diseases/meningitis/en/

Vaccines	Assumed use case	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. being kept frozen)?*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
(ID: Lyophilized SDV)				outreach for post-exposure prophylaxis.[s]	**No data**
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	No. VVM 30	Yes. Likely given the heat stability of current products	Yes. For school and community based vaccination and outbreak response.[t]	Not known. Improved heat-stability is likely based on product attributes. **No data**
Yellow Fever (Lyophilized SDV or 10-dose)	Routine Campaigns Outbreak response	No VVM 14	No. A study to analyse CTC potential for YF in multidose vial format by one manufacturer did not support the CTC indication based on stability of the lyophilized product and stability of the reconstituted product at 40°C.[u] New YF formulations may be more stable, however.	Yes, for both use case scenarios	Not known. Improved heat-stability is likely based on product attributes. **No data**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. Stored as frozen liquid at -80°C for long term storage. [v]Can be stored at 4°C for four weeks after thawing. [w]	No data, but unlikely.	Yes. for both use case scenarios.[x]	Not known. Improved heat-stability is likely based on product attributes. **No data**

[s] *WHO Expert Consultation on Rabies, third report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1012). Licence: CC BY-NC-SA 3.0 IGO.*
[t] *https://www.who.int/wer/2008/wer8306.pdf*
[u] *PATH internal data, from Yellow Fever Vaccine CTC Stability Studies. Presented at WHO teleconference. 2 March 2015 March*
[v] *https://www.who.int/immunization/sage/meetings/2018/october/2_Ebola_SAGE2018Oct_BgDoc_20180919.pdf*
[w] *https://www.nejm.org/doi/suppl/10.1056/NEJMoa1502924/suppl_file/nejmoa1502924_protocol.pdf*
[x] *http://www.whogis.com/immunization/research/target-product-profile/WHO_Ebola_vaccine_TPP_version_final.pdf*

Vaccines	Assumed use case	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. being kept frozen)?*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (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	No data **No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data	No data	Yes, for both use case scenarios	Not known. Improved heat-stability is likely based on product attributes. **No data**
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.	Not known. Improved heat-stability is likely based on product attributes. **No data**

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

*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 applicable vaccines	No data for any of the vaccines assessed.	**No data**

1.2 Criteria on coverage and equity

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

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

Table 7

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

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

*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*

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

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

*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
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	The liquid vaccine comparators (such as pentavalent) and the SDIs do not require reconstitution so are rated similarly.	An SDI has the same number of components as the comparators (applicator + implant vs. vaccine vial and AD N&S). Some devices (Nemaura) have no applicator or an integrated applicator, so will have fewer components.	An SDI requires fewer and less complex preparation steps than the comparators.	An SDI is a fixed dose, so should improve dose control.	Pentavalent vaccine can be delivered SC or IM. SDIs deliver vaccine to the SC layer.	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	Hepatitis B vaccine does not require reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for pentavalent (above)	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
HPV (liquid SDV or two-dose vial)	HPV vaccine does not require reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for pentavalent (above)	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
MR (Lyophilised SDV or 10-dose)	MR requires reconstitution An SDI does not require reconstitution.	An MR-SDI requires fewer components than the comparator (vaccine vial, diluent, reconstitution syringe, AD N&S).	Fewer and less complex preparation steps	Fixed, prefilled dose	MR should be delivered SC. SDIs target SC tissue.	**Better**

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
	Better	**Better**	**Better**	**Better**	**Neutral**	
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial)	MenAfriVac requires reconstitution An SDI does not require reconstitution	See assessment for MR (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for pentavalent (above)	**Better**
	Better	**Better**	**Better**	**Better**	**Neutral**	
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	IPV does not require reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	IPV can be delivered ID SC, or IM. SDIs should be suitable for delivery of full-dose IPV, and possibly fractional doses in light of recent data on fractional IM doses [4]	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	Yes: Rabies vaccine currently requires reconstitution	See assessment for MR (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	Rabies can be delivered IM or ID, but the route of delivery effects the amount of antigen required.[5] SDI should be suitable for delivery of full dose, but not fractional doses of rabies.	**Mixed**
	Better	**Better**	**Better**	**Better**	**Worse**	
Typhoid conjugate (Liquid SDV or 5-dose)	Typhoid conjugate does not require reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for pentavalent (above)	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
Yellow Fever (Lyophilized SDV or 10-dose)	Yes: YF vaccine requires reconstitution	See assessment for MR (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for MR (above)	**Better**
	Better	**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
Ebola (rVSV-ZEBOV) (Liquid SDV)	rVSV-ZEBOV does not require reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	It is assumed that rVSV-ZEBOV can be delivered SC or IM. See assessment for pentavalent (above)	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	HIV priming dose (ALVAC) requires reconstitution	See assessment for MR (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	See assessment for MR (above)	**Better**
	Better	**Better**	**Better**	**Better**	**Neutral**	
Influenza (pandemic) (VAL 506440) (Liquid SDV)	VAL 506440 is assumed to be liquid and not need reconstitution	See assessment for pentavalent (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	It is assumed that VAL 506440 can be delivered SC or IM See assessment for pentavalent (above).	**Better**
	Neutral	**Neutral** / **Better**	**Better**	**Better**	**Neutral**	
RSV (pre-fusion F protein) (lyophilized SDV)	Yes. Pre-fusion F protein RSV requires reconstitution.	See assessment for MR (above)	Fewer and less complex preparation steps	Fixed, prefilled dose	It is assumed that pre-fusion F protein RSV can be delivered SC or IM. See assessment for pentavalent (above)	**Better**
	Better	**Better**	**Better**	**Better**	**Neutral**	

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

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

Table 9

Vaccines	Assumed use case	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
Pentavalent (DT-containing) (liquid SDV or 10-dose vial)	Routine	No, as this is a routine vaccine.	Yes/probably. Data from unpublished usability studies suggest that some SDIs are easier to use than N&S.[aa] **Better**	SDIs might be suitable for self-administration. However, this is a childhood vaccine so administration by lesser trained HCWs or caregiver/parent is more relevant in this case. **N/A**	**Better**
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	Health facilities Outreach Home births	Yes. It would be useful if the vaccine could be administered by midwives or traditional birth attendants.	See assessment for pentavalent **Better**	See assessment for pentavalent **N/A**	**Better**
HPV (liquid SDV or two-dose vial)	Outreach to schools and communities *The initial MAC (typically 5 or 6 age cohorts rather than 1 may be special circumstance for CTC*	Yes. Could potentially be delivered by lesser trained personnel in these settings.	See assessment for pentavalent **Better**	SDIs might be suitable for self-administration and could potentially be used by adolescent vaccinees. **Better**	**Considerably better**
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.	See assessment for pentavalent **Better**	SDIs might be suitable for self-administration and self-administration might be beneficial in campaign settings when adults or adolescents are being vaccinated **Better**	**Considerably better**

[aa] *Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019.*

Vaccines	Assumed use case	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
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.	See assessment for pentavalent **Better**	Men A SDIs are expected to be suitable for self-administration and this might be appropriate for older vaccine recipients **Better**	**Considerably better**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No, in the case of routine vaccine. Can be delivered as a co-formulation with other routine IM vaccines.[bb] Yes, It would be beneficial if lesser trained personnel could deliver the vaccine in campaign/ outbreak settings	See assessment for pentavalent **Better**	IPV-SDIs are expected to be suitable for self-administration. However, self-administration is not suitable for the intended target population relevant for IPV-SDIs. **N/A**	**Better**

[bb] http://polioeradication.org/polio-today/polio-prevention/the-vaccines/ipv/

Vaccines	Assumed use case	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
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.[cc] 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 [6,7]. Rabies vaccine can also be given via outreach to at-risk populations for pre-exposure prophylaxis.[dd]	See assessment for pentavalent **Better**	Rabies-SDI are expected to be suitable for self-administration **Better**	**Considerably better**
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	Yes. Delivery by lesser-trained personnel could facilitate catch-up vaccination and vaccination in response to confirmed outbreaks of typhoid fever and in humanitarian emergencies.[ee]	See assessment for pentavalent **Better**	Typhoid conjugate-SDIs are expected to be suitable for self-administration and this might be appropriate for older vaccine recipients. **Better**	**Considerably better**
Yellow Fever	Routine Campaigns	Yes, for campaign and outbreak response.	See assessment for pentavalent	YF-SDIs are expected to be suitable for self-administration	**Considerably better**

[cc] https://www.who.int/immunization/policy/position_papers/pp_rabies_summary_2018.pdf
[dd] https://www.who.int/wer/2013/wer8805.pdf?ua=1
[ee] https://www.who.int/immunization/policy/position_papers/PP_typhoid_2018_summary.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. caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
(Lyophilized SDV or 10-dose)	Outbreak response		**Better**	**Better**	
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. The ability to deliver the vaccine by lesser trained personnel could help facilitate outbreak response.[ff]	See assessment for pentavalent	rVSV-ZEBOV-SDIs are expected to be suitable for self-administration	**Considerably better**
			Better	**Better**	
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	Yes. For outreach and campaigns	See assessment above for MR	ALVAC SDIs are expected to be suitable for self-administration	**Considerably better**
			Better	**Better**	
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	Yes, for both use case scenarios	See assessment for pentavalent	Pandemic influenza -SDIs are expected to be suitable for self-administration	**Considerably better**
			Better	**Better**	
RSV (pre-fusion F protein) (lyophilized SDV)	Expected to be a routine maternal vaccine, and possibly administered on a seasonal basis.	Yes	See assessment for pentavalent	RSV-pre-fusion F protein-SDIs are expected to be suitable for self-administration	**Considerably better**
			Better	**Better**	

[ff] https://www.healthpolicy-watch.org/evidence-shows-ring-vaccination-strategy-effective-in-limiting-ebola-outbreak-in-drc/

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 applicable vaccines	No clinical data for any of the vaccines assessed	**No data**

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
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	SDIs are a single-dose presentation. Comparator is available as liquid in SDV or MDV with preservative. Reluctance to open a MDV with preservative would result in more wastage and missed opportunities compared to the single dose innovation.	**Better (MDV)**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	SDIs are a single-dose presentation. Comparator is available as liquid in SDV or MDV with preservative. Reluctance to open a MDV with preservative would result in more wastage and missed opportunities compared to the single dose innovation.	**Better (MDV)**

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**
HPV (SDV or 2-dose vial)	SDIs are a single-dose presentation. Comparator is available as liquid in SDV or 2-dose vial without preservative. Reluctance to open a MDV without preservative would result in more wastage and missed opportunities compared to the single dose innovation.	**Considerably better (MDV)**
MR (Lyophilised SDV or 10-dose)	SDIs are a single dose presentation. Comparator is available as lyophilised vaccine in SDV or 10 dose vial without preservative. Reluctance to open a MDV without preservative would result in more wastage and missed opportunities compared to the single dose innovation. Reluctance to open a MDV is regarded as a problem for MR vaccine for routine immunization [8].	**Considerably better (MDV)**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	SDIs are a single dose presentation. Comparator is available as lyophilised vaccine in SDV or 10 dose vial without preservative. Reluctance to open a MDV without preservative would result in more wastage and missed opportunities compared to the single dose innovation.	**Considerably better (MDV)**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	SDIs are a single-dose presentation. Comparator is available as liquid in SDV or MDV with preservative. Reluctance to open a MDV with preservative would result in more wastage and missed opportunities compared to the single dose innovation	**Better (MDV)l**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	SDIs are a single-dose presentation. Comparator is available as a lyophilised vaccine in SDV, but this contains multiple (5 or 10) fractional doses for ID delivery. Depending on the vaccine, the vials may or may not contain preservative. Reluctance to open a vial could therefore be an issue, but there are no recent data on this point.	**Considerably better (ID; no preservative)** **Better (ID; preservative)**
Typhoid conjugate (Liquid SDV or 5-dose)	SDIs are a single-dose presentation. Comparator is available as liquid in SDV or MDV with preservative, although vaccine should be discarded after 6 hours. Reluctance to open an MDV might therefore be an issue, resulting in more wastage and missed opportunities compared to the single-dose innovation.[gg]	**Better (MDV)**

[gg] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=347

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**
Yellow Fever (Lyophilized SDV or 10-dose)	SDIs are a single dose presentation. Comparator is available as a lyophilised vaccine in SDV or 10 dose vial without preservative. Reluctance to open a MDV might be expected to be a problem for YF vaccine in routine immunization, however, at least one study found that most YF vaccine wastage was due to doses remaining in opened-MDVs that were unused at the end of the session [9]	**Considerably better (MDV)**
Ebola (rVSV-ZEBOV) (Liquid SDV)	SDIs are a single dose presentation. Comparator is available as a frozen liquid SDV without preservative. [hh]Therefore, reluctance to open a MDV is not a problem with current presentations.	**Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	SDIs are a single dose presentation. The comparator is a single-dose vial similar to the innovation. It is not known whether or not it will contain a preservative.	**Neutral**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	SDIs are a single dose presentation. Comparator is available as a liquid in a SDV; it is not known whether or not it will contain a preservative.	**Neutral**
RSV (pre-fusion F protein) (Lyophilized SDV)	SDIs are a single-dose presentation similar to the comparator which is available as lyophilised vaccine in SDV. It is unknown whether this vaccine is expected to contain a preservative.	**Neutral**

[hh] https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf

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

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

Table 12

Parameter assessment				
Vaccines	***Does the innovation include features that may improve pain experienced by the recipient following vaccination?***	***Does the innovation include features that may improve perception of ease of administration (i.e. convenience for the vaccinees/caregivers)?***	***Does the innovation include features that may improve/impact any other benefit related to acceptability by vaccinees/caregivers?***	**Overall score**
All applicable vaccines assessed	In one study with Bioneedles with no vaccine, some subjects reported a mild burning sensation (but not pain) at the time of injection. Some subjects reported moderate pain several hours after injection however [10] In a human factors study with Implavax®, at least one participant commented that the process was pain-free.[ii]	In one unpublished human factors study with Implavax®, subjects commented favourably on the speed of the injection process. In addition, adults, parents of infants and parents of children expressed a strong preference for Implavax® compared with N&S. [ii] No vaccine was involved.	There is no data available on this from the perspective of the recipient.	**Better**
	Neutral	**Better**	**No data**	

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

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

[ii] *ImplaVax™ Unique needle free solid dose vaccine platform delivering enhanced immunogenicity with ultimate convenience and no cold chain. Enesi Pharma, 4 April 2018. (via PATH)*

Table 13

<table>
<tr><th>Vaccines</th><th colspan="2">Does the innovation require fewer components?</th><th>Or does the innovation include labelling that facilitates product tracking?</th><th>Overall score</th></tr>
<tr><td rowspan="2">Liquid vaccines:
• Pentavalent (DT-containing)
(Liquid SDV or 10-dose vial)
• Hepatitis B (birth dose)
(Liquid SDV or 10-dose MDV)
• HPV
(SDV or 2-dose vial)
• Polio (IPV)
(IM: Liquid SDV or 10-dose)
(ID: Liquid SDV or 5-dose)
• Typhoid conjugate
(Liquid SDV or 5-dose)
• Ebola (rVSV-ZEBOV)
(Liquid SDV)
• Influenza (pandemic) (VAL 506440)
(Liquid SDV)</td><td colspan="2">No. An SDI has the same number of components as the comparators (applicator + implant vs. vaccine vial and AD N&S). Some SDIs (Nemaura) might be usable without an applicator or have integrated applicator.</td><td></td><td>Neutral/Better</td></tr>
<tr><td>Neutral (separate applicator)</td><td>Better (integrated applicator)</td><td>N/A</td><td></td></tr>
<tr><td rowspan="2">Lyophilised vaccines:
• Measles rubella
(Lyophilised SDV or 10-dose)
• Men A (MenAfriVac)
(Lyophilized SDV or 10-dose vial)
• Rabies
(IM: Lyophilized SDV)
(ID: Lyophilized SDV)
• Yellow Fever
(Lyophilized SDV or 10-dose)
• HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only
(Lyophilized SDV)
• RSV (pre-fusion F protein)
(Lyophilized SDV)</td><td colspan="2">Yes. An SDI requires fewer components (applicator + implant) than the comparators (vaccine vial, diluent, reconstitution syringe, AD N&S).</td><td></td><td rowspan="2">Better</td></tr>
<tr><td colspan="2">Better</td><td>N/A</td></tr>
</table>

1.3 Criteria on safety

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

*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

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

Indicator: Likelihood of contamination and reconstitution errors

*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.*

[jj] *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?* [kk]	*Overall score*
Liquid vaccines: • **Pentavalent (DT-containing)** (Liquid SDV or 10-dose vial) • **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) • **HPV** (SDV or 2-dose vial) • **Polio (IPV)** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) • **Typhoid conjugate** (Liquid SDV or 5-dose) • **Ebola (rVSV-ZEBOV)** (Liquid SDV) • **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	No. Liquid vaccines, like SDIs, do not require reconstitution.	Some SDI devices have mechanisms to prevent re-use and others do not so the rating is neutral.	Some SDIs have a re-usable applicator or actuator. In at least one case, the implant cassette is designed to prevent contact of the actuator with the skin or body fluids.	The comparators require that a delivery device be filled, however there is no need to fill SDIs. For at least two of the systems, the implant is provided in a pre-loaded cassette or applicator.	No. SDIs are likely to require a similar number of steps compared with N&S injection.	No. Liquid vaccines, like SDIs, do not require reconstitution.	**Better**
	Neutral	**Neutral**	**Neutral**	**Better**	**Neutral**	**Neutral**	

[kk] *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?* [kk]	*Overall score*
Lyophilised vaccines: • **Measles rubella** (Lyophilised SDV or 10-dose) • **Men A (MenAfriVac) (**Lyophilized SDV or 10-dose vial) • **Rabies** (IM: Lyophilized SDV) (ID: Lyophilized SDV) • **Yellow Fever** (Lyophilized SDV or 10-dose) • **HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only** (Lyophilized SDV) • **RSV (pre-fusion F protein)** (Lyophilized SDV)	Yes: SDIs avoid the need for reconstitution unlike the lyophilized vaccine comparators.	Some SDI devices have mechanisms to prevent re-use and others do not so the rating is neutral.	Some SDIs have a re-usable applicator or actuator. In at least one case, the implant cassette is designed to prevent contact of the actuator with the skin or body fluids.	The comparators require that a delivery device be filled, however there is no need to fill SDIs. For at least two of the systems, the implant is provided in a pre-loaded cassette or applicator.	Yes. SDIs are likely to require fewer steps than AD N&S and SDV plus diluent and RUP syringe	Yes. SDIs avoid the need for reconstitution while the lyophilized vaccine comparators require reconstitution.	**Better**
	Better	**Neutral**	**Neutral**	**Better**	**Better**	**Better**	

Indicator: Likelihood of needle stick injury[e,ll]

*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 applicable vaccines	Most SDIs are sharps free [3].[mm] Although some may have a concealed needle.[nn]	Most SDIs are sharps free whereas the comparator would require sharps to prepare and/or administer the vaccine [3].**Error! Bookmark not defined.** **Error! Bookmark not defined.**	Some SDI devices have autodisable mechanisms to prevent re-use or autodisable like the comparators. **Error! Bookmark not defined.** **Error! Bookmark not defined.**	Since most SDIs are sharps free, they do not require a sharps injury prevention feature [3].**Error! Bookmark not defined.** SDI designs that do contain a concealed needle do retract after use.**Error! Bookmark not defined.**	As most SDIs are sharps free and some designs with a concealed needle can retract, there is no risk of injury after vaccination.	**Better**
	Better	**Better**	**Neutral**	**Better**	**Better**	

[ll] *For all vaccines being assessed the assessment and score of this indicator remains the same as in Phase 1.*
[mm] *Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019*
[nn] *Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019*

1.4 Criteria on economic costs

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

Notes:

- The assessments in Table 17 are high-level assessments of costs.
- For combination products such as SDIs with an applicator, 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.
- We do not have data on the vaccine prices or estimated cost of goods sold (COGS) for some innovations, especially those that are in early stages of development, including SDIs. 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 the 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.*

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

Table 17

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
Liquid vaccines: **Pentavalent (DT-containing)** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **Polio (IPV)** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	**SDI with an integrated disposable applicator** There are many unknowns that will impact the purchase cost of an SDI (accounting for wastage) including the need for reformulation, the yield of the manufacturing process and delivery efficiency. There are also uncertainties about the price of the SDI with an integrated disposable applicator given that none are made at commercial scale at present. Therefore, this parameter is scored as 'No data'.	**SDI with an integrated disposable applicator** Since the SDI is a combination product and does not require a separate AD syringe, the purchase cost of delivery devices will be eliminated, a savings of $0.04 per dose.	**SDI with an integrated disposable applicator** We assume these devices (e.g., Nemaura) would be disposed of as sharps waste in a safety box (device includes hidden needle). There are no publicly available estimates of the packaged volume of the SDI with a disposable applicator but measurement of prototypes by PATH estimated a volume of 21 cm^3 without secondary packaging. This is compared to 42 cm^3 for AD N&S. Therefore, the safety box costs would decrease, though these cost savings are less than $0.01 per dose.	Overall score: **No data** • No data on the COGS or purchase price of an SDI. • However, for combination product innovations like SDI, the vaccine price in this presentation is likely greater than for SDV and MDV. • Delivery device and safety box costs decrease but 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, we would assume that overall score for SDI is likely to be worse but score it as no data because of unknown vaccine price data.
	No data	**Better**	**Better**	

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
	SDI with a separate reusable applicator There are many unknowns that will impact the purchase cost of an SDI (accounting for wastage) including the need for reformulation, the yield of the manufacturing process and delivery efficiency. Therefore, this parameter is scored as 'No data'.	**SDI with a separate reusable applicator** There are uncertainties about the price of the applicator for an SDI with a separate reusable applicator given that none are made at commercial scale at present. Therefore, this parameter is scored as 'No data'.	**SDI with a separate reusable applicator** We assume the cassette with the SDI used with a reusable applicator is needle-free and would be disposed of as biohazard waste. There is no publicly available data on the volume of the cassette but estimates from Enesi assume the smallest volume for the cassette could be 20cm^3. This is compared to 42 cm^3 for AD N&S which is thrown into a safety box. Therefore, the safety box costs would decrease, though these cost savings are less than $0.01 per dose.	Overall score: **No data** • No data on the COGS or purchase price of an SDI or the separate reusable applicator. • However, for product innovations like SDI, the vaccine price in this presentation is likely greater than for SDV and MDV. • Safety box costs decrease but these are insignificant. • In summary, we would assume that overall score for SDI is likely to be worse but score it as no data because of unknown data for the vaccine and reusable applicator.
	No data	**No data**	**Better**	
Lyophilised vaccines: **Measles rubella** (Lyophilised SDV or 10-dose) **Men A (MenAfriVac)** **(**Lyophilized SDV or 10-dose vial) **Rabies** (IM: Lyophilized SDV) (ID: Lyophilized SDV) **Yellow Fever** (Lyophilized SDV or 10-dose)	**SDI with an integrated disposable applicator** There are many unknowns that will impact the purchase cost of an SDI (accounting for wastage) including the need for reformulation, the yield of the manufacturing process and delivery efficiency. There are also uncertainties about the price of the SDI with an integrated disposable applicator given that none are made at commercial scale at present. Therefore, this parameter is scored as 'No data'.	**SDI with an integrated disposable applicator** Since the SDI is a combination product and does not require a separate AD and reconstitution syringe, the purchase cost of delivery devices will be eliminated, a savings of ~$0.08 per dose for SDV and ~$0.05 for MDV.	**SDI with an integrated disposable applicator** We assume these devices (e.g., Nemaura) would be disposed of as sharps waste in a safety box (device includes hidden needle). There are no publicly available estimates of the packaged volume of the SDI with a disposable applicator but measurement of prototypes by PATH estimated a volume of 21 cm^3 without outer packaging. This is compared to 42 cm^2 for AD	Overall score: **No data** Same overall score rationale as for SDI with an integrated disposable applicator used with liquid vaccines.

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV) **RSV (pre-fusion F protein)** (Lyophilized SDV)			N&S and 38cm^3 for the reconstitution syringe. Therefore, the safety box costs would decrease, though these cost savings are less than $0.01 per dose.	
	No data	**Better**	**Better**	
	SDI with a separate reusable applicator There are many unknowns that will impact the purchase cost of an SDI (accounting for wastage) including the need for reformulation, the yield of the manufacturing process and delivery efficiency. Therefore, this parameter is scored as 'No data'.	**SDI with a separate reusable applicator** There are uncertainties about the price of the applicator for an SDI with a separate reusable applicator given that none are made at commercial scale at present. Therefore, this parameter is scored as 'No data'.	**SDI with a separate reusable applicator** We assume the cassette with the SDI used with a reusable applicator is needle-free and would be disposed of as biohazard waste. There is no publicly available data on the volume of the cassette but estimates from Enesi assume the smallest volume for the cassette could be 20 cm^3. This is compared to 42 cm^3 for AD N&S and 38 cm^3 for the reconstitution syringe which both need to be disposed in a safety box. Therefore, the safety box costs would decrease, though these cost savings are less than $0.01 per dose.	Overall score: **No data** Same overall score rationale as for SDI with a separate reusable applicator used with liquid vaccines.
	No data	**No data**	**Better**	

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

Note:

Previous costing studies 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.

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

Table 18

Vaccines	*Does the innovation reduce the economic costs of cold chain storage and transport for a vaccine regimen?*	*Does the innovation reduce the economic costs of out of cold chain storage and transport for a vaccine regimen including delivery technology(ies)?*	*Does the innovation reduce the economic costs of time spent by the vaccinators when preparing and administering the vaccine?*	*Does the innovation reduce the economic costs of time spent by staff involved in stock management*	Overall score
Liquid vaccines: **Pentavalent (DT-containing)** (Liquid SDV or 10-dose vial) **Hepatitis B (birth dose)** (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **Polio (IPV)** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Typhoid conjugate** (Liquid SDV or 5-dose)	**SDI with an integrated disposable applicator** We assume SDIs would be stored in the cold chain. The volume of an SDI was estimated at 21 cm^3 based on PATH measurements of prototypes. But the final packaged volume of SDIs is unknown. Volumes of SDV and MDV vary by vaccine type and manufacturer. For pentavalent vaccine, examples of cold chain volume per dose for SDV are 10.3 cm^3 and 14.03 cm^3. MDV have smaller cold chain volumes per dose such as 2.1 cm^3. The cold chain volume per dose would increase with SDIs. As a reference point for the magnitude of these costs, using PATH's VTIA model estimates, the cold chain storage costs for	**SDI with an integrated disposable applicator** An SDI would eliminate the need for separate injection devices and so there would be no out of cold chain storage and transport costs with a SDI with a combined disposable applicator. As a reference point for the magnitude of these costs, out of cold chain storage and transport costs for injection devices would be ~$0.01 for an AD N&S.	**SDI with an integrated disposable applicator** There is no data on the estimated time it would take to administer a vaccine using a SDI. A SDI has fewer steps to prepare and administer the vaccine which may reduce the time spent by vaccinators but overall time to prepare and administer the vaccine in a SDI is unknown. 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 previous time and motion studies have estimated that the time to administer a liquid vaccine in a SDV would be 19.3 seconds and 15.2 seconds in a MDV. So the vaccinator time costs would be	**SDI with an integrated disposable applicator** There are no attributes on this innovation that would reduce the economic costs of staff involved in stock management.	Overall score: **No data** • The volume stored and transported in the cold chain is likely to increase with SDI compared to SDV and MDV. • The volume store and transported out of the cold chain would decrease but this cost is less than costs for cold chain. • No data on the economic costs of time spent by vaccinators. • Overall score is no data because of unknown relative magnitude of change in costs of vaccinator time versus other

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
Ebola (rVSV-ZEBOV) (Liquid SDV)	20 cm^3 of cold chain space would be ~$0.04.		likely be around $0.01 per dose for liquid vaccines.		delivery cost components.
	Worse	**Better**	**No data**	**Neutral**	
	SDI with a separate reusable applicator We assume SDIs would be stored in the cold chain. The volume of the cassette for an SDI with a separate reusable applicator was estimated to have possible volumes of 20, 35 and 50 cm^3, based on information provided by Enesi. Volumes of SDVs and MDVs vary by vaccine type and manufacturer. For pentavalent vaccine, examples of cold chain volume per dose for SDVs are 10.3 cm^3 and 14.03 cm^3. MDVs have smaller cold chain volumes per dose such as 2.1 cm^3. So the cold chain volume per dose would increase with SDIs.	**SDI with a separate reusable applicator** The reusable applicator was assumed to be 90 cm^3 but is used for multiple vaccinations (assumed 1000 vaccinations) and so the volume per dose is small (0.09 cm^3) compared to the volume of an AD N&S (42 cm^3). The estimated cost savings for out of cold chain storage and transport costs would be ~$0.01 for an AD N&S as above.	**SDI with a separate reusable applicator** Same assessment as above	**SDI with a separate reusable applicator** There are no attributes on this innovation that would reduce the economic costs of staff involved in stock management.	Overall score: **No data** Same overall score rationale as for SDI with an integrated disposable applicator used with liquid vaccines.
	Worse	**Better**	**No data**	**Neutral**	
Lyophilised vaccines: **Measles rubella** (Lyophilised SDV or 10-dose)	**SDI with an integrated disposable applicator** We assume SDIs would be stored in the cold chain. The volume of a SDI was estimated at 21 cm^3 based on PATH measurements of prototypes.	**SDI with an integrated disposable applicator** An SDI would eliminate the need for separate injection devices and so there would be no out of cold chain storage and transport costs	**SDI with an integrated disposable applicator** There is no data on the estimated time it would take to administer a vaccine using a SDI. A SDI has fewer steps to prepare and administer the	**SDI with an integrated disposable applicator** There are no attributes on this innovation that would	Overall score: **No data** Same overall score rationale as for SDI with an integrated disposable applicator used with liquid vaccines.

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
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial) **Rabies** (IM: Lyophilized SDV) (ID: Lyophilized SDV) **Yellow Fever** (Lyophilized SDV or 10-dose) **HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only** (Lyophilized SDV) **RSV (pre-fusion F protein)** (Lyophilized SDV)	But the final packaged volume is unknown. Volumes of SDVs and MDVs vary by vaccine type and manufacturer. For MR vaccine, examples of cold chain volume per dose for SDVs are 14 cm^3 and 21 cm^3. MDVs have smaller cold chain volumes per dose such as 2.1 cm^3. So the cold chain volume per dose would increase with SDI. As a reference point for the magnitude of these costs, using PATH's VTIA model estimates, the cold chain storage costs for 20 cm^3 of cold chain space would be ~$0.04.	with a SDI with an integrated disposable applicator. As a reference point for the magnitude of these costs, out of cold chain storage and transport costs would be ~$0.02 for an AD N&S and reconstitution syringe.	vaccine which may reduce the time spent by vaccinators but overall time to prepare and administer the vaccine in a SDI is unknown. 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 previous time and motion studies have estimated that the time to administer a lyophilized vaccine in a SDV would be 48 seconds and 20.9 seconds in a MDV. So vaccinator time costs would be ~$0.02 per dose for a lyophilized vaccine in a SDV.	reduce the economic costs of staff involved in stock management.	
	Worse	**Better**	**No data**	**Neutral**	
	SDI with a separate reusable applicator We assume SDIs would be stored in the cold chain. The volume of the cassette for an SDI with a separate reusable applicator was estimated to have possible volumes of 20, 35 and 50 cm^3, based on information provided by Enesi. Volumes of SDVs and MDVs vary by vaccine type and manufacturer. For MR vaccine, examples of cold chain volume	**SDI with a separate reusable applicator** The reusable applicator was assumed to be 90 cm^3 but it can be used for multiple vaccinations and so the volume per dose is small (0.09 cm^3) compared to the volume of an AD N&S (42 cm^3) and reconstitution syringe (30 cm^3).	**SDI with a separate reusable applicator** Same assessment as above.	**SDI with a separate reusable applicator** There are no attributes on this innovation that would reduce the economic costs of staff involved in stock management.	Overall score: **No data** Same overall score rationale as for SDI with an integrated disposable applicator used with liquid vaccines.

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
	per dose for SDVs are 14 cm^3 and 21 cm^3. MDVs have smaller cold chain volumes per dose such as 2.1 cm^3. So the cold chain volume per dose would increase with SDIs.	The cost saving estimates stated above would be about the same.			
	Worse	**Better**	**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 applicable vaccines	Training costs: Training of vaccinators would be required to introduce SDIs.	**Overall score:** • Vaccinators would need to be trained on how to use SDI. • However, there are no other upfront or recurrent costs with SDI.
	Worse	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for SDIs.	
	Neutral	

1.5 Criteria on environmental impact

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

*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 applicable vaccines assessed	Unlikely. SDIs are likely to have a similar volume to an SDV (and would be biohazardous waste). Some SDIs would also have a separate (non-biohazardous) applicator.	Some SDIs are likely to be regarded as sharps free.	SDIs are relatively complex devices and will consist of plastics (probably more than one type) and in some cases metal too.	**Better**
	Neutral	**Better**		

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

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity[qq]

Notes:

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

- 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-SDIs and the clinical studies required to demonstrate safety of any given vaccine-SDI 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) prior to licensure with the new device. 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
Pentavalent (Liquid SDV or 10-dose vial)	Immunological endpoints (serum antibody titres) have been used for non-inferiority trials and approval of pentavalent vaccine in new delivery devices in the past [11]. It is assumed that similar endpoints could be used to assess SDIs.	**Low complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV	Seroprotection against hepatitis B is defined as having anti-HBs concentration of ≥ 10 mIU/ml [11]. Therefore it should be possible to conduct non-inferiority trials with and immunological endpoint, as was done for approval of new liquid formulations of pentavalent vaccine (which includes a HepB component) [12] and also initial studies of HepB vaccine in Uniject [11].	**Low complexity**

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

Vaccines	*Is the clinical development pathway complex?*	Overall score
HPV (SDV or 2-dose vial)	Non-inferiority trials using immunological endpoints (anti-HPV GMTs) have been used to compared 2 vs 3-dose schedules [13]. It is assumed that similar endpoints could be used to evaluate SDIs,	**Low complexity**
MR (Lyophilised SDV or 10-dose)	Immunogenicity assays have been used as endpoints for non-inferiority trials of MMR vaccines of different potencies [14]. It is assumed that similar endpoints could be used to evaluate SDIs,	**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) [15], and SBA titres were used for the approval of MenAfriVac [16]. It is assumed that similar endpoints could be used to evaluate MenA- and MenACWYX-SDIs.	**Low complexity**
IPV (IM: Liquid SDV or 10-dose), (ID: Liquid SDV or 5-dose)	Immunological endpoints (serum antibodies) have been used for non-inferiority trials of IPV vaccine [17] or IPV containing hexavalent vaccine [18]. It assumed similar endpoints could be used for IPV-SDI	**Low complexity**
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 [19,20] and it assumed similar endpoints could be used for rabies-SDI. A strategy to guide the clinical evaluation of new rabies vaccines has recently been proposed [7].	**Low complexity**
Typhoid conjugate (Liquid SDV or 5-dose)	According to WHO guidelines, immunogenicity endpoints (antibody titres) can and have been used for approval of typhoid conjugate vaccines [21].[rr] It is assumed a similar approach could be used for typhoid-SDIs.	**Low complexity**
Yellow Fever (Lyophilized SDV or 10-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) [22].	**Low complexity**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Immunological correlates of protection have not been established for Ebola virus [23,24], and it has only been possible to demonstrate efficacy of the most advanced candidate rVSV-ZEBOV) using ring vaccination trials [25]. However, given that rVSV-ZEBOV has been granted conditional marketing approval[ss], bridging studies with an immunological endpoint should be possible.	**Moderate complexity**

[rr] https://www.who.int/biologicals/areas/vaccines/TYPHOID_BS2215_doc_v1.14_WEB_VERSION.pdf
[ss] *https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ervebo*

Vaccines	*Is the clinical development pathway complex?*	Overall score
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	Ongoing phase III clinical trials of HIV vaccines have prevention of HIV acquisition as the primary endpoint,[tt] 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 [26].	**High complexity**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	WHO guidelines refer to three different types of pandemic vaccines: vaccines against novel inter-pandemic influenza strains; vaccines for stockpiling; vaccines developed following the outbreak of a pandemic. [uu]The approach for licensure of each of these, particularly the post-pandemic vaccines will differ, but is likely to involve immunological endpoints similar to those used for seasonal influenza vaccines. [uu]	**Low complexity**
RSV (pre-fusion F protein) (Lyophilized 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 [27]	**Moderate complexity**

[tt] Kundai Chinyenze 2018. Presentation at WHO PDVAC 2018. Available at https://www.who.int/immunization/research/meetings_workshops/15_Chinyenze_HIV_vaccines.pdf?ua=1

[uu] *https://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf*

Indicator: Technical development challenges

The WHO Delivery Technologies Working group, which is comprised of industry members and global health stakeholders, was invited to complete a survey[vv] *following a consultation on challenges facing development of SDIs. Nine member organizations responded to the survey and eight member organizations responded to the question on technical challenges. The following challenges were identified as the most important technical challenges facing the development of SDIs (most frequently identified challenges first):*

- Formulation of adjuvanted vaccines by SDI (i.e. eliminating adjuvant or identifying suitable adjuvant) (6/8)
- Reactogenicity/potential for granuloma formation (6/8)
- Quantity of vaccine required (i.e. payload limitation of SDI) (5/8)
- Achieving acceptable immune response (4/8)
- Combining multiple antigens within an SDI (4/8)
- Developing easy-to-use applicator (4/8)
- Achieving pain-free delivery (4/8)
- Other (acceptability; programmatic challenges; bloodborne transmission; achieving uniformity of filled dose) (3/8)
- Packaging size (including applicator) (2/8)
- Ability of the vaccine to withstand heat exposure (i.e. CTC) (1/8)

Additional responses included:

- The biggest benefits would be thermostability and ease-of-use but it's not clear if either could be achieved (limited- to no-data); quantity of payload could also be a limitation; [it is] also unclear whether adjuvanted vaccines would be reactogenic.
- The most challenging would be developing a single platform for a number of different antigens and especially adjuvants (e.g. split, conjugated, etc.)

Notes:

Table 22 describes vaccine-specific technical hurdles, not technical issues that apply to all SDI formats such as manufacturing process and controls. In general, the vaccine-specific issues relate to:

- The possible requirement to remove adjuvants
- payload limitations for some SDIs
- vaccine stability.

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.*

[vv] Survey carried out after DTWG telecons on SDIs held on 22 and 28 November 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
Pentavalent (Liquid SDV or 10-dose vial)	Pentavalent vaccine is combination vaccine and contains aluminium-salt based adjuvant. Challenges likely to be overcome: • The antigen content in a human dose is in the hundreds of micrograms [ww] and is likely to be compatible with most SDIs, providing the adjuvant is not required. • A formulation and process that preserves the stability of each antigen within the vaccine during manufacture will be required. This might or might not require a lyophilisation step which could be incompatible with aluminium-salt based adjuvants. Some SDIs have been produced without lyophilisation[xx], but this might not be a suitable process for large-scale manufacture. • Analytical assays will be required for each antigen in the combination. Key challenges/unknowns: • It is not known whether the current manufacturing process will produce bulk antigen at a high-enough concentration to be incorporated into an SDI, or whether additional steps will be required, which might reduce the overall yield of the process. For example, antigens have to be in a volume of ~4 µl for incorporation into Bioneedles [28]. • It is possible that SDIs might require an unadjuvanted formulation, which might not be sufficiently immunogenic in humans. There are no published data on this point with pentavalent or DT-containing vaccines, other than a study in mice with Bioneedles containing tetanus toxoid vaccine with and without aluminium phosphate adjuvant [29].	**High complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV	Hepatitis B vaccine is monovalent and adjuvanted. Challenges likely to be overcome: • The antigen content in a human dose (5 -20 µg) [30] is compatible with the expected payload capacity for SDIs. • A formulation that preserves the stability of the vaccine during manufacture will required. Bioneedles have been produced with hepatitis B vaccine with and without adjuvant [3]. Key challenges/unknowns: • It is not known whether current the manufacturing process will produce bulk antigen at a high-enough concentration to be incorporated into an SDI, or whether additional steps will be required, which might reduce the overall yield of the process. • It might not be possible to produce some SDIs that include an adjuvant, in which case the combination product might not be sufficiently immunogenic. However, one study has shown that hepatitis B-containing Bioneedles could be produced with or without alumimum hydroxide adjuvant, at least at laboratory scale [3].	**Moderate complexity**

[ww] *Quinvaxem package insert. Available at https://www.who.int/immunization_standards/vaccine_quality/pq_283_dtphepbhib_1dose_cPAD_Crucell_Korea_PI.pdf?ua=1 Accessed 29/10/2019*
[xx] *Faz Chowdhury, Nemaura, personal communication, 22 October 2019.*

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
HPV (SDV or 2-dose vial)	HPV vaccines are 4- or 9-valent virus-like particles (VLPs) and are adjuvanted. Challenges likely to be overcome: • A formulation that is compatible with and stabilizes all 4- or 9- HPV types will be required. • Analytical assays for all 4- or 9 HPV types will be required • The antigen content of the nine-valent HPV vaccine is ~270 µg. [yy] This should be compatible with SDIs. Key challenges/unknowns: • It is not known whether the current manufacturing process will produce bulk antigen at a high-enough concentration to be incorporated into an SDI, or whether additional steps will be required, which might reduce the overall yield of the process. • It is possible that SDIs will require an unadjuvanted formulation. It is not known whether this will be sufficiently immunogenic in humans. Reformulation for use as an SDI might impact one or more of the nine components of the vaccine.	**High complexity**
MR (Lyophilised SDV or 10-dose)	Measles rubella vaccines are live-attenuated virus vaccines. Challenges likely to be overcome: • Developing stabilizing formulations of live virus vaccines can be challenging particularly if protein excipients (such as gelatin) are not included. However, heat-stable dry formulations of measles have been produced by various methods other than lyophilization [31] Key challenges/unknowns: • The standard methods and cell-lines used for production of measles (and possibly rubella) might not produce bulk harvests with sufficient potency to be incorporated into an SDI. Either non-standard cell lines might be required for virus production or additional processing steps used to concentrate antigen.	**Moderate complexity**

[yy] *Gardasil-9 package insert. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=306*

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
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	MenAfriVac, MenACWY and MenACWYX vaccines are polysaccharide-protein conjugate vaccines. MenAfrivac and MenACWYX contain aluminium phosphate adjuvant in the diluent; other MenACWY vaccines are not adjuvanted Challenges likely to be overcome: • The fact that some MenACWY vaccines do not require an adjuvant suggests that it might be possible to have non-adjuvanted formulations that are sufficiently immunogenic. • The antigen content of MenA and MenACWY antigens is in the order of 10s of micrograms [zz,aaa], including carrier protein, and is likely to be within the payload capacity of SDIs. • Heat-stable, dry formulations of MenA vaccine have been produced using spray-drying [32] and the vaccine is relatively stable and can be used in a CTC. Therefore, it seems likely that a stable, SDI-compatible formulation can be developed. • Formulations and analytical assays for all 4- or 5 meningococcal capsular polysaccharides will be required. Key challenges/unknowns: • It is possible that further concentration of bulk antigen might be required	**Moderate complexity**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	IPV is an inactivated whole-virus vaccine with no adjuvant. Challenges likely to be overcome: • A formulation that stabilizes all three IPV types during SDI manufacture and subsequent storage will be required. It has been difficult in the past to develop stabilising formulations of IPV, however a lyophilisation process has been developed [33] that allows incorporation of IPV into Bioneedles and maintains potency [1]. Key challenges/unknowns: • It is not known whether a full human dose of IPV can be incorporated into SDIs. One study has shown that it is possible to lyophilise IPV and retain potency during incorporation into Bioneedles. However, the Bioneedles only contained ~1/15 of the standard dose [1].	**Moderate complexity**

[zz] *Nimenrix package insert, available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301*
[aaa] *Menactra package insert, available athttps://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=269*

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
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	Rabies is an inactivated whole virus vaccine with no adjuvant Challenges likely to be overcome: • Potency testing of rabies vaccines is by intra-cerebral challenge of mice, which is cumbersome and variable [34] Key challenges/unknowns: • Current lyophilised formulations of rabies vaccine are relatively heat-stable. However, they contain large amounts of excipients, including proteins such as serum albumin and gelatin. These can be present in 10s of mgs per dose and this might not be compatible with incorporation into SDIs. [bbb,ccc]	**Moderate complexity**
Typhoid conjugate (Liquid SDV or 5-dose)	Typhoid conjugate is a polysaccharide-protein conjugate vaccine with no adjuvant Challenges likely to be overcome: • The antigenic content of the current vaccine is low and compatible with SDIs (25 µg polysaccharide, although the amount of tetanus toxoid carrier protein is not stated). [ddd] • It has been possible to produce heat-stable dry formulations of other polysaccharide protein-conjugate vaccine (MenAfriVac) by spray-drying [32], so formulating conjugate typhoid vaccine for SDIs is likely to be feasible. Key challenges/unknowns • None identified	**Moderate complexity**
Yellow Fever (Lyophilized SDV or 10-dose)	Yellow fever vaccine is a live-attenuated virus. Challenges likely to be overcome: • Spray-dried micropellets containing YF vaccine have been produced [35], suggesting that it might be possible to formulate YF vaccine for SDIs. Key challenges/unknowns: • It is not known whether current processes yield bulk antigen of sufficient concentration for incorporation onto MAPs.	**Moderate complexity**

[bbb] *Rabavert package insert. Available at https://www.fda.gov/media/83874/download*
[ccc] *Imovax rabies package insert. Available at https://www.vaccineshoppe.com/image.cfm?doc_id=5983&image_type=product_pdf*
[ddd] *Typbar TCV package insert. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=347*

Vaccines	*How complex are the technical challenges to overcome for successful product development (i.e. difficulties applying the innovation to a combination vaccine, reformulation requirements, vaccine not well characterized, etc)?*	Overall score
Ebola (rVSV-ZEBOV) (Liquid SDV)	rVSV-ZEBOV is a live virus-vectored vaccine. It is currently stored as a frozen liquid. Challenges likely to be overcome: • The current production method for rVSV-ZEBOV yields bulk vaccine at 5 – 50 times the potency of a standard human dose [36]. The lower end of this range might be unsuitable for incorporation into SDIs without further concentration. Key challenges/unknowns: • Lyophilization of VSV, even in the presence of stabilisers, results in significant loss of potency (> 4 logs) [37]. Producing a dry formulation for incorporation into SDIs might be challenging. Attempts to produce a thermostable, lyophilised formulation are ongoing.[eee]	**High complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	ALVAC-HIV + bivalent subtype C gp120 is a heterologous prime-boost vaccine. The priming dose(s) are a live, recombinant virus vector (ALVAC) that is lyophilized. The boost (not considered here) is a recombinant protein with oil in water adjuvant and is liquid. Challenges likely to be overcome: • The stability of ALVAC vectors in SDIs has not been studied Key challenges/unknowns: • There are no known studies using ALVAC or similar vectors with SDIs. It is not known whether it will be possible to formulate ALVAC for use with SDIs.	**Moderate complexity**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Several different types of vaccines against influenza pandemics are and have been developed. The VIPS assessment is using an mRNA vaccine as an exemplar. Challenges likely to be overcome: • None identified Key challenges/unknowns: • There are very few clinical data to indicate whether mRNA vaccines will be highly or sufficiently immunogenic in humans. Two phase I clinical trials of pandemic mRNA vaccines induced immune responses (but there was no standard vaccine comparator) [38]. A clinical trial of a mRNA rabies vaccine (with a different formulation) was relatively poorly immunogenic [39] • VAL 506440 consists of mRNA packaged into lipid nanoparticles (LNPs) and LNPs appear to be important for immunogenicity [40]. It is not known whether the structure and function of the LNPs can be maintained during incorporation into SDIs.	**High complexity**

[eee] *J Blue 2016. Development, manufacturing and supply of MSD's Ebola vaccine. Presentation at ECDI Vaccine Technology VI. Available at https://dc.engconfintl.org/vaccine_vi/23/ Accessed 31/10/2019*

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
RSV (pre-fusion F protein) (Lyophilized SDV)	RSV pre-fusion F protein is a recombinant subunit vaccine Challenges likely to be overcome: • Early clinical trials evaluated the vaccine with and without adjuvant and found that the adjuvant had no beneficial effect [41]. It seems likely therefore that adjuvant will not be required. • The amounts of antigen used in clinical trials are compatible with the likely payload of SDIs [41]. Key challenges/unknowns: • The pre-fusion F protein vaccine is still in development so there is little information on many of the challenges that might face its use with SDIs.	**Moderate complexity**

Indicator: Complexity of manufacturing the innovation

In a survey[fff] of members of the WHO Delivery Technologies Working group, the following manufacturing challenges facing the development of SDIs were identified (most frequently named challenges first). Eight members responded to the survey:

- Concentration of bulk antigen (5/8)
- Aseptic production (4/8)
- Quality control and inspection (4/8)
- Process development and validation (4/8)
- Assembly and packaging (4/8)
- Achieving structural integrity (for skin penetration) vs. solubility (4/8)
- Manufacturing time per unit (3/8)
- Manufacturing yield (2/8)

Additional responses included:

- Limited volume/payload could require concentrated bulk antigen in which case yield could be an issue; unclear if solid dose implants would still have acceptable properties at elevated temperatures (37° C) that might be seen in some environments.

Notes:
SDIs are still early in development; manufacturing processes for SDIs incorporating vaccines are still at laboratory-scale. In addition to the vaccine-specific issues listed above (such as payload, whether or not adjuvants can be incorporated), there are generic challenges that are likely to apply to all SDI formats. Therefore, for Table 23 the same assessment applies to all vaccines assessed.

[fff] Survey carried out after DTWG telecons on SDI technology on 22 and 29 November 2019

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
All applicable vaccines assessed	SDIs of all formats are produced using novel manufacturing processes. Key challenges: • A dry formulation of the vaccine (+/- adjuvant is needed). For some SDIs, vaccine is filled into a cavity in the SDI and lyophilised [29]. In others, the vaccine plus excipients form the whole implant. It seems likely, that as with other methods for vaccine production, drying times will limit the rate of production. • The combination of excipients plus vaccine need to be formed into a needle, dried and have the necessary structural strength to maintain sharpness and rigidity to penetrate the skin but still be sufficiently soluble to release vaccine after implantation into the skin. • Manufacturing processes will have to be aseptic, as terminal sterilisation will not be possible for vaccines.	**High complexity**

Indicator: Robustness of the innovation-vaccine pipeline

Notes:

In table 24 it has been assumed throughout that:

- There are 3 'developers of the technology' (i.e. SDIs for use with vaccines - see phase I TN for details), namely: Enesi Pharma, Nemaura, Intravacc. Therefore, on a non-vaccine-specific basis, the number of developers would be assessed as 'moderately robust'. However, the pipeline is less robust when considered at the vaccine-specific level.
- Developers have been assessed as to whether or not they have a programme on the specific vaccine in question.
    - Where possible only products that are in 'full' preclinical development (i.e. with a clear path and intention to enter clinical trials) or clinical development have been listed.
    - In cases where studies have been published, and it is possible, but not clear whether the programme will progress to clinical studies, the key publications have been listed.
    - Exploratory, preclinical studies, especially by academic groups have not been included.

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

Table 24

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Pentavalent (Liquid SDV or 10-dose vial)	The number of SDI developers with a pentavalent (or DT-containing) vaccine SDI in pre-clinical or clinical development is not known. Early preclinical studies were published several years ago with Bioneedles [29].	There are multiple producers of liquid pentavalent or other DTP-containing vaccines. There are six WHO PQ manufacturers of pentavalent vaccine.[ggg]
	No data	**Highly robust**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	The number of SDI developers with hepatitis B birth dose vaccine SDIs in pre-clinical or clinical development is not known. Preclinical studies were published several years ago with Bioneedles [3].	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ products. [hhh]
	No data	**Highly robust**
HPV (SDV or 2-dose vial)	The number of SDI developers with HPV vaccine SDIs in pre-clinical or clinical development is not known.	There are two manufacturers of three licensed HPV vaccines. Both have WHO PQ products.[hhh] Several other manufacturers are developing HPV vaccines. UNICEF does not expect any new HPV vaccines to be WHO PQ'ed before 2021.[iii]
	No data	**Moderately robust**
MR (Lyophilised SDV or 10-dose)	One SDI developer (Enesi) has been awarded a grant by the BMGF for work on MR vaccine SDIs.[jjj] The level of funding and extent of the project goals have not been disclosed however. Intravacc has an agreement with Serum Institute of India Ltd for the joint development of MR-Bioneedles.[kkk]	There are multiple producers of measles vaccine and a single producer of stand-alone rubella. Two manufacturers have WHO PQ MR vaccines.[hhh]
	Not robust	**Moderately robust**

[ggg] https://extranet.who.int/gavi/PQ_Web/Browse.aspx?nav=3. *Accessed 21/10/2019*
[hhh] https://extranet.who.int/gavi/PQ_Web/Browse.aspx?nav=3 *Accessed 10/10/2019*
[iii] *UNICEF 2018. HPV vaccine supply and demand update.* https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf. *Accessed 21/10/2019*
[jjj] https://www.enesipharma.com/enesi-pharma-awarded-grant-funding-to-develop-and-evaluate-implavax-enabled-solid-dose-vaccines-targeting-measles-and-rubella-grant-funding-provided-by-the-bill-melinda-gates-foundation/. *Accessed 01/11/2019*
[kkk] https://www.intravacc.nl/#serum-institute-of-india-and-intravacc-to-develop-bioneedles . *Accessed 01/11/2019*

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	The number of SDI developers with meningococcal vaccine SDIs in pre-clinical or clinical development is not known.	There is only one manufacturer of MenAfriVac and one manufacturer known to be developing a MenACWYX vaccine.[lll]
	No data	**Not robust**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	One SDI developer (Bioneedles) has developed formulations for, and conducted early small animal testing of SDIs containing IPV [1,33].	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV.[hhh] There are however supply constraints[mmm] and only two suppliers to UNICEF [42]. New manufacturers of PQ IPV are expected to enter the market from 2020.[mmm]
	Not robust	**Moderately robust**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	The number of SDI developers with rabies vaccine SDIs in pre-clinical or clinical development is not known	There are several manufacturers of rabies vaccines. Four manufacturers have WHO PQ products.[hhh]
	No data	**Moderately robust**
Typhoid conjugate (Liquid SDV or 5-dose)	The number of SDI developers with typhoid conjugate vaccine SDIs in pre-clinical or clinical development is not known.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ. [hhh]
	No data	**Not robust**
Yellow Fever (Lyophilised SDV or 10-dose)	The number of SDI developers with YF vaccine SDIs in pre-clinical or clinical development is not known	There are several manufacturers of YF vaccines. Four manufacturers have WHO PQ products.[hhh]
	No data	**Moderately robust**
Ebola (rVSV-ZEBOV) (Liquid SDV)	The number of developers with a rVSV-ZEBOV SDI in development is not known.	There is only one manufacturer of this candidate Ebola vaccine. Other Ebola vaccines have different characteristics
	No data	**Not robust**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	The number of MAP developers with an ALVAC SDI for HIV vaccination in full pre-clinical or clinical development is not known	There are several heterologous prime-boost HIV vaccines in development, using several different virus vectors. Only one of these uses ALVAC as the priming dose [43]
	No data	**Not robust**

[lll] https://www.seruminstitute.com/product_horizon.php

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

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Influenza (pandemic) (VAL 506440) (Liquid SDV)	The number of developers of a mRNA pandemic flu vaccine SDI is not known.	There are a very few developers of mRNA vaccines against pandemic flu: Moderna [nnn]; Curevac (universal flu vaccine)[ooo] and Vir (universal flu vaccine)[ppp]. Other pandemic influenza vaccines have different characteristics
	No data	**Not robust**
RSV (pre-fusion F protein) (Lyophilized SDV)	The number of developers with a pre-fusion F protein RSV-SDI is not known	The pre-fusion F protein RSV vaccine being considered is produced by GSK. Several other manufacturers, including Pfizer have similar vaccines in development.[qqq]
	No data	**Moderately robust**

1.7 Criteria on commercial feasibility[rrr]

In a survey[sss] of members of the WHO Delivery Technologies Working group, the following challenges to commercialisation of SDIs were identified (most frequently identified challenges first). Eight members responded to the survey:

- Applicator supply chain (and reverse logistics) (5/8)
- Acceptability of implants (e.g. perception of pain, concern about implant) (5/8)
- Establishing partnerships to support development and commercialization (4/8)
- Market potential and uptake (4/8))
- Product development funding (3/8)
- Investment in manufacturing scale up (3/8)
- Interest from country stakeholders (3/8)
- IP landscape and freedom to operate (2/8)
- Regulatory strategy (1/8))

[nnn] https://www.modernatx.com/pipeline. *Accessed 10/10/2019*
[ooo] https://www.curevac.com/our-pipeline *Accessed 10/10/2019*
[ppp] https://www.vir.bio/pipeline/#focus *Accessed 10/10/2019*
[qqq] https://www.who.int/immunization/research/meetings_workshops/3_Karron_RSV_vaccines_PDVAC_2019.pdf?ua=1 *Accessed 10/10/2019*

[sss] *Survey carried out after DTWG telecons on MAP technology held on 3rd and 4th October 2019*

Additional responses included:

- Bioneedles could have a specific use case in emergencies and might need to be evaluated along with MAPs (where MAPs have limitations that could be addressed by implants).

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

Summary feedback from country consultation:

- SDIs were ranked #6 useful innovation
- Immunisation staff ranked SDIs as 8th out of 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's challenges and decision-makers 5th - based on weighted scores approach.
- Both groups mentioned the benefits of ease of use and logistics, increased acceptability to recipient/caregivers due to less pain, saved time of immunisation, decreased vaccine wastage due to single dose presentation, and improved safety by reduced needle-stick injuries and contamination risk and use of wrong diluent.
- Both groups also mentioned other benefits such as improved waste disposal, potential to improve vaccine coverage and delivery of correct vaccine dose.
- Both groups raised concerns about time to use and complexity of administering SDIs, need for community sensitisation and risk of reduced acceptability to patients/caregivers, impact on cold chain volume, overall cost, storage and logistics.
- Immunisation staff reported safety as possible challenges.
- Decision makers were also concerned about price per dose, and training and equipment needs - though 15 out of 28 decision makers interviewed expressed interest in purchasing SDIs, 10 stated potential interest, 3 participants said they would not be interested.
- Decision makers enquired whether a slow release implant could reduce the number of doses in the schedule and possibility of delivering more than one vaccine in one implant.
- Some decision makers expressed conflicting comments about this innovation. For example "Maybe good because less pain, could reduce logistics, but only if all vaccines are in this format, otherwise it complicates logistics."
- Both groups reported that they preferred disposable version of the device compared to the one with an applicator.
- Most immunisation staff respondents commented that easing logistics had to do with the lack of need for syringes and/or diluents and ability to take fewer items on outreach.

[ttt] *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.*

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**

Indicator: Potential breadth of the target market

Notes:

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

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

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

Table 26

Vaccines	*How broad is the potential target market?*	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	Global demand for whole-cell pertussis (wP) containing pentavalent vaccines has been estimated to be between 300 – 350 M doses per year between 2015 – 2035.[uuu] Most HICs and upper-middle income countries use acellular pertussis (aP), rather than wP-containing vaccines. This should not impact the feasibility of use with the innovation, but this would need to be confirmed.	**Large**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	WHO recommends a birth dose of hepatitis B. In 2015, 97 (49%) of countries had introduced HepB birth dose, but coverage rates vary and were approximately 35% globally in 2015 [30]. Adoption of birth dose by national immunization programmes has not matched the implementation of 3-dose hepatitis B vaccination starting later in infancy [30].	**Large**
HPV (SDV or 2-dose vial)	The WHO recommends that all countries should introduce HPV vaccination into national immunization programmes [44]. As of May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV into the national routine immunization schedule. But, despite carrying the greatest share of disease burden, LICs and MICs are lagging in the introduction of HPV vaccine. To date, the majority of the countries have self-procured HPV vaccines (74% in 2017).[vvv] A global demand forecast for HPV vaccine has been developed; base demand is estimated to be 55M doses in 2019, reaching ~100M doses in 2025 and stabilizing at ~110M annual doses from 2028 onward.[vvv]	**Large**
MR (Lyophilised SDV or 10-dose)	The average forecasted global MR demand through 2021 is approximately 400 million doses per year, split between the Gavi 71 countries (approx. 37%), India (39%), Indonesia (10%) and other non-Gavi-countries (14%).[www] Most HIC and MIC countries use MMR rather than MR vaccine [45].	**Large**

[uuu] *Gavi 2017. Pentavalent vaccine supply and procurement roadmap. Available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=11&cad=rja&uact=8&ved=2ahUKEwjvq5a3mK3lAhX0uXEKHZMwAwEQFjAKegQIBRAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Fpenta-roadmap-public-summary%2F&usg=AOvVaw1aoI5AGH3l7W6xumJ6N4Z- Accessed 21/10/2019*

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

[www] *Gavi. MR Vaccine Supply and Procurement Roadmap UPDATE November 2017. Available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=13&cad=rja&uact=8&ved=2ahUKEwjg-5z6zJPlAhX1sHEKHb0uBzsQFjAMegQIAxAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Fmeasles-rubella-vaccine-roadmap--public-summary%2F&usg=AOvVaw0dBkb8Zzc4OcWaRo09WXGg. Accessed 11/10/2019*

Vaccines	*How broad is the potential target market?*	Overall score
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 [46]. 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 [47]. HICs (such as USA, UK, Australia) are increasingly introducing vaccination of adolescents with polyvalent meningococcal vaccines [48]. Demand for MenACWY conjugate vaccine outside China and the meningitis belt was estimated to be 16.7M doses.[xxx]	**Moderate (MenA)** **Large (polyvalent)**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	The market for IPV is uncertain. IPV was introduced into all routine immunization schedules in 2016. However long-term future markets will depend on the timing of polio-eradication, post-certification polio-vaccination strategies and country preferences for stand-alone IPV vs. IPV in combination vaccines such as hexavalent vaccines. High-income and many middle-income countries have already introduced IPV either as a stand-alone antigen or, more commonly, in a combination vaccine. In 2016, 42 countries reported using the hexavalent (DTaP-Hib-HepB-IPV) combination vaccine and 39 reported using pentavalent (DTaP-Hib-IPV) vaccine in their routine immunization schedules. [yyy]	**Moderate**
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 [49]. Gavi estimates cumulative demand of 304M doses (20M/year) between 2021 and 2035. [zzz]	**Small / moderate**
Typhoid conjugate (Liquid SDV or 5-dose)	Gavi TCV demand forecast for Gavi 73 supported countries has wide range of estimated demand from over 100 million doses per year to as low as 10 million doses per year.[aaaa] Factors such as whether the vaccine is used for routine vaccination of infants or vaccination of high-risk infants impact forecast demand by approximately 4-fold [50].	**Small / moderate**

[xxx] *WHO 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*
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Vaccines	*How broad is the potential target market?*	Overall score
Yellow Fever (Lyophilised SDV or 10-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.[bbbb] 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 [51].	**Moderate**
Ebola (rVSV-ZEBOV) (Liquid SDV)	The future demand for Ebola vaccines is unknown and it is likely that the commercial market will be limited. Governments and non-governmental organizations will be the only likely buyers.[cccc] Presumably primarily for stockpiling to control outbreaks, eg by ring vaccination with rVSV-ZEBOV.	**Small**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized 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 [52].	**Large**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	In theory, in the event of a pandemic, there would be enough vaccine for the entire global population (approximately 7.4 bn). Current manufacturing capacity for influenza vaccines is ~6.3 bn doses, sufficient to immunize 43% of the population if two doses are required [53]. However, this assumes production of a pandemic vaccine after the start of a pandemic and once the pandemic strain has been isolated. Other strategies, such as stockpiling vaccine are possible.	**Small**
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 [54].	**Large**

[bbbb] *Yellow Fever Supply and Procurement Roadmap UPDATE 20th March 2017. Available at.* https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&cad=rja&uact=8&ved=2ahUKEwj898uc5pPlAhUGTBUIHZjiBugQFjACegQICBAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Fyellow-fever-roadmap-public-summary%2F&usg=AOvVaw0UdzCWsJx5LDChXSTEGlHE . Accessed 11/10/2019

[cccc] Gavi. Ebola Vaccine Supply and Procurement Roadmap March 2018. Available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=13&cad=rja&uact=8&ved=2ahUKEwjl4cGJ6JPlAhX0TxUIHZnZBEEQFjAMegQIARAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Febola-roadmap---public-summary%2F&usg=AOvVaw0P3yrwuNwVD0fea6Tv-4mK Accessed 11/10/2019

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

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/stakeholder support for the vaccine-innovation pairing?*	*Do partnerships exist between at least one of the technology developers and a vaccine manufacturer or have vaccine manufacturers expressed interest?*	Overall score
MR (lyo; MDV)	One SDI developer has funding from the Bill and Melinda Gates Foundation to work on MR-SDIs. [eeee]	Intravacc has an agreement with Serum Institute of India to co-develop MR-Bioneedles.[ffff]	**Moderate interest**
	Moderate interest	**Moderate interest**	
All other assessed vaccines	No known donor/stakeholder support.	No known partnerships	**No interest**
	No interest	**No interest**	

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

[eeee] *https://www.enesipharma.com/enesi-pharma-awarded-grant-funding-to-develop-and-evaluate-implavax-enabled-solid-dose-vaccines-targeting-measles-and-rubella-grant-funding-provided-by-the-bill-melinda-gates-foundation/. Accessed 01/11/2019*

[ffff] *https://www.intravacc.nl/#serum-institute-of-india-and-intravacc-to-develop-bioneedles . Accessed 01/11/2019*

Indicator: Known barriers to global access to the innovation

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

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

Table 28

Vaccines	Parameter assessment	Overall score
	Are there known barriers to Global Access to the innovation as applied to the vaccine ?	
All applicable vaccines	Not known, no data available for any of the vaccines assessed.	**No data**

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

SDIs can potentially address a number of challenges for a range of compatible vaccines, including: difficult preparation and the need for trained staff; needle-stick injuries; reconstitution errors; missed opportunities due to vaccine wastage or reluctance to open a MDV; contamination risks of MDVs; accuracy of delivering to the correct depth and resistance to heat exposure and facilitating use within the CTC (assuming that the formulation developed for use with the SDI confers improved heat stability). It is possible that resistance to freeze-damage might also be feasible, but more data are required. The problems addressed by SDIs are very similar to those that might be addressable by MAPs.

It should be technically feasible to combine many of the VIPS priority vaccines (existing and pipeline) with SDIs, potentially all injected vaccines that are delivered SC and possibly IM could be feasible. The exceptions will be orally delivered vaccines and those injectable vaccines that require an adjuvant that might be incompatible with the dry formulations used with SDIs, and vaccines that need to be delivered ID. There will however be challenges with some vaccines in terms of whether sufficient vaccine can be loaded into a SDI, whether or not adjuvant will need to be removed to facilitate manufacture (which might compromise immunogenicity) and the challenges in involved in developing an entirely new manufacturing process.

SYNERGIES WITH OTHER VIPS INNOVATIONS

Vaccines need to be (re-)formulated for use with SDIs, which provides an opportunity to improve heat stability, and means that SDIs should enable CTC-use for some vaccines, and would be synergistic with:

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

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

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