Microarray patches (MAPs)

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

Technology overview:

MAPs consist of an array of hundreds or thousands of micro-projections on a 'patch'. The projections are coated with, or composed of, vaccine in a dry formulation. When applied to the skin, the vaccine is delivered into the dermis and/or epidermis, which are rich in antigen presenting cell (APCs).

Several different formats of MAPs are being developed:

- With, or without, applicators; when present, the applicator can be a separate component or integrated with the MAP. The most advanced MAPs in development either have no applicator or an integrated applicator. **Therefore, MAPs with a separate applicator are not considered in this assessment;**
- Solid micro-projections coated with vaccine;
- Micro-projections formed of vaccine plus biocompatible excipients that dissolve or biodegrade in the skin;
- Hydrogel micro-projections that swell in the skin and act as a conduit for diffusion of the active ingredient from a backing layer (primarily in development for drug delivery).

In theory, MAPs could be used for administration of any type of vaccine, although there might be some vaccine-specific limitations: it might not be possible to formulate some vaccines so that they remain potent during the manufacture or storage of MAPs; some vaccines (in particular those formulated with an adjuvant) might have unacceptable levels of local reactogenicity when delivered into the skin; and in some cases, MAPs might not have the payload capacity for the vaccine plus necessary excipients, or it might not be possible to concentrate the antigen sufficiently so that it can be loaded onto the MAP.

Summary of vaccine and innovation compatibility:

Microarray patches (MAPs) 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, in particular:

1. **Reactogenicity:** MAPs deliver vaccines to the skin rather than intramuscularly (IM) or sub-cutaneously (SC). The subsequent initial immune response takes place near the skin surface and is more visible as local reactogenicity, than with IM or SC injections. While this administration route may offer the potential for dose-sparing for some vaccines, reactogenicity seen with MAP delivery of some 'more-reactogenic' formulations might not be acceptable to recipients.
   The reactogenicity seen with MAP delivery of some 'more-reactogenic' vaccines might not be acceptable to recipients.
   The inherent reactogenicity of any of the priority vaccines has NOT been considered in this analysis, and no vaccines have been excluded on this basis. Reactogenicity due to inclusion of an adjuvant HAS been considered (see below).

2. **Adjuvants:** The reactogenicity is very likely to be exacerbated by the presence of adjuvants. These might therefore need to be removed from vaccine formulations if they are to be used with MAPs, which may reduce their immunogenicity. There are some limited preclinical data to suggest that the immunogenicity elicited by some MAP formats can compensate for the absence of an adjuvant. The manufacturing process for some MAP formats is not compatible with aluminium-salt-based adjuvants, so they will have to be excluded from vaccine formulations used with these MAPs.
   We have assumed that it will be technically feasible to remove the adjuvant from the formulation of certain vaccines such as HPV and HepB. However, we have assumed that this will not be feasible or undertaken for:
   - *Pentavalent and other DTP containing vaccines. These are complex vaccines with multiple antigens so reformulation will be a significant challenge. They are also low-cost and it is assumed to be unlikely that a manufacturer would be willing to support the cost and effort required to develop formulations for MAPs.*
   - *RTS,S. This is a new vaccine containing a potent, proprietary adjuvant. It is unlikely that there will be an interest in removing this adjuvant and potentially reducing the immunogenicity of the vaccine.*
   - *HIV. The boost component of this vaccine contains an adjuvant. Given the challenges in developing HIV vaccines, it is unlikely that stakeholders will risk potentially compromising the immunogenicity of an HIV vaccine by removing the adjuvant.*

3. **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 onto a MAP in a very small volume.
   The amount of vaccine required to be loaded onto a MAP relative to the yields of the manufacturing process has NOT been considered in this analysis, and no vaccines have been excluded on this basis.

4. **Route of delivery**. MAPs 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 MAPs.

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

Problem statements to be addressed:

The problem statements applying to each vaccine that could potentially be addressed by MAPs are presented in Table 1. The key properties of MAPs 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 be improved.
- **Vaccine ineffectiveness/wastage due to heat exposure:** Vaccines need to be reformulated into a dry format for administration by MAPs. A dry presentation doesn't guarantee thermostability, 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 (including influenza and MR) stability at high temperatures can be obtained with different MAP formats [1–4].
- **Cold chain requirements during outreach.** If formulations developed for MAPs 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:** MAPs are a single-dose format. As such they remove the need for reconstitution and associated errors.
- **Contamination risks with multi-dose vials**. Because MAPs 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:** MAPs are intended to be sharps-free and easy to use. Early data from clinical trials and usability studies support this [1,5,6]
- **Needle-stick injuries:** MAPs are sharps free and eliminate the risk of needle-stick injury (NSI).
- **Vaccine wastage or missed opportunities due to multi dose-vials:** MAPs 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 microprojections are a fixed length and are designed to penetrate the skin only as far as the dermis or epidermis depending on the design of the MAP. The correct route of delivery should therefore be targeted, providing the MAP is applied correctly. This can be facilitated by use of an applicator that reproducibly generates the force required for skin penetration. MAPs can (or should) incorporate feedback mechanisms to ensure correct application. The MAPs most advanced in development either have no applicator or an integrated applicator. Therefore, MAPs with a separate applicator are not considered in this assessment
- **Administration of the vaccine is painful, which reduces acceptability.** It is possible, but not yet demonstrated that administration of MAPs might be less painful than injection by needle and syringe.
- **Need for dose-sparing.** MAPs deliver vaccine to the dermis and epidermis that are rich in antigen presenting cells. Studies in animal models with a range of different vaccines have shown that delivery of reduced amounts of antigen by MAPs can induce immune responses comparable to those seen following injection of the standard dose of vaccine (so-called ‘dose-sparing’). To date this has been evaluated and demonstrated in only one clinical trial, this trial used a monovalent influenza vaccine [4].
- **Negative impact on the environment due to waste-disposal practices.** Depending on the design of the MAP device, they might be more favourable for disposal than current vials and needles and syringe.

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Vaccine problem statements to be addressed[d]	Comparator dose(s) per container
Licensed vaccines							
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** • **Reduced acceptability due to painful administration** • **Difficult preparation requiring trained personnel**	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** • **Cold chain requirements during outreach** • **Vaccine ineffectiveness/wastage due to heat exposure** • **Difficult preparation requiring trained personnel**	SDV or 2-dose vial and delivery by IM injection with an AD N&S.

[a] *From a long list of vaccines, 17 VIPS priority vaccines were selected to cover a wide spectrum of different vaccine platforms, routes of administration, vaccine presentations and delivery strategies. The 17 vaccines also represent different families 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 includes 11 licensed vaccines that are WHO PQ'd, GAVI funded and UNICEF procured, as well as 6 pipeline candidate vaccines. Refer to the document 'Scope of vaccines' for the detailed explanation.*

[b] *Vaccines to be assessed were selected on the basis of 1) Technical applicability of the vaccine with the innovation, 2) Identification of vaccine-specific problem statements and 3) Ability of the innovation to solve vaccine-specific problem statements. The vaccines are not listed in any priority order. Problem statements are listed in order of importance according to the results from the online country consultation.*

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

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Vaccine problem statements to be addressed[d]	Comparator dose(s) per container
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** • **Reduced acceptability due to painful administration** • **Vaccine wastage or missed opportunities due to multi-dose vial** • **Needle-stick injuries**	• IM (0.5ml/dose): SDV • ID (0.1ml/dose): SDV (5 fractional doses)

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Vaccine problem statements to be addressed[d]	Comparator dose(s) per container
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	• **Vaccine wastage or missed opportunities due to multi-dose vial** • **Reconstitution related safety issues** • Vaccine ineffectiveness/wastage due to freeze exposure. [e] • **Needle-stick injuries** • **Negative impact on the environment due to waste disposal practices**	SDV or 10-dose vial
Pipeline vaccines[f]							
Ebola (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
HIV (ALVAC-HIV + bivalent Subtype C	Heterologous live attenuated recombinant viral vector +	Lyophilized prime; liquid booster (gp120) not	Yes (recombinant protein booster)	Not known	IM	• *Heterologous prime-boost regimen with different vaccine types and presentations.* • ***Reconstitution-related safety issues***	As still in Phase 2b/3, assume SDV

[e] *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*

[f] *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	Vaccine problem statements to be addressed[d]	Comparator dose(s) per container
gp120). ALVAC prime only[g]	recombinant protein booster	assessed (see Table 2)				• ***Difficult preparation requiring trained personnel***	
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
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002)	Live attenuated	Lyophilised	No	No	ID	• ***Difficult to deliver vaccine to the correct injection depth*** • ***Reconstitution-related safety issues*** • ***Difficult preparation requiring trained personnel***	SDV or 20-dose vial
RSV (pre-fusion F protein)	Subunit	Lyophilised	No	Not known	IM	• ***Reconstitution safety issues.*** • ***Difficult preparation requiring trained personnel***	SDV

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

** Must be discarded after 6 hours

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

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Pentavalent (DT containing)	Inactivated subunit plus PS-PCV	Liquid	Yes	Yes	IM	Complex vaccines with multiple antigens so reformulation will be a significant challenge. They are also low-cost and it is assumed to be unlikely that a manufacturer would be willing to support the cost and effort required to develop formulations for MAPs.
Rotavirus	Live-attenuated	Liquid	No	No	Oral	Live oral vaccine, not suitable for parenteral delivery.
ETEC (ETVAX)	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized adjuvant	Yes	No	Oral	Oral vaccine, unlikely to be suitable for parenteral delivery.
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 MAPs. 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 MAPs. We have assumed that there will be reluctance to remove the adjuvant from this vaccine.

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

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
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	Phase I clinical data (unpublished) has been generated to demonstrate feasibility of delivery of unadjuvanted HepB vaccine by MAP.[ij] In a study in non-human primates, HepB-MAPs delivering 24 µg or 48 µg non-adjuvanted HepB vaccine, induced lower antibody responses than IM injection of 10 µg of adjuvanted or non-adjuvanted HepB vaccine. The antibody titres induced by MAPs were still above the threshold believed to correlate with protection in humans [7]	**No data**
HPV (liquid SDV or two-dose vial)	No clinical data In a study in non-human primates, MAP delivery of 14 µg 9-valent HPV vaccine (unadjuvanted) was equivalent in terms of antibody response induced to the same dose given ID. MAP delivery of 28 µg HPV vaccine (unadjuvanted) was similar to 70 µg ID (unadjuvanted). But all MAP and ID doses of unadjuvanted vaccine were significantly less immunogenic than 70 µg (adjuvanted) given IM [8]	**No data**
MR (Lyophilised SDV or 10-dose)	No clinical data. In a study in non-human primates, MAPs induced protective titres of neutralizing antibodies to the M and R components of the vaccine [9]	**No data**

[i] *The assessment and scoring for this and other indicators are 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.*
[j] *LTS Lohmann has completed a phase I clinical study of an unadjuvanted Hep B MAP. PATH personal communication 7 January 2020*

Vaccines	*Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?*	Overall score
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial)	No clinical data. Dose-sparing by ID injection with N&S was seen in a clinical trial using a 1/5 dose of a meningococcal ACWY conjugate vaccine [10].	**No data**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No clinical data. Dose-sparing by ID delivery using N&S or jet-injector has been seen in several clinical trials [11], and with MAPs in preclinical studies in rats [12,13]). However, dose-sparing has also been reported with IM delivery of IPV in humans [14], so MAPs might not be essential to achieve dose-sparing. MAP delivery of IPV has also been reported in NHPs [15].	**No data**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	No clinical data. ID delivery has been used for several years for dose-sparing of rabies vaccines (reviewed in [16]).	**No data**
Typhoid conjugate (Liquid SDV or 5-dose)	No clinical data	**No data**
Yellow Fever (Lyophilized SDV or 10-dose)	No clinical data. Dose-sparing has been reported with ID [17] and SC [18] delivery of YF.	**No data**
Ebola (rVSV-ZEBOV) (Liquid SDV)	No clinical data	**No data**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	No clinical data	**No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No clinical data. ID delivery of mRNA vaccines against H10N8 induced antibodies and seroconversion. Depending on the dose used, the responses were higher or lower than the equivalent dose injected IM. Local injection site reactogenicity was higher with ID rather than IM injection [19].	**No data**

Vaccines	*Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?*	Overall score
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	No clinical data.	**No data**
RSV (pre-fusion F protein) (Lyophilized, SDV)	No clinical data	**No data**

Indicator: Vaccine effectiveness

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

Table 4

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

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

Score legend: Green: Better than the comparator (The innovation includes features that may increase heat stability or likely to enable CTC qualification ; White: Neutral, no difference with the comparator (The innovation has the same heat stability and/or CTC qualification as the current vaccine) ; Red: Worse than the comparator (The innovation includes features that may decrease heat stability or less likely to enable CTC qualification); N/A: the indicator measured is not applicable for the innovation; Grey: no data available to measure the indicator.

Table 5

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?*[l]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
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]	Not known. Improved heat-stability is likely based on product attributes. **No data**
HPV (liquid SDV or two-dose vial)	Outreach to schools and communities *The initial multi-age cohort (typically 5 or 6 age cohorts rather than 1) may be a 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]	Yes. A stability study with nine-valent unadjuvanted HPV vaccine coated onto silicon MAPs showed the vaccine to be stable for ≥ 3 months at 25°C and 37°C. There was no 'standard formulation' control [8]. **Better**

[k] *Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.*
[l] *This parameter is not used for scoring purposes, it is contextual/background information.*
[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. such as being kept frozen)?*[l]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*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]	Yes: Measles MAPs were stable at 25°C for 112 days and at 40°C for 28 days [20]. MR MAPs were stable at 40°C for ≥ 4 weeks. There was no standard vaccine control [9]. **Better**
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 a MAP formulation of IPV was stable at 25°C for ≥ 14 days [21]. In another study, IPV retained ≥70% activity after storage for 2 months at 25°C [22] **Better**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	Emergency basis for post-exposure prophylaxis	No. VVM 30	Yes. May be sufficiently heat stable in dry format	Yes. For storage in remote communities without cold chain, and for emergency outreach for post-exposure prophylaxis.[s]	Not known Improved heat-stability is likely based on product attributes. **No data**

[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/

[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.*

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?*[l]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
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 data	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 to -60°C for long term storage. Can be stored at 2-8°C for no more than two weeks or at room temperature for four hours after thawing.[u]	No data, but unlikely.	Yes. for both use case scenarios.[v]	No data **No data**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to	No data	No data	Yes. For outreach and campaigns	No data

[t] https://www.who.int/wer/2008/wer8306.pdf

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

[v] 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. such as being kept frozen)?*	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
(Lyophilized SDV)	susceptible populations				**No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data	No data	Yes, for both use case scenarios	No data **No data**
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002) (Lyophilized SDV or 20-dose)	Routine-use in neonates and adolescents Could be co-administered with hepatitis B birth dose.	No: VVM 14 or 30 (based on BCG)	No data.	CTC use could be beneficial for birth-dose outreach to homes, storage at remote health facilities without cold chain, or outreach to adolescents.[w]	Not known. Early data with coated MAPs indicate BCG MAPs were stable at room temperature for 1 week and at 4°C for ≥ 7 weeks in one study [23], and for two months at room temperature in a second study with a different MAP formulation [24]. **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.	No data **No data**

[w] *WHO Preferred Product Characteristics for New Tuberculosis Vaccines. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.*

Indicator: Ability of the vaccine presentation to withstand freeze exposure

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

Table 6

Parameter assessment		
Vaccines	***Does the innovation paired with the vaccine improve freeze exposure?***	**Overall score**
All applicable vaccines	No data for any of the priority vaccines assessed. A study with a split, seasonal influenza vaccine formulated for use with a MAP showed that it was able to withstand repeated freeze-thaw cycles, the standard formulation was also resistant to freeze-damage however [2]	**No data**

1.2 Criteria on coverage and equity

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

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

Table 7

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

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

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

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

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
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	MAPs, like the HepB birth-dose liquid vaccine comparators, do not require reconstitution	A MAP has only one component for delivery and therefore requires fewer vaccine product components than the comparators (vaccine vial and AD N&S).	A MAP requires fewer and less complex preparation steps than the comparators.	A MAP is a fixed dose as it is prefilled onto the MAP device. It will however need to be applied with sufficient pressure to penetrate the skin and worn for a certain period of time.	HepB birth-dose vaccine is delivered SC or IM. HepB vaccine has been administered ID in clinical trials. Therefore, MAPs would be a new route of delivery, however targeting to this route is expected to be better.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	
HPV (liquid SDV or two-dose vial)	Same as HepB above.	Same as HepB above.	Fewer and less complex preparation steps.	Same as HepB above.	Same as HepB above.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	

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

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
MR (Lyophilised SDV or 10-dose)	MR vaccine requires reconstitution MR- MAP vaccine does not require reconstitution	An MR MAP has only one component for delivery and therefore requires fewer vaccine product components than the comparators (vaccine vial, diluent, reconstitution syringe, AD N&S).	Fewer and less complex preparation steps.	A MAP vaccine is a fixed and prefilled dose.	MR vaccine should be delivered SC. Therefore, MAPs would be a new route of delivery however targeting to this route is expected to be better.	**Considerably better**
	Better	**Better**	**Better**	**Better**	**Better**	
Men A (MenAfriVac) (Lyophilized SDV or 10-dose vial)	MenAfriVac requires reconstitution MenA-MAP vaccine does not require reconstitution	Same as MR above.	Fewer and less complex preparation steps	Same as MR above.	Same as Hep B above	**Considerably better**
	Better	**Better**	**Better**	**Better**	**Better**	
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	IPV does not require reconstitution	Same as HepB above.	Fewer and less complex preparation steps	Same as HepB above.	IPV can be delivered IM or ID (for fractional dosing). MAPs might improve targeting the dermis/epidermis for ID delivery.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	Rabies vaccine currently requires reconstitution. Rabies-MAP vaccine does not require reconstitution	Same as MR above.	Fewer and less complex preparation steps	A MAP vaccine is a fixed and prefilled dose. The amount of vaccine required is different for IM and ID. Therefore, MAPs could improve dose-control	Rabies can be delivered IM or ID (for fractional dosing). MAPs might improve targeting the dermis/epidermia for ID delivery.	**Considerably better**
	Better	**Better**	**Better**	**Better**	**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
Typhoid conjugate (Liquid SDV or 5-dose)	Typhoid conjugate does not require reconstitution	Same as Hep-B above.	Fewer and less complex preparation steps	Same as Hep-B above.	Same as Hep B above	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	
Yellow Fever (Lyophilized SDV or 10-dose)	YF vaccine currently requires reconstitution	Same as MR above.	Fewer and less complex preparation steps	Same as MR above.	Same as MR above.	**Considerably better**
	Better	**Better**	**Better**	**Better**	**Better**	
Ebola (rVSV-ZEBOV) (Liquid SDV)	rVSV-ZEBOV does not require reconstitution	Same as HepB above.	Fewer and less complex preparation steps	Same as HepB above.	It is assumed that rVSV-ZEBOV can be delivered SC or IM. MAPs would be a new route of delivery however targeting to this route is expected to be better.	**Better**
	Neutral	**Better**	**Better**	**Better**	**Better**	
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	HIV priming dose (ALVAC) requires reconstitution	Same as MR above.	Fewer and less complex preparation steps	Same as MR above.	See assessment for MR (above).	**Considerably better**
	Better	**Better**	**Better**	**Better**	**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
Influenza (pandemic) (VAL 506440) (Liquid SDV)	VAL 506440 is assumed to be liquid and does not need reconstitution	Same as Hep-B above.	Fewer and less complex preparation steps	Same as Hep-B above.	It is assumed that VAL 506440 can be delivered SC or IM. Early clinical data suggest that ID delivery might be too reactogenic [19], so it is possible that MAP delivery might not be feasible therefore this has been scored as "No data", as important information is required before an assessment can be made.	**Mixed**
	Neutral	**Better**	**Better**	**Better**	**No data**	
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	VPM1002 is based on BCG, so will require reconstitution in the standard formulation. M.Tb -MAP vaccine does not require reconstitution	Same as MR above.	Fewer and less complex preparation steps	Same as MR above.	VPM 1002 is based on BCG so will need to be delivered ID. MAPs cannot penetrate deeper than the dermis, so targeting the correct route should be improved.	**Considerably better**
	Better	**Better**	**Better**	**Better**	**Better**	
RSV (pre-fusion F protein) (Lyophilized, SDV)	Pre-fusion F protein RSV is lyophilized and requires reconstitution. RSV- MAP vaccine does not require reconstitution	Same as MR above.	Fewer and less complex preparation steps	Same as MR above.	See assessment for rVSV-ZEBOV	**Considerably 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**	**Better**	

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

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

Table 9

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
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 below for MR	Although MAPs are expected to be suitable for self-administration [5], self-administration is not suitable for the intended target population of HepB birth dose.	**Better**
			Better	**N/A**	

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
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 a special circumstance for CTC*	Yes. HPV vaccine is often provided by outreach to schools and communities and could potentially be delivered by lesser trained personnel in these settings.	See assessment below for MR. **Better**	HPV-MAPs are expected to be suitable for self-administration [5] and could potentially be delivered 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.	Yes/probably. Data from one usability /acceptability study modelling use of MR-MAPs suggested that caregivers would prefer trained vaccinators with the highest level of education possible to administer MAPs. However this was due to lack of confidence in the unskilled vaccinators rather than the features of the MAP device itself [6]. In another study in Ghana, community health workers who support campaigns and deliver oral polio vaccines felt	MR-MAPs are expected to be suitable for self-administration [5], and self-administration might be beneficial in campaign or outbreak settings when adults or adolescents are being vaccinated.	**Considerably better**

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
			they could correctly apply a MAP.[z]		
			Better	**Better**	
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	Campaign settings during initial introduction	Yes. During initial introduction and it would be beneficial if lesser trained personnel could deliver the vaccine in these campaign settings.	See assessment above for MR	Men A-MAPs are expected to be suitable for self-administration and this might be appropriate for older vaccine recipients [5].	**Considerably better**
			Better	**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.[aa] Yes, It would be beneficial if lesser trained personnel could deliver the vaccine in campaign/ outbreak settings	See assessment above for MR	IPV-MAPs are expected to be suitable for self-administration [5]. However, self-administration is not suitable for the intended target population relevant for IPV-MAPs.	**Better**
			Better	**N/A**	

[z] *PATH. Evaluation of Microarray Patches for Human Factors— Considerations and Program Feasibility. Seattle: PATH; 2017. Available at:* https://www.path.org/resources/evaluation-of-microarray-patches-for-human-factors-considerations-and-program-feasibility/

[aa] 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/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) 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.[bb] 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 [15, 38]. Rabies vaccine can also be given via outreach to at-risk populations for pre-exposure prophylaxis.[cc]	See assessment above for MR **Better**	Rabies-MAP are expected to be suitable for self-administration [5]. **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.[dd]	See assessment above for MR **Better**	Typhoid conjugate-MAPs are expected to be suitable for self-administration and this might be appropriate for older vaccine recipients. [5]. **Better**	**Considerably better**

[bb] https://www.who.int/immunization/policy/position_papers/pp_rabies_summary_2018.pdf
[cc] https://www.who.int/wer/2013/wer8805.pdf?ua=1
[dd] 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/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
Yellow Fever (Lyophilized SDV or 10-dose)	Routine Campaigns Outbreak response	Yes, for campaign and outbreak response.	See assessment above for MR **Better**	YF-MAPs are expected to be suitable for self-administration [5]. **Better**	**Considerably 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.[ee]	See assessment above for MR **Better**	rVSV-ZEBOV-MAPs are expected to be suitable for self-administration [5]. **Better**	**Considerably 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 **Better**	HIV-MAPs are expected to be suitable for self-administration [5]. **Better**	**Considerably better**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	Yes, for both use case scenarios	See assessment above for MR **Better**	Pandemic influenza -MAPs are expected to be suitable for self-administration [5]. **Better**	**Considerably better**

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

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and/or self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g.volunteers and caregivers/parents) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002) (Lyophilized SDV or 20-dose)	Routine-use in neonates and adolescents Could be co-administered with hepatitis B birth dose.	Yes. For the birth dose it would be useful if the vaccine could be administered (ID) by midwives or traditional birth attendants. Delivery by lesser trained personnel (or self-administration) could be an advantage for routine vaccination of adolescents	See assessment above for MR **Better**	VPM1002-MAPs are expected to be suitable for self-administration which could be relevant for post-exposure immunization in adults [5]. However, self-administration is not suitable for the primary intended target indication (birth dose) for this vaccine. **N/A**	**Better**
Respiratory syncytial virus (RSV) (pre-fusion F protein) (Lyophilized SDV)	Expected to be a routine maternal vaccine, and possibly administered on a seasonal basis.	Yes	See assessment above for MR **Better**	RSV-pre-fusion F protein-MAPs are expected to be suitable for self-administration [5]. **Better**	**Considerably better**

Indicator: Ability to facilitate dose sparing

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

Table 10

Vaccines	*Does the innovation improve dose sparing of the vaccine?*	Overall score
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	No clinical data.	**No data**

Vaccines	*Does the innovation improve dose sparing of the vaccine?*	Overall score
	In a study in non-human primates, HepB-MAPs delivering 24 µg or 48 µg non-adjuvanted HepB vaccine, induced **lower** antibody responses than IM injection of 10 µg of adjuvanted or non-adjuvanted HepB vaccine. The antibody titres induced by MAPs were still above the threshold believed to correlate with protection in humans [7].	
HPV (liquid SDV or two-dose vial)	No clinical data. In a study in non-human primates MAP delivery of 14 µg 9-valent HPV vaccine (unadjuvanted) was equivalent in terms of antibody response induced to the same dose given ID. MAP delivery of 28 µg HPV vaccine (unadjuvanted) was similar to 70 µg ID (unadjuvanted). But all MAP and ID doses of unadjuvanted vaccine were significantly less immunogenic than 70 µg (adjuvanted) given IM [8].	**No data**
MR (Lyophilised SDV or 10-dose)	No clinical data. There are no clinical or preclinical data to suggest that MAP delivery of MR will result in dose-sparing.	**No data**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	No clinical data. Dose-sparing by intradermal delivery was seen in a clinical trial using a 1/5 dose of an unadjuvanted meningococcal ACWY conjugate vaccine [10], suggesting that dose-sparing with a MAP might also be possible.	**No data**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	No clinical data. Dose-sparing by ID delivery using N&S or jet-injector has been seen in several clinical trials [11], and with MAPs in preclinical studies in rats [12,13]. However, dose-sparing has also been reported with IM delivery of IPV in humans [14], so MAPs might not be essential to achieve dose-sparing. MAP delivery of IPV has also been reported in NHPs [15].	**No data**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	No clinical data. ID delivery has been used for several years for dose-sparing of rabies vaccines (reviewed in [16]), suggesting that dose-sparing with a MAP might be possible, but a MAP might not be essential for this purpose.	**No data**
Typhoid conjugate (Liquid SDV or 5-dose)	No clinical data. The clinical data obtained with a meningococcal ACWY conjugate vaccine (see above) [10] might also apply to typhoid conjugate vaccine, as they are both unadjuvanted, polysaccharide-protein conjugate vaccines, therefore MAPs would be a potential candidate for this vaccine.	**No data**

Vaccines	*Does the innovation improve dose sparing of the vaccine?*	Overall score
Yellow Fever (Lyophilized SDV or 10-dose)	No clinical data. Dose-sparing has been reported with ID [17] and SC [18] delivery of YF, suggesting that dose-sparing with a MAP might be possible but a MAP might not be essential for this purpose as unknown if it would improve dose sparing.	**No data**
Ebola (rVSV-ZEBOV) (Liquid SDV)	No clinical data.	**No data**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	No clinical data.	**No data**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No clinical data. ID delivery of mRNA vaccines against H10N8 induced antibodies and seroconversion in a phase I clinical trial. Depending on the dose used, these responses were higher or lower than the equivalent dose injected IM. Local injection site reactogenicity was higher with ID rather than IM injection [19]. Dose-sparing has been observed in a phase I trial of seasonal influenza vaccine delivered by MAP. In this study, a 1/6 dose delivered by MAP induced similar antibody titres to the full dose injected IM. The full-dose delivered by MAP induced significantly higher antibody titres than IM injection [4]. This study used a standard, split seasonal influenza vaccine however, not a mRNA, nucleic acid vaccine.	**No data**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	No clinical data. ID is the standard route of delivery for BCG, and it is assumed that this will be the case for VPM 1002 which is a recombinant BCG. MAPs are not expected therefore to result in dose-sparing.	**No data**
RSV (pre-fusion F protein) (Lyophilized SDV)	No clinical data.	**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**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	MAPs are a single-dose presentation. Comparator is available as liquid in SDV or 10-dose vial 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)**
HPV (SDV or 2-dose vial)	MAPs are a single-dose presentation. Comparator is available as liquid in SDV or 2-dose vial without preservative. Reluctance to open a MDV with preservative would result in more wastage and missed opportunities compared to the single dose innovation.	**Considerably better (MDV)**
MR (Lyophilised SDV or 10-dose)	MAPs are a single dose presentation. Comparator is available as lyophilised vaccine in SDV or 10-dose vial without preservative. Reluctance to open a MDV with 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 [25]	**Considerably better (MDV)**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	MAPs are a single dose presentation. Comparator is available as lyophilised vaccine in SDV or 10-dose vial without preservative. Reluctance to open a MDV with 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)	MAPs are a single-dose presentation. Comparator is available as liquid in SDV or 5 or 10-dose vial 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**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	MAPs are a single-dose presentation. Comparator is available as a lyophilised vaccine in SDV for IM delivery, 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; with preservative)
Typhoid conjugate (Liquid SDV or 5-dose)	MAPs are a single-dose presentation. Comparator is available as liquid in SDV or MDV with preservative, although vaccine should be discarded after 6 hours.[ff] Reluctance to open an MDV might therefore be an issue, resulting in more wastage and missed opportunities compared to the single-dose innovation.	**Considerably better (MDV)**
Yellow Fever (Lyophilized SDV or 10-dose)	MAPs 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 [26]	**Considerably better (MDV)**
Ebola (rVSV-ZEBOV) (Liquid SDV)	MAPs are a single dose presentation. Comparator is available as a frozen liquid SDV without preservative.[gg] 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)	MAPs 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)	MAPs 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**

[ff] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=347
[gg] https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf

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**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	MAPs are a single dose presentation. Comparator is available as a lyophilised vaccine in SDV or 20 dose vial without preservative. Reluctance to open a MDV might be regarded as a problem for Mtb vaccine for routine immunization as this has been identified as an issue for BCG. [hh]	**Considerably better (MDV)**
RSV (pre-fusion F protein) (Lyophilized SDV)	MAPs 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**

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.*

[hh] *Doses per container partnership snapshot. Available at: https://www.jsi.com/JSIInternet/Inc/Common/_download_pub.cfm?id=22167&lid=3. Accessed 11 December 2019.*

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	Possibly. The micro-projections on a MAP are shorter than N&S and might be expected to be associated with less pain. The amount of pain felt by recipients will be subject- and vaccine-specific however. In clinical trials with influenza vaccines, delivery by MAPs was associated with similar or slightly less (but not statistically significant) self-reported pain [1,3,27] Pain will be vaccine specific and there are no data for the VIPS priority vaccines however.	Possibly. There are fewer steps involved for the HCW which might improve acceptability. In vaccine MAP clinical studies, acceptability scores were similar for MAPs and IM, but overall most subjects preferred MAPs to IM injection [3,5,28]. 81–98% caretakers would accept MAPs for vaccination as demonstrated in usability study in Benin, Nepal, and Vietnam [6]. The recipient will have to wear the MAPs for a period of time, however. This is likely to be acceptable if it is seconds [6], but not if it is minutes or hours.	Yes. In a usability study (modelling MR-MAPs), MAPs were reported as appearing to be painless, avoiding fear of needles and appearing safer than N&S [6].	**Better**
	No data	**Better**	**Better**	

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

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

Table 13

Vaccines	***Does the innovation require fewer components?***	***Or does the innovation include labelling that facilitates product?***	**Overall score**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Yes. Most MAPs have a single component (MAP or MAP with integrated applicator), excluding packaging. This is fewer components than the comparator (AD syringe + vaccine vial).	MAPs do not include labelling that improves product tracking.	**Better**
	Better	**N/A**	

Vaccines	*Does the innovation require fewer components?*	*Or does the innovation include labelling that facilitates product?*	Overall score
HPV (SDV or 2-dose vial)	See assessment for HepB	See HepB assessment.	**Better**
	Better	**N/A**	
MR (Lyophilised SDV or 10-dose)	Yes. Most MAPs have a single component (MAP or MAP with integrated applicator), excluding packaging. This is fewer components that the comparator (AD syringe + vaccine vial + reconstitution syringe + diluent).	See HepB assessment.	**Better**
	Better	**N/A**	
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	See assessment for HepB	See HepB assessment.	**Better**
	Better	**N/A**	
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	
Typhoid conjugate (Liquid SDV or 5-dose)	See assessment for HepB	See HepB assessment.	**Better**
	Better	**N/A**	
Yellow Fever (Lyophilized SDV or 10-dose)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	
Ebola (rVSV-ZEBOV) (Liquid SDV)	See assessment for hepatitis B birth dose	See HepB assessment.	**Better**
	Better	**N/A**	
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	

Vaccines	*Does the innovation require fewer components?*	*Or does the innovation include labelling that facilitates product?*	Overall score
Influenza (pandemic) (VAL 506440) (Liquid SDV)	See assessment for hepatitis B birth dose	See HepB assessment.	**Better**
	Better	**N/A**	
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	
RSV (pre-fusion F protein) (Lyophilized SDV)	See assessment for MR	See HepB assessment.	**Better**
	Better	**N/A**	

1.3 Criteria on safety

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

*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.*

[ii] *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 14

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.*

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?* [ii]	*Overall score*
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	No: MAPs, like the liquid vaccine comparators, do not require reconstitution.	Dependent on the design, MAPs may be re-applied, but in general the safety risks associated with reuse are expected to be low. Some MAP designs will be AD, to prevent re-use. The comparators are also delivered with AD syringe devices.	MAPs are unlikely to involve non-sterile components (same as the comparators). Low-bioburden conditions have been used for production of MAPs for phase I trials. It is not certain however that this will be acceptable for commercial manufacture.	Yes. MAPs, unlike the comparators, do not require filling of a delivery device which minimizes the contamination risk. With some MAP designs, the user might be able to touch and contaminate the microprojections before application, although the risk of this is believed to be minimal.	Yes. MAPs are likely to require fewer steps than AD N&S and SDV.	MAPs, like the liquid vaccine comparators, do not require reconstitution.	**Better**
	Neutral	**Neutral**	**Neutral**	**Better**	**Better**	**Neutral**	

[ii] *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?* [ii]	*Overall score*
MR (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) **M. Tb (next generation BCG, VPM 1002)** (Lyophilized SDV or 20-dose) **RSV (pre-fusion F protein)** (Lyophilized SDV)	Yes: MAPs avoid the need for reconstitution and the comparators require reconstitution.	No. Dependent on the design, MAPs may be re-applied, but in general the safety risks associated with reuse are expected to be low. Some MAP designs will be AD, to prevent re-use) The comparator is vaccine delivered by AD syringe and reconstituted using a re-use prevention syringe.	Same as above.	Same as above.	Yes. MAPs are likely to require fewer steps than the comparators which require reconstitution, mixing, and filling of an AD N&S for delivery. AD N&S and SDV plus diluent and RUP syringe	Yes. MAPs avoid the need for reconstitution and the comparators require reconstitution.	**Better**
	Better	**Neutral**	**Neutral**	**Better**	**Better**	**Better**	

Indicator: Likelihood of needle stick injury

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

Table 16

Vaccines	*Does the innovation contain fewer sharps?*	*Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?*	*Does the innovation include an auto disable feature and is that better than the comparator?*	*If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?* [kk]	*Does the innovation reduce the risk of injury after vaccine administration?*	Overall score
All applicable vaccines	The assumption is that MAPs will be considered biohazard waste that can be disposed of within the clinical waste system and will not contain sharps. Solid-coated MAPs could, in theory transfer bodily fluids or tissues from the vaccinee after they have been removed. However, because an applicator is required to generate sufficient force to penetrate the skin, transfer is likely to be possible only through open wounds.	MAPs do not contain sharps and all the comparators require the use of sharps.	Some MAP designs have a feature to prevent re-use or auto-disable like the comparators.	MAPs do not contain sharps and therefore do not require a sharps injury prevention feature, which is better than the comparators.	MAP designs should not pose a risk of injury after they have been used. Dissolving microneedles will remain in the vaccinee, and solid microneedles require an applicator to generate sufficient force for penetration.	**Better**
	Better	**Better**	**Neutral**	**Better**	**Better**	

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

1.4 Criteria on economic costs

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

Notes:

- The assessments in Table 17 are high-level assessments of costs.
- For combination products such as MAPs, 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 MAPs. However, previous costing studies have shown that for the comparators (SDV and MDV), between the three cost categories accounted for here (purchase cost of vaccine, purchase cost of delivery devices, safety box costs), the purchase cost of vaccines will be largest share of the costs compared to the purchase cost of delivery devices and safety box costs.
    - Given that an AD N&S costs ~$0.04, a reconstitution syringe costs ~$0.04 but can be shared across multiple doses when used with a MDV, and the safety box costs are estimated at $0.005 per AD N&S, the magnitude of difference increases the higher the vaccine price.

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

[II] *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*
All applicable vaccines	There are many unknowns that will impact the purchase cost of the vaccine regimen (accounting for wastage) including the yield of the manufacturing process and delivery efficiency. There are also uncertainties about the device cost given that none are made at commercial scale at present. This parameter is scored as 'No data' because of unknown price data.	Since the MAP is a combination product and does not require a separate AD syringe or reconstitution syringe, the purchase costs of delivery devices will be eliminated, a savings of $0.04 per dose compared to a liquid vaccine. When compared to a lyophilized vaccine, the savings in delivery devices would be $0.08 per dose for a SDV and ~$0.05 per dose for MDV because of removal of need for AD and reconstitution syringes.	As stated in a previous section, the assumption is that MAPs will be considered biohazard waste that can be disposed of within the clinical waste system and will not contain sharps. For the comparator, the AD N&S (with a volume of 42 cm^3) is thrown into the safety box. For a lyophilized vaccine, a reconstitution syringe is also needed and has a volume of 38 cm^3. Therefore, the purchase costs of safety boxes will be reduced with a MAP, though these cost savings are less than $0.01 per dose based on PATH VTIA model estimates.	**No data** • No data in the COGS or purchase price of a MAP. • However, for combination products such as MAPs, it is likely that the COGS and procurement price will be greater than for SDV and MDV (including the cost of the vaccine). Also, previous costing studies have shown that for the comparators, the vaccine price (including the vial) 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.
	No data	**Better**	**Better**	

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

Note:

Previous costing studies have shown that for the comparators 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
All applicable vaccines **MAP with no applicator or an integrated applicator**	**SDV assessment** The volume of a MAP can range from 5 to >25 cm^3 (based on measured prototype devices by PATH), but there is no data on the final packaged volume. Therefore, the costs for storage and transport are unknown. A SDV can have a cold chain storage and transportation volume that varies by vaccine type and manufacturer. For example, the cold chain volume can be 9.7cm^3 (meningococcal conjugate vaccine)[mm], 14.53 cm^3 (Hep B)[nn], 21.09 cm^3 (measles containing vaccine)[oo], 30 cm^3 (rabies vaccine from Serum)[pp] and 18.6 cm^3 (IPV vaccine)[qq]. Given the unknowns, we score it as no data.	**SDV assessment** The MAP does not require a separate AD syringe, diluent or reconstitution syringe and so there would be no volume stored and transported out of the cold chain, even for a MAP with an applicator as the applicator would be co-packaged with the MAP. Therefore, this would reduce economic costs of out of cold chain storage and transport.	**SDV assessment** A MAP would be easier to administer than an injectable vaccine and the steps for preparing and administering the vaccine would be reduced compared to an injectable vaccine. But there is no data on the time needed to administer a MAP. Also given the possibility of self-administration, this would reduce the time spent by vaccinators for vaccine administration. However, whether vaccines can be self-administered is also unknown. Because of these unknowns, we score this as no data. As a reference point, for the magnitude of these costs for the comparators, the average human resource costs per minute were estimated at ~$0.03 per minute by PATH's VTIA model. Previous time and motion studies have estimated that the time to administer a liquid	**SDV assessment** There are no attributes on this innovation that would impact the time spend by staff involved in stock management.	**No data** • The costs for storage and transport in the cold chain is unknown because of no volume data for the MAP; the impact on the vaccinator time costs for preparing and administering the vaccine is also unknown. • For the SDV, a previous costing study for IPV estimated that these two cost components account for 72% of delivery costs.[rr] For the MAP, if both the volume stored and transported in the cold chain and the vaccinator time increase, then delivery costs will

[mm] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301*
[nn] *https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=68*
[oo] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=145*
[pp] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=322*
[qq] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=325*
[rr] *Mvundura M, Hsu JS, Frivold C, Kristensen D, Boyle S, Zehrung D, Jarrahian C. Evaluating the cost per child vaccinated with full versus fractional-dose inactivated poliovirus vaccine. Vaccine X. 2019 Jul 15;2:100032.*

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
			vaccine in a SDV would be 19.3 seconds and 15.2 seconds in a MDV. So the vaccinator time would be very much less than $0.01 per dose for the comparators.		increase compared to the SDV.
	No data	**Better**	**No data**	**Neutral**	
	MDV assessment Given that the volume of a MAP can range from 5 to >25 cm^3, it is likely that the cold chain storage and transportation volume of MAP volume will be larger than the per dose volume in a MDV, but the actual volume is unknown. Therefore, the costs for storage and transport are unknown MDVs have much smaller cold chain volumes than SDVs but volumes vary by type of vaccine and manufacturer. Examples of volumes per dose in a MDV are 4.2 cm^3 (measles containing vaccine in 5-dose vials)[ss], 3.38 cm^3 (IPV in 10 dose vials)[tt], or 2.1 cm^3 (meningococcal conjugate vaccine in 10-dose vials).[uu] As a reference point for the magnitude of these costs, using PATH's VTIA model estimates,	**MDV assessment** Same as SDV assessment.	**MDV assessment** Same as SDV assessment.	**MDV assessment** Same as SDV assessment.	**No data** • The costs for storage and transport in the cold chain is unknown because of no volume data for the MAP but it is most likely larger than a MDV; the impact on the vaccinator time costs for preparing and administering the vaccine is also unknown. • For the MDV, a previous costing study for IPV estimated that these two cost components account for 36% of delivery costs.[ee] For the MAP, if both the volume stored and transported in the cold chain and the

[ss] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=139*
[tt] *https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=372*
[uu] *WHO prequalified vaccines. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=196*

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
	the cold chain storage costs for 20 cm^3 of cold chain space would be ~$0.04.				vaccinator time costs increase, then delivery costs will increase compared to the MDV
	No data	**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?*	*Overall score*
All applicable vaccines	Training costs: Training of vaccinators would be required to introduce MAPs.	Overall score: **Worse** • Vaccinators have to be trained on how to use MAPs. • There are no other upfront or recurrent costs with MAPs.
	Worse	
	Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for MAPs.	
	Neutral	

1.5 Criteria on environmental impact

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

*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
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV) **HPV** (SDV or 2-dose vial) **IPV** (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose) **Typhoid conjugate** (Liquid SDV or 5-dose) **Ebola (rVSV-ZEBOV)** (Liquid SDV) **Influenza (pandemic) (VAL 506440)** (Liquid SDV)	Possibly. MAPs are likely to have a similar volume to a SDV (which would be biohazardous waste when empty), but avoid the need for AD N&S, which would be sharps waste (and biohazardous)	Yes. MAPs are likely to be regarded as sharps free.	Not known. Different developers are producing MAPs made from different materials. Some MAPs are likely to consist of a mixture of polymers, plastics and metal	**Better**
	Better	**Better**		

[vv] *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).*

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
MR (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) **M. Tb (next generation BCG, VPM 1002)** (Lyophilized SDV or 20-dose) **RSV (pre-fusion F protein)** (Lyophilized SDV)	Possibly. MAPs are likely to have a similar volume to a SDV (which would be biohazardous waste when empty), but avoid the need for AD N&S and RUP which would be sharps waste (and biohazardous) and diluent vial disposal **Better**	Yes. MAPs are likely to be regarded as sharps free and avoid the need for AD N&S and RUP syringe **Better**	See assessment as above.	**Better**

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity[ww]

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-MAPs combinations and the clinical studies required to demonstrate safety of any given vaccine-MAPs combination have not been assessed. Two generic safety issues that will need to be considered are:
    - For MAPs with dissolving microprojections, there might be biocompatibility issues with the dissolvable delivery components, that may change the duration of assessment for the biocompatibility depending on the resorption profile of the polymer.
    - For all MAPs, local reactogenicity at the application site is likely to be more significant that for injection with N&S, due to MAPs initiating immune responses close to the surface of the skin.
- 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.

*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
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 [29]. 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) [30] and also initial studies of HepB vaccine in Uniject [29].	**Low complexity**

[ww] *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 [31]. It is assumed that similar endpoints could be used to evaluate HPV-MAPs,	**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 [32]. It is assumed that similar endpoints could be used to evaluate MR-MAPs,	**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) [33], and SBA titres were used for the approval of MenAfriVac [34]. It is assumed that similar endpoints could be used to evaluate MenA- and MenACWYX-MAPs.	**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 [35] or IPV containing hexavalent vaccine [36]. It assumed similar endpoints could be used for IPV-MAPs	**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 [37,38] and it is assumed similar endpoints could be used for rabies-MAPs. A strategy to guide the clinical evaluation of new rabies vaccines has recently been proposed [39].	**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 [40].[xx] It is assumed a similar approach could be used for typhoid-MAPs.	**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) [41]. It is assumed a similar approach could be used for YF-MAPs.	**Low complexity**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Immunological correlates of protection have not been established for Ebola virus [42,43], and it has only been possible to demonstrate efficacy of the most advanced candidate rVSV-ZEBOV) using ring vaccination trials [44]. However, given that rVSV-ZEBOV has been granted conditional marketing approval[yy], bridging studies with an immunological endpoint should be possible.	**Moderate complexity**
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,[zz] 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 [45]	**High complexity**

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

Vaccines	*Is the clinical development pathway complex?*	Overall score
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. [aaa]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. [aaa]	**Low complexity**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	There are no accepted immunological correlates of protection for vaccines against BCG [46]. Therefore, clinical endpoints will be needed (prevention of infection or recurrence or disease) [bbb] and large phase III trials of long duration.	**High 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 [47]	**Moderate complexity**

[aaa] https://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf
[bbb] https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1

Indicator: Technical development challenges

In a survey[ccc] of the WHO Delivery Technologies Working group, which includes industry members and global health stakeholders, the following technical challenges facing the development of MAPs were identified (most frequently identified challenges first). Twenty members responded to the survey:

- Time the MAP must be worn for successful delivery (12/20)
- Quantity of vaccine required (i.e. higher dosage is required; dose-sparing not feasible) (11/20)
- Achieving acceptable immune response (11/20)
- Combining multiple antigens on a MAP (10/20)
- Delivery of adjuvanted vaccines by MAP (i.e. eliminating adjuvant or identifying suitable adjuvant) (8/20)
- Reproducibility of successful application (8/20)
- Ability of the vaccine to withstand heat exposure (i.e. controlled temperature chain qualification) (8/20)
- Maximizing efficiency of antigen delivery (as a percentage delivered) (6/20)
- Packaging size (3/20)

Write-in responses to this survey question included:

- Combination to determine costs; data to make the public business case (besides final proof for licensure) (1/20)
- Local reactogenicity, amplified by certain antigens (1/20)
- Commercial 'line of sight' LOS (1/20)
- MAP surface area/payload requirement; drug release and reproducibility on various skin types (adult, peds, ethnic groups, age difference in skin elasticity, etc) (1/20)

Table 22 assesses these and other challenges on a vaccine-specific basis.

*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.*

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

Table 22

Vaccines	*How complex are the technical challenges to overcome for successful product development (i.e. difficulties applying the innovation to a combination vaccine, reformulation requirements, vaccine not well characterized, etc.)?*	Overall score
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) [48] is compatible with the expected payload capacity for MAPs. • A formulation that preserves the stability of the vaccine during manufacture will be required for development with MAPs. Dissolvable HepB MAPs have been produced [7,49], and other heat-stable dry formulations of HepB have been obtained using processes such as spray drying [50], suggesting formulation development is likely to be successful. • Sufficient stability will be required to support continued use of HepB vaccines in the CTC. 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 a MAP, or whether additional steps will be required, which might reduce the overall yield of the process. Preclinical studies have required bulk antigen to be concentrated ~4-fold for MAP manufacture [49]. • It is likely that MAPs will require an unadjuvanted formulation of hepatitis B. It is not known whether this will be sufficiently immunogenic in humans or whether there will be a negative impact on duration of protection.. In non-human primates, unadjuvanted HepB vaccine delivered by MAP was less immunogenic than adjuvanted or non-adjuvanted HepB vaccine injected IM, but still induced antibodies above the threshold believed to be protective [7]. • There are significant differences in several aspects of the physiology of skin of neonates compared with older infants and adults [51]. Skin properties change significantly during the first few hours after birth (including, but not limited to the presence of the vernix caseosa) [51]. All of these factors could influence whether MAPs can be applied and successfully deliver vaccine. Conducting a trial in neonates to optimise MAP application and vaccine delivery might be difficult.	**Moderate / high complexity**

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. Functional stability of all 9-HPV VLP types coated on MAPs has been demonstrated after 3 months storage at 25°C and 37°C [8]. • Analytical assays for all 4- or 9 HPV types will be required. • Sufficient stability will be required to support continued use of HPV vaccines in the CTC. Key challenges/unknowns: • The antigen content of the nine-valent HPV vaccine is ~270 µg. This might exceed what can be loaded onto a MAP. [ddd] • It is not known whether the current manufacturing process will produce bulk antigen at a high-enough concentration to be incorporated into a MAP, or whether additional steps will be required, which might reduce the overall yield of the process. • It is likely that MAPs will require an unadjuvanted formulation. It is not known whether this will be sufficiently immunogenic in humans. In non-human primates, 28 µg of a 9-valentt HPV vaccine delivered by MAP induced similar antibody responses to 70 µg injected ID (unadjuvanted), but both of these were significantly less immunogenic than 70 µg (adjuvanted) given IM [8].	**High complexity**
Measles rubella (Lyophilised SDV or 10-dose)	Measles rubella vaccines are live-attenuated. 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, measles MAPs stable at 25°C for 112 days and at 40°C for 28 days [20], and MR MAPs stable at 40°C for ≥ weeks have been produced [9]. Key challenges/unknowns: • The minimum antigen content for MR vaccines is ≥ 1,000 $CCID_{50}$ per virus per dose [52,53]. It is not known whether this will be achievable with a MAP. • 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 a MAP. Preclinical studies have used non-standard cell lines that produce measles virus at higher titres [15,54]. Either non-standard cell lines might be required for virus production or additional processing steps used to concentrate antigen. • In a phase I clinical trial, trans-cutaneous delivery of measles vaccine (not by MAP) resulted in very low titres of serum antibody, but stronger mucosal responses than injected vaccine [55]. Although these might be beneficial, it would be difficult to run phase III trials and get approval for a vaccine with such a different mode of action.	**Moderate complexity**

[ddd] *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)	MenA, MenACWY and MenACWYX vaccines are polysaccharide-protein conjugate vaccines. MenAfrivac and MenACWYX contain aluminium phosphate adjuvant in the diluent; other MenACWY vaccines are not adjuvanted Challenges likely to be overcome: • Formulations without an adjuvant are likely to be required. 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 Men ACWY antigens is in the order of 10s (tens) of micrograms (µg) per dose[eee,fff], including carrier protein, and is likely to be within the payload capacity of MAPs. • Sufficient stability will be required to support continued use of MenA vaccine in the CTC. Heat-stable, dry formulations of MenA vaccine have been produced using spray-drying [50] and the vaccine is relatively stable and can be used in a CTC. Therefore, it seems likely that a stable, MAP-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 not known whether the current manufacturing process will produce bulk antigen at a high-enough concentration to be incorporated into a MAP, or whether additional steps will be required, which might reduce the overall yield of the process.	**Moderate complexity**
Polio (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: • Preclinical studies have used additional concentration steps so that sufficient antigen can be loaded onto MAPs [12,13,15]. • Preclinical studies suggest that IPV is likely to be immunogenic when formulated on MAPs [12,13,15] Key challenges/unknowns: • A formulation that stabilizes all three IPV types during MAP manufacturing and subsequent storage will be required. It has been difficult in the past to develop stabilising formulations of IPV, particularly IPV3 [56] including for use with MAPs [15]. A formulation for stabilizing IPV on coated MAPs has been developed. IPV was stable upon storage, but there was some loss of potency of IPV3 during and within 6 hours of drying [21].	**Moderate complexity**

[eee] *Nimenrix package insert, available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301*
[fff] *Menactra package insert, available at https://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 [57] 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 milligrams (mg) per dose and this is unlikely to be compatible with incorporation into MAPs. [ggg,hhh]	**Moderate / high complexity**
Typhoid conjugate (Liquid SDV or 5-dose)	Typhoid conjugate is a polysaccharide-protein conjugate vaccine with no adjuvant Challenges likely to be overcome: • It seems likely that the vaccine will be sufficiently immunogenic on the MAP (as discussed in Table 10); no adjuvant is required in the standard liquid formulation. • The antigenic content of the current vaccine is low and compatible with the expected payload of MAPs (25 µg polysaccharide, although the amount of tetanus toxoid carrier protein is not stated). [iii] Key challenges/unknowns • There is no information regarding how easy/difficult it will be to produce a formulation of the vaccines suitable for use with MAPs that is stable during drying and subsequent storage.	**Moderate complexity**

[ggg] *Rabavert package insert. Available at https://www.fda.gov/media/83874/download*
[hhh] *Imovax rabies package insert. Available at https://www.vaccineshoppe.com/image.cfm?doc_id=5983&image_type=product_pdf*
[iii] *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
Yellow Fever (Lyophilized SDV or 10-dose)	Yellow fever vaccine is a live-attenuated virus. Challenges likely to be overcome: • There is no information regarding how easy/difficult it will be to produce a formulation of the vaccine suitable for use with MAPs that is stable during drying and subsequent storage. Current formulations of YF vaccine can contain tens of milligrams of stabilising sugars per dose. [jjj] This would not be compatible with MAPs. Spray-dried heat stable YF vaccine formulations have been produced recently however [58]. Key challenges/unknowns: • It is not known whether current processes yield bulk antigen of sufficient concentration for incorporation onto MAPs. • Data, albeit limited, from non-human primates indicated that ID delivery of a YF virus-based vaccine (Chimerivax) resulted in prolonged viremia of vaccine virus [59] , which some experts have suggested might be a safety concern.	**Moderate / high complexity**
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 yields bulk vaccine at 5 – 50 times the potency of a standard human dose [60]. The lower end of this range is unlikely to be suitable for incorporation into MAPs without further concentration. Key challenges/unknowns: • There are few data available to indicate how difficult/easy it will be to produce a formulation of the vaccines suitable for use with MAPs that is stable during drying and subsequent storage. • The current frozen liquid vaccine formulation includes human serum albumin [60]. The presence of additional protein excipients might be an issue if there are payload restrictions for MAPs.	**Moderate / 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 on MAPs has not been studied Key challenges/unknowns: • There are no known studies using ALVAC on MAPs, however early preclinical studies have used other similar pox virus vectors such as MVA [61,62]. It is not known whether a sufficiently high dose can be loaded onto a MAP.	**Moderate complexity**

[jjj] *Yellow fever vaccine package insert. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=177*

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
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: • 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) [19]. A clinical trial of a mRNA rabies vaccine (with a different formulation) was relatively poorly immunogenic [63] Key challenges/unknowns: • VAL 506440 consists of mRNA packaged into lipid nanoparticles (LNPs) and LNPs appear to be important for immunogenicity [64]. It is not known whether the structure and function of the LNPs can be maintained during incorporation into MAPs. • In a phase I trial of an H10N8 influenza mRNA vaccine formulated in LNPs, ID injection was associated with sufficient local reactogenicity that enrolment into that part of the study was halted [19].	**Moderate / high complexity**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	VPM 1002 is a live recombinant BCG vaccine Challenges likely to be overcome: • None identified Key challenges/unknowns: • BCG is a relatively reactogenic vaccine, 95% of BCG vaccine recipients experience a reaction at the injection site characterized by a papule which may progress to become ulcerated, with healing after 2–5 months leaving a superficial scar [65]. Early clinical data with influenza vaccines suggests that MAP-delivery of vaccines might result in more local reactogenicity than injection by N&S [1,3,27]. It is possible or likely that MAP delivery of BCG might result in unacceptable levels of local reactogenicity in a significant proportion of recipients. • BCG is currently administered as a birth dose. There are significant differences in several aspects of the physiology of skin of neonates compared with older infants and adults [51]. Skin properties change significantly during the first few hours after birth (including, but not limited to the presence of the vernix caseosa) [51]. All of these factors could influence whether MAPs can be applied and successfully deliver vaccine.	**High complexity**

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 [66]. 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 MAPs [66] 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 MAPs.	**Moderate complexity**

Indicator: Complexity of manufacturing the innovation

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

- Aseptic production (11/20)
- Concentration of bulk antigen (10/20)
- Manufacturing process validation (9/20)
- Manufacturing yield (7/20)
- Quality control and inspection (7/20)
- Coating/filling microarrays with vaccine (7/20)
- Manufacturing time per unit (5/20)
- Assembly and packaging (2/20)

Write-in responses to this survey question included:

- Combination of above at GMP/pilot scale to determine (especially yield and manufacturing time/unit) – cost (1/20)
- Impact on COGS and production capacity (1/20)
- Manufacturing scale up; drug performance at release/on stability (1/20)
- Product sterility (1/20)

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

Most of the issues that have the greatest effect on the complexity of manufacturing MAPs are generic to each MAP format and are not vaccine specific. The vaccine-specific issues will be related to yield and stability and are listed in Table 22. Therefore, for Table 23 the same assessment applies to all vaccines assessed.

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	MAPs of all formats are produced using novel manufacturing processes. Leading MAP developers are designing production lines for commercial scale manufacture and also pilot lines for 1/5 scale manufacture. To date however, these have not been built. In addition to the challenges identified by the DTWG (above), other key issues that need to be addressed include: • The drying time required for some MAP formats; this can dramatically limit the rate of production. • In line quality controls. • Whether MAP manufacturing can be done under non aseptic or low bio-burden conditions	**High complexity**

Indicator: Robustness of the innovation-vaccine pipeline

Notes:

In table 24 it has been assumed throughout that:

- There are 3 - 8 ‘developers of the technology’ (i.e. MAPs for use with vaccines - see phase I TN for details), including: Corium; Fujifilm; Micron Biomedical/Georgia Tech; Vaxess; Vaxxas.
- 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 (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There is at least one MAP developer with a hepatitis B birth dose MAP in pre-clinical/ clinical development. [lll] Preclinical studies have been published by two groups, including GSK [7,67]	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ hepatitis B vaccine. [mmm]
	Moderately robust	**Highly robust**
HPV (SDV or 2-dose vial)	The number of MAP developers with a HPV-MAP in full pre-clinical or clinical development is not known. Non-human primate studies with an HPV-MAP have been published by Merck [8]	There are two manufacturers of licensed HPV vaccines. Both have WHO PQ products.[mmm] Several other manufacturers are developing HPV vaccines. UNICEF does not expect any new HPV vaccines to be WHO PQ'ed before 2021[nnn]
	Not robust	**Moderately robust**
MR (Lyophilised SDV or 10-dose)	Three MAP developers have been undertaking preclinical development of MR-MAPs funded by the Bill and Melinda Gates Foundation,[ooo] and two (Vaxxas and Micron Biomedical) have been funded to continue to Phase I clinical trials initiating in 2020/2021. Non-human primate studies with an MR-MAP have been published [9].	There are multiple producers of measles vaccine and a single producer of stand-alone rubella. Two manufacturers have WHO PQ MR vaccines. [mmm]
	Moderately robust	**Moderately robust**

[lll] *LTS Lohmann has completed a phase I clinical study of an unadjuvanted Hep B MAP. PATH personal communication 7 January 2020*
[mmm] *https://extranet.who.int/gavi/PQ_Web/Browse.aspx?nav=3 Accessed 10/10/2019*
[nnn] *UNICEF 2018. HPV vaccine supply and demand update. https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf. Accessed 21/10/2019*
[ooo] *https://www.gatesfoundation.org/search#q/k=microarray%20patch Accessed 10/10/2019*

Vaccines (current presentations)	*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 MAP developers with a meningococcal-MAP in full 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.[ppp]. There are two PQ manufacturers of lyophilized Men ACWY vaccines. [qqq], [rrr]
	No data	**Moderately robust**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Seven MAP developers have undertaken development of IPV-MAPs; several of these in a project supported by the WHO and the Bill and Melinda Gates Foundation[sss] and other sources. Most have been discontinued. At least two programmes (Vaxxas and Micron Biomedical) are ongoing.	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV.[mmm] but only two supply to UNICEF and there are supply constraints [68]. New products are expected to enter the market in 2023-2024 [68].
	Moderately robust	**Not robust**
Rabies (IM: Lyophilized SDV) (ID: Lyophilized SDV)	One MAP developer is undertaking preclinical development of a rabies MAP.[ttt]	There are several manufacturers of rabies vaccines. Four manufacturers have WHO PQ products.[mmm]
	Not robust	**Moderately robust**
Typhoid conjugate (Liquid SDV or 5-dose)	The number of MAP developers with a typhoid conjugate-MAP in full pre-clinical or clinical development is not known.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ. [mmm]
	No data	**Not robust**
Yellow Fever (Lyophilized SDV or 10-dose)	The number of MAP developers with a YF-MAP in full pre-clinical or clinical development is not known.	There are several manufacturers of YF vaccines. Four manufacturers have WHO PQ products.
	No data	**Moderately robust**
Ebola (rVSV-ZEBOV)	The number of developers with a rVSV-ZEBOV MAP in full pre-clinical or clinical development not known.	There is only one manufacturer of this candidate Ebola vaccine. Other Ebola vaccines have different characteristics.

[ppp] https://www.seruminstitute.com/product_horizon.php
[qqq] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301
[rrr] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=267
[sss] GPEI. Polio post-certification strategic plan. Available at: http://polioeradication.org/wp-content/uploads/2017/11/polio-post-certification-strategic-plan-draft-17112017.pdf. Accessed 10/10/2019
[ttt] Developer response in survey carried out after DTWG telecons on MAP technology held on 3rd and 4th October 2019

Vaccines (current presentations)	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
(Liquid SDV)	**No data**	**Not robust**
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only (Lyophilized SDV)	The number of MAP developers with an ALVAC-MAP 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 [69]
	No data	**Not robust**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	The number of developers of a mRNA pandemic flu vaccine MAP in full pre-clinical or clinical development is not known.	There are a few developers of mRNA vaccines against pandemic flu: Moderna [uuu]; Curevac (universal flu vaccine)[vvv] and Vir (universal flu vaccine)[www].
	No data	**Moderately robust**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	The number of developers with VPM 1002 (recombinant BCG) MAP in full pre-clinical or clinical development is not known	There is only one developer of the VPM 1002 vaccine, although 20 – 30 different recombinant BCG vaccines have been tested in preclinical models. [70]
	No data	**Not robust**
RSV (pre-fusion F protein) (Lyophilized SDV)	The number of developers with a pre-fusion F protein RSV-MAP in full pre-clinical or clinical development 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.[xxx]
	No data	**Moderately robust**

1.7 Criteria on commercial feasibility[yyy]

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

- Regulatory strategy (12/20)
- Market potential and uptake (11/20)
- Investment in manufacturing scale up (11/20)

[uuu] https://www.modernatx.com/pipeline. *Accessed 10/10/2019*
[vvv] https://www.curevac.com/our-pipeline *Accessed 10/10/2019*
[www] https://www.vir.bio/pipeline/#focus *Accessed 10/10/2019*
[xxx] https://www.who.int/immunization/research/meetings_workshops/3_Karron_RSV_vaccines_PDVAC_2019.pdf?ua=1 *Accessed 10/10/2019*
[yyy] *These indicators will be evaluated in an absolute manner, not relative to a comparator.*
[zzz] *Survey carried out after DTWG telecons on MAP technology held on 3rd and 4th October 2019*

- Clinical development pathway (8/20)
- Establishing partnerships to support development and commercialization (9/20)
- Product development funding (6/20)
- Interest from country stakeholders (5/20)
- Intellectual property landscape/freedom to operate (3/20)

Write-in responses to this survey question included:

- Uncertainty re: value proposition in HICs which will determine financial attractiveness of the product (1/20)
- Establish a successful business model between manufacturer and developer; reasonable royalties and reasonable business approach (including Technology Transfer or other model to provide access to knowhow). Furthermore, GMP and manufacturing experience with product developers is limited and a risk for successful (rapid) commercialization (1/20)
- Education and training of MAPs for self-administration is critical and impact of lost dose due to mishandling (1/20)
- COGs compared to vials; would new storage equipment other than cold chain be required; differences in expiration of product--ensuring stability is as long as traditional vials; if dosage is needed in a series, how to store products in appropriate conditions (1/20)
- cGMP facility for Vaccine MAPs manufacturing (1/20)

Some of these issues are assessed on a vaccine-specific basis in Tables 25, 27 and 28.

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

Summary feedback from country consultation:

- MAPs was ranked #1 most useful innovation
- Immunisation staff and decision-makers ranked MAPs as 1st of the 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's current challenges.
- Both groups mentioned the benefits of ease of use and logistics, increased acceptability due to less pain, saved time of immunisation, improved safety by reduced needle-stick injuries, reduced contamination risk, use of wrong diluent and AEFIs.
- Both groups also mentioned other benefits such as potential of improving coverage and reducing missed opportunities, decreased wastage, and ability to enable delivery outside health facility/less trained personnel.
- Both groups raised concerns about the need for community sensitisation, overall cost, cold chain volume and skin reaction/different absorption by skin type.
- Immunisation staff reported time requirement of administering MAPs, complexity of the technology, no indication of vaccine delivery completion and difficulties in self-administration as possible challenges.

[aaaa] *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.*

- Decision makers were also concerned about the possible increase in price per dose and training needs - though 25 out of 28 decision makers interviewed expressed interest in purchasing MAPs, 3 stated potential interest, no participants said they would not be interested.
- Decision makers provided feedback that caregivers could provide MAPs to their own children.
- Immunisation staff mentioned that they would prefer smaller MAPs without applicators and would be good to combine multiple vaccines to give at once.

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
MR	An end-user acceptability study in Benin, Nepal and Vietnam found overall interest in the use of MAPs for MR vaccination, particularly in health facilities. Interest was expressed at all levels of the health system, including central and district levels of the EPI [5]	**Mixed interest**
All other vaccines assessed		**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 likely that for most vaccines MAPs would only be used for certain segments of the existing market for the vaccine, especially when they are first introduced. However, there is no information on the size of these markets or use-cases at present, so no assumptions have been made on how much of the current market would be taken up by the MAP-vaccine combinations.

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
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 [48]. Adoption of birth dose by national immunization programmes has not matched the implementation of 3-dose hepatitis B vaccination starting later in infancy [48].	**Large**
HPV (SDV or 2-dose vial)	The WHO recommends that all countries should introduce HPV vaccination into national immunization programmes. 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).[bbbb] 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.[bbbb]	**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%).[cccc] Most HIC and MIC countries use MMR rather than MR vaccine. It is possible that a MR-MAP would be used to target specific, hard-to-reach populations only, or be used only in campaigns [71].	**Large**
Men A (MenAfriVac) **(**Lyophilized SDV or 10-dose vial)	For Men A conjugate vaccines, WHO recommends mass vaccination campaigns in countries in the African meningitis belt, followed by introduction into routine childhood immunisation [72]. 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, special immunization activities 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 [73]. HICs (such as USA, UK, Australia) are increasingly introducing vaccination of adolescents with polyvalent meningococcal vaccines [74]. Demand for MenACWY conjugate vaccine outside China and the meningitis belt was estimated to be 16.7M doses.[dddd]	**Moderate (MenA)** **Large (polyvalent)**

[bbbb] *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*

[cccc] *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=2ahUKEwjq-5z6zJPlAhX1sHEKHb0uBzsQFjAMegQIAxAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Fmeasles-rubella-vaccine-roadmap--public-summary%2F&usg=AOvVaw0dBkb8Zzc4OcWaRo09WXGq. Accessed 11/10/2019*

[dddd] *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*

Vaccines	*How broad is the potential target market?*	Overall score
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. [eeee]	**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 [75]. Gavi estimates cumulative demand of 304M doses (20M/year) for GAVI supported countries (LMICs) between 2021 and 2035. [ffff]	**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.[gggg] 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 [76].	**Small / moderate**
Yellow Fever (Lyophilized 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 million doses in 2021.[hhhh] 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 [77].	**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.[iiii] Presumably primarily for stockpiling to control outbreaks, e.g. by ring vaccination with rVSVΔG-ZEBOV.	**Small**

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

[ffff] *Gavi Vaccine Investment Strategy Programme and Policy Committee Meeting 18-19 October 2018. 06a -Annex C: Rabies Investment Case. Available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=2ahUKEwi3552I3JPlAhWtRxUIHaaNDeUQFjAAegQIBhAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fstrategy%2Fppc-meeting-18-19-october-2018---vis-06a---annex-c--rabies-investment-case%2F&usg=AOvVaw2vSpic5nRUViWih8d-usft. Accessed 11/10/2019.*

[gggg] *Gavi TCV Supply and Procurement Roadmap July 2018. Available at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&cad=rja&uact=8&ved=2ahUKEwj0iK-F4ZPlAhUVVBUIHYUOBuYQFjAEegQIBRAC&url=https%3A%2F%2Fwww.gavi.org%2Flibrary%2Fgavi-documents%2Fsupply-procurement%2Ftyphoid-conjugate-vaccine-roadmap--public-summary%2F&usg=AOvVaw0hQPOOgsyErwyY9iOSSd42 Accessed 11/10/2019*

[hhhh] *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*

[iiii] *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*

Vaccines	*How broad is the potential target market?*	Overall score
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 [78].	**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 [79]. 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**
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	The WHO recommends BCG vaccination in countries or settings with a high incidence of tuberculosis and/or high leprosy burden. In these countries, a single dose of BCG vaccine should be given to all healthy neonates at birth [65]. The estimated global demand for BCG vaccine is ~325 M doses in 2019. [jjjj]	**Large**
RSV (pre-fusion F protein) (Lyophilized SDV)	Gavi has estimated the cumulative demand for RSV vaccine for maternal immunization for 2021-2035 to be 289M doses for Gavi supported countries. There is expected to be a large market in HICs, for example RSV is the leading cause of hospitalization in infants in the USA [80].	**Large**

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

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

*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
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There is no known donor/stakeholder support for HepB MAPs.	One vaccine manufacturer has conducted its own preclinical studies [67]; one has partnered with a MAP developer for clinical research.	**Mixed interest**
	No interest	**Moderate interest**	
HPV (SDV or 2-dose vial)	There is no known donor/stakeholder support for HPV MAPs.	One vaccine manufacturer/technology developer collaborated to conduct preclinical studies [8]. However, a formal partnership to advance HPV-MAPs has not yet been established.	**Mixed interest**
	No interest	**Moderate interest**	
MR (lyo; MDV)	Three MAP developers have been undertaking preclinical development of MR-MAPs funded by the Bill and Melinda Gates Foundation. [ooo] Funding has also been provided for two phase 1 studies and is expected to continue through phase 2. The Foundation hopes to identify an industry	SIIL provided bulk MR antigen for pre-clinical MAP development, but there are no established partnerships that exist.	**Mixed interest**

[kkkk] *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.*

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
	partner to advance MR-MAPs beyond phase 2 and commercialize the product.		
	Significant interest	**Moderate interest**	
Men ACWY(X) conjugate (Lyo; SDV; MDV)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
IPV (Liquid; MDV)	Two MAP developers have received funding to develop IPV-MAPs in a project supported by the WHO and the Bill and Melinda Gates Foundation to the point of clinical trial readiness. [sss] Although projects have been on hold due to IPV supply constraints, the global health community continues to be interested in IPV-MAPs.	Bilthoven Biotech (SIIL) provided bulk IPV antigen for pre-clinical MAP development, but there are no established partnerships that exist.	**Moderate interest**
	Moderate interest	**Moderate interest**	
Rabies (Lyo; SDV)	No known donor/ stakeholder support	One vaccine manufacturer has provided bulk rabies antigen for pre-clinical MAP development and conducted analytical testing to support preclinical studies. [llll] No established partnerships currently exist.	**Mixed interest**
	No interest	**Moderate interest**	
Typhoid conjugate (Liquid; MDV)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
Yellow Fever (Lyophilized SDV or 10-dose)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
Ebola (rVSV-ZEBOV) (Liquid SDV)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
HIV (ALVAC-HIV + bivalent Subtype C gp120). ALVAC prime only	No known donor/ stakeholder support	No known partnerships	**No interest**

[llll] *Developer response in survey carried out after DTWG telecons on MAP technology held on 3rd and 4th October 2019*

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
(Lyophilized SDV)	**No interest**	**No interest**	
Influenza (pandemic) (VAL 506440) (Liquid SDV)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
M. Tb (next generation BCG, VPM 1002) (Lyophilized SDV or 20-dose)	No known donor/ stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	
RSV (pre-fusion F protein) (Lyophilized SDV)	No known donor/stakeholder support	No known partnerships	**No interest**
	No interest	**No interest**	

Indicator: Known barriers to global access to the innovation

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

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

Table 28

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

MAPs 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 MAP confers improved heat stability). It is possible that resistance to freeze-damage might also be feasible, but more data are required.

It should be technically feasible to combine many of the VIPS priority vaccines (existing and pipeline) with MAPs, potentially all injected vaccines. 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 MAPs. There will however be challenges with some vaccines in terms of whether sufficient vaccine can be loaded onto a MAP and/or whether removing adjuvant from a vaccine formulation (which might be necessary) will compromise immunogenicity.

SYNERGIES WITH OTHER VIPS INNOVATIONS

Vaccines need to be (re-)formulated for use with MAPs, which provides an opportunity to improve heat stability. This has been demonstrated with several vaccines to date [2,9,20]. Therefore, MAPs 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.

References

[1] Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet 2017. https://doi.org/10.1016/S0140-6736(17)30575-5.

[2] Mistilis MJ, Joyce JC, Esser ES, Skountzou I, Compans RW, Bommarius AS, et al. Long-term stability of influenza vaccine in a dissolving microneedle patch. Drug Deliv Transl Res 2017;7:195–205. https://doi.org/10.1007/s13346-016-0282-2.

[3] Fernando GJP, Hickling J, Jayashi Flores CM, Griffin P, Anderson CD, Skinner SR, et al. Safety, tolerability, acceptability and immunogenicity of an influenza vaccine delivered to human skin by a novel high-density microprojection array patch (Nanopatch™). Vaccine 2018;36:3779–88. https://doi.org/10.1016/j.vaccine.2018.05.053.

[4] Forster AH, Witham K, Depelsenaire ACI, Veitch M, Wells JW, Wheatley A, et al. Safety, tolerability, and immunogenicity of influenza vaccination with a high-density microarray patch: Results from a randomized, controlled phase I clinical trial. PLoS Med 2020;17:e1003024. https://doi.org/10.1371/journal.pmed.1003024.

[5] Norman JJ, Arya JM, McClain MA, Frew PM, Meltzer MI, Prausnitz MR. Microneedle patches: usability and acceptability for self-vaccination against influenza. Vaccine 2014;32:1856–62. https://doi.org/10.1016/j.vaccine.2014.01.076.

[6] Guillermet E, Alfa DA, Phuong Mai LT, Subedi M, Demolis R, Giersing B, et al. End-user acceptability study of the nanopatch™; a microarray patch (MAP) for child immunization in low and middle-income countries. Vaccine 2019. https://doi.org/10.1016/j.vaccine.2019.02.079.

[7] Choi YH, Perez-Cuevas MB, Kodani M, Zhang X, Prausnitz MR, Kamili S, et al. Feasibility of Hepatitis B Vaccination by Microneedle Patch: Cellular and Humoral Immunity Studies in Rhesus Macaques. J Infect Dis 2019. https://doi.org/10.1093/infdis/jiz399.

[8] Meyer BK, Kendall MAF, Williams DM, Bett AJ, Dubey S, Gentzel RC, et al. Immune response and reactogenicity of an unadjuvanted intradermally delivered human papillomavirus vaccine using a first generation Nanopatch™ in rhesus macaques: An exploratory, pre-clinical feasibility assessment. Vaccine X 2019;2:100030. https://doi.org/10.1016/j.jvacx.2019.100030.

[9] Joyce JC, Carroll TD, Collins ML, Chen M-H, Fritts L, Dutra JC, et al. A Microneedle Patch for Measles and Rubella Vaccination Is Immunogenic and Protective in Infant Rhesus Macaques. J Infect Dis 2018;218:124–32. https://doi.org/10.1093/infdis/jiy139.

[10] Jonker EFF, van Ravenhorst MB, Berbers GAM, Visser LG. Safety and immunogenicity of fractional dose intradermal injection of two quadrivalent conjugated meningococcal vaccines. Vaccine 2018;36:3727–32. https://doi.org/10.1016/j.vaccine.2018.05.064.

[11] Okayasu H, Sein C, Chang Blanc D, Gonzalez AR, Zehrung D, Jarrahian C, et al. Intradermal Administration of Fractional Doses of Inactivated Poliovirus Vaccine: A Dose-Sparing Option for Polio Immunization. J Infect Dis 2017;216:S161–7. https://doi.org/10.1093/infdis/jix038.

[12] Muller DA, Pearson FE, Fernando GJP, Agyei-Yeboah C, Owens NS, Corrie SR, et al. Inactivated poliovirus type 2 vaccine delivered to rat skin via high density microprojection array elicits potent neutralising antibody responses. Sci Rep 2016;6:22094. https://doi.org/10.1038/srep22094.

[13] Muller DA, Fernando GJP, Owens NS, Agyei-Yeboah C, Wei JCJ, Depelsenaire ACI, et al. High-density microprojection array delivery to rat skin of low doses of trivalent inactivated poliovirus vaccine elicits potent neutralising antibody responses. Sci Rep 2017;7:12644. https://doi.org/10.1038/s41598-017-13011-0.

[14] Resik S, Mach O, Tejeda A, Jeyaseelan V, Fonseca M, Diaz M, et al. Immunogenicity of intramuscular fractional dose of inactivated poliovirus vaccine. J Infect Dis 2019. https://doi.org/10.1093/infdis/jiz323.

[15] Edens C, Dybdahl-Sissoko NC, Weldon WC, Oberste MS, Prausnitz MR. Inactivated polio vaccination using a microneedle patch is immunogenic in the rhesus macaque. Vaccine 2015. https://doi.org/10.1016/j.vaccine.2015.01.089.

[16] Warrell MJ. Simplification of Rabies Postexposure Prophylaxis: A New 2-Visit Intradermal Vaccine Regimen. Am J Trop Med Hyg 2019. https://doi.org/10.4269/ajtmh.19-0252.

[17] Roukens AH, Vossen AC, Bredenbeek PJ, van Dissel JT, Visser LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. PLoS ONE 2008;3:e1993. https://doi.org/10.1371/journal.pone.0001993.

[18] Martins RM, Maia M de LS, Farias RHG, Camacho LAB, Freire MS, Galler R, et al. 17DD yellow fever vaccine: a double blind, randomized clinical trial of immunogenicity and safety on a dose-response study. Hum Vaccin Immunother 2013;9:879–88. https://doi.org/10.4161/hv.22982.

[19] Feldman RA, Fuhr R, Smolenov I, Mick Ribeiro A, Panther L, Watson M, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37:3326–34. https://doi.org/10.1016/j.vaccine.2019.04.074.

[20] Edens C, Collins ML, Goodson JL, Rota PA, Prausnitz MR. A microneedle patch containing measles vaccine is immunogenic in non-human primates. Vaccine 2015. https://doi.org/10.1016/j.vaccine.2015.02.074.

[21] Wan Y, Hickey JM, Bird C, Witham K, Fahey P, Forster A, et al. Development of Stabilizing Formulations of a Trivalent Inactivated Poliovirus Vaccine in a Dried State for Delivery in the Nanopatch™ Microprojection Array. J Pharm Sci 2018;107:1540–51. https://doi.org/10.1016/j.xphs.2018.01.027.

[22] Kolluru C, Gomaa Y, Prausnitz MR. Development of a thermostable microneedle patch for polio vaccination. Drug Deliv Transl Res 2019;9:192–203. https://doi.org/10.1007/s13346-018-00608-9.

[23] Hiraishi Y, Nandakumar S, Choi S-O, Lee JW, Kim Y-C, Posey JE, et al. Bacillus Calmette-Guérin vaccination using a microneedle patch. Vaccine 2011;29:2626–36. https://doi.org/10.1016/j.vaccine.2011.01.042.

[24] Chen F, Yan Q, Yu Y, Wu MX. BCG vaccine powder-laden and dissolvable microneedle arrays for lesion-free vaccination. J Control Release 2017;255:36–44. https://doi.org/10.1016/j.jconrel.2017.03.397.

[25] Wallace AS, Willis F, Nwaze E, Dieng B, Sipilanyambe N, Daniels D, et al. Vaccine wastage in Nigeria: An assessment of wastage rates and related vaccinator knowledge, attitudes and practices. Vaccine 2017;35:6751–8. https://doi.org/10.1016/j.vaccine.2017.09.082.

[26] Usuf E, Mackenzie G, Ceesay L, Sowe D, Kampmann B, Roca A. Vaccine wastage in The Gambia: a prospective observational study. BMC Public Health 2018;18:864. https://doi.org/10.1186/s12889-018-5762-5.

[27] Hirobe S, Azukizawa H, Hanafusa T, Matsuo K, Quan Y-S, Kamiyama F, et al. Clinical study and stability assessment of a novel transcutaneous influenza vaccination using a dissolving microneedle patch. Biomaterials 2015;57:50–8. https://doi.org/10.1016/j.biomaterials.2015.04.007.

[28] Griffin P, Elliott S, Krauer K, Davies C, Rachel Skinner S, Anderson CD, et al. Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects. Vaccine 2017;35:6676–84. https://doi.org/10.1016/j.vaccine.2017.10.021.

[29] Otto BF, Suarnawa IM, Stewart T, Nelson C, Ruff TA, Widjaya A, et al. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. Vaccine 1999;18:498–502. https://doi.org/10.1016/s0264-410x(99)00242-x.

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

[31] Neuzil KM, Canh DG, Thiem VD, Janmohamed A, Huong VM, Tang Y, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. JAMA 2011;305:1424–31. https://doi.org/10.1001/jama.2011.407.

[32] MMR-161 Study Group. Immunogenicity and safety of measles-mumps-rubella vaccine at two different potency levels administered to healthy children aged 12-15 months: A phase III, randomized, non-inferiority trial. Vaccine 2018;36:5781–8. https://doi.org/10.1016/j.vaccine.2018.07.076.

[33] Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection--serum bactericidal antibody activity. Vaccine 2005;23:2222–7. https://doi.org/10.1016/j.vaccine.2005.01.051.

[34] Frasch CE, Preziosi M-P, LaForce FM. Development of a group A meningococcal conjugate vaccine, MenAfriVac(TM). Hum Vaccin Immunother 2012;8:715–24. https://doi.org/10.4161/hv.19619.

[35] Clarke E, Saidu Y, Adetifa JU, Adigweme I, Hydara MB, Bashorun AO, et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles-rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. Lancet Glob Health 2016;4:e534-547. https://doi.org/10.1016/S2214-109X(16)30075-4.

[36] Vesikari T, Rivera L, Korhonen T, Ahonen A, Cheuvart B, Hezareh M, et al. Immunogenicity and safety of primary and booster vaccination with 2 investigational formulations of diphtheria, tetanus and Haemophilus influenzae type b antigens in a hexavalent DTPa-HBV-IPV/Hib combination vaccine in comparison with the licensed Infanrix hexa. Hum Vaccin Immunother 2017;13:1505–15. https://doi.org/10.1080/21645515.2017.1294294.

[37] Warrell MJ. Rabies post-exposure vaccination in 2 visits within a week: A 4-site intradermal regimen. Vaccine 2019;37:1131–6. https://doi.org/10.1016/j.vaccine.2019.01.019.

[38] Quiambao BP, Ambas C, Diego S, Bosch Castells V, Korejwo J, Petit C, et al. Intradermal post-exposure rabies vaccination with purified Vero cell rabies vaccine: Comparison of a one-week, 4-site regimen versus updated Thai Red Cross regimen in a randomized non-inferiority trial in the Philippines. Vaccine 2019;37:2268–77. https://doi.org/10.1016/j.vaccine.2019.02.083.

[39] Tarantola A, Tejiokem MC, Briggs DJ. Evaluating new rabies post-exposure prophylaxis (PEP) regimens or vaccines. Vaccine 2019;37 Suppl 1:A88–93. https://doi.org/10.1016/j.vaccine.2018.10.103.

[40] Mohan VK, Varanasi V, Singh A, Pasetti MF, Levine MM, Venkatesan R, et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis 2015;61:393–402. https://doi.org/10.1093/cid/civ295.

[41] Vaccines and vaccination against yellow fever. WHO position paper -- June 2013. Wkly Epidemiol Rec 2013;88:269–83.

[42] Medaglini D, Santoro F, Siegrist C-A. Correlates of vaccine-induced protective immunity against Ebola virus disease. Semin Immunol 2018;39:65–72. https://doi.org/10.1016/j.smim.2018.07.003.

[43] Lévy Y, Lane C, Piot P, Beavogui AH, Kieh M, Leigh B, et al. Prevention of Ebola virus disease through vaccination: where we are in 2018. Lancet 2018;392:787–90. https://doi.org/10.1016/S0140-6736(18)31710-0.

[44] Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet 2017;389:505–18. https://doi.org/10.1016/S0140-6736(16)32621-6.

[45] Kim JH, Excler J-L, Michael NL. Lessons from the RV144 Thai phase III HIV-1 vaccine trial and the search for correlates of protection. Annu Rev Med 2015;66:423–37. https://doi.org/10.1146/annurev-med-052912-123749.

[46] Satti I, McShane H. Current approaches toward identifying a correlate of immune protection from tuberculosis. Expert Rev Vaccines 2019;18:43–59. https://doi.org/10.1080/14760584.2019.1552140.

[47] Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS, WHO RSV Vaccine Consultation Expert Group. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. Vaccine 2016;34:190–7. https://doi.org/10.1016/j.vaccine.2015.05.093.

[48] Hepatitis B vaccines: WHO position paper – July 2017. Wkly Epidemiol Rec 2017;92:369–92.

[49] Perez Cuevas MB, Kodani M, Choi Y, Joyce J, O'Connor SM, Kamili S, et al. Hepatitis B vaccination using a dissolvable microneedle patch is immunogenic in mice and rhesus macaques. Bioeng Transl Med 2018;3:186–96. https://doi.org/10.1002/btm2.10098.

[50] Chen D, Kapre S, Goel A, Suresh K, Beri S, Hickling J, et al. Thermostable formulations of a hepatitis B vaccine and a meningitis A polysaccharide conjugate vaccine produced by a spray drying method. Vaccine 2010;28:5093–9. https://doi.org/10.1016/j.vaccine.2010.04.112.

[51] Visscher MO, Adam R, Brink S, Odio M. Newborn infant skin: physiology, development, and care. Clin Dermatol 2015;33:271–80. https://doi.org/10.1016/j.clindermatol.2014.12.003.

[52] Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec 2017;92:205–27.

[53] Rubella vaccines: WHO position paper. Wkly Epidemiol Rec 2011;86:301–16.

[54] Edens C, Collins ML, Ayers J, Rota PA, Prausnitz MR. Measles vaccination using a microneedle patch. Vaccine 2013;31:3403–9. https://doi.org/10.1016/j.vaccine.2012.09.062.

[55] Etchart N, Hennino A, Friede M, Dahel K, Dupouy M, Goujon-Henry C, et al. Safety and efficacy of transcutaneous vaccination using a patch with the live-attenuated measles vaccine in humans. Vaccine 2007;25:6891–9. https://doi.org/10.1016/j.vaccine.2007.07.014.

[56] Kraan H, van Herpen P, Kersten G, Amorij J-P. Development of thermostable lyophilized inactivated polio vaccine. Pharm Res 2014;31:2618–29. https://doi.org/10.1007/s11095-014-1359-6.

[57] Toinon A, Moreno N, Chausse H, Mas E, Nicolai MC, Guinchard F, et al. Potency test to discriminate between differentially over-inactivated rabies vaccines: Agreement between the NIH assay and a G-protein based ELISA. Biologicals 2019;60:49–54. https://doi.org/10.1016/j.biologicals.2019.05.004.

[58] Clénet D, Hourquet V, Woinet B, Ponceblanc H, Vangelisti M. A spray freeze dried micropellet based formulation proof-of-concept for a yellow fever vaccine candidate. Eur J Pharm Biopharm 2019;142:334–43. https://doi.org/10.1016/j.ejpb.2019.07.008.

[59] Dean CH, Alarcon JB, Waterston AM, Draper K, Early R, Guirakhoo F, et al. Cutaneous delivery of a live, attenuated chimeric flavivirus vaccine against Japanese encephalitis (ChimeriVax)-JE) in non-human primates. Hum Vaccin 2005;1:106–11. https://doi.org/10.4161/hv.1.3.1797.

[60] Monath TP, Fast PE, Modjarrad K, Clarke DK, Martin BK, Fusco J, et al. rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment. Vaccine X 2019;1:100009. https://doi.org/10.1016/j.jvacx.2019.100009.

[61] Pearson FE, McNeilly CL, Crichton ML, Primiero CA, Yukiko SR, Fernando GJP, et al. Dry-coated live viral vector vaccines delivered by nanopatch microprojections retain long-term thermostability and induce transgene-specific T cell responses in mice. PLoS ONE 2013;8:e67888. https://doi.org/10.1371/journal.pone.0067888.

[62] Pearson FE, O'Mahony C, Moore AC, Hill AVS. Induction of CD8(+) T cell responses and protective efficacy following microneedle-mediated delivery of a live adenovirus-vectored malaria vaccine. Vaccine 2015. https://doi.org/10.1016/j.vaccine.2015.03.039.

[63] Alberer M, Gnad-Vogt U, Hong HS, Mehr KT, Backert L, Finak G, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet 2017;390:1511–20. https://doi.org/10.1016/S0140-6736(17)31665-3.

[64] Armbruster N, Jasny E, Petsch B. Advances in RNA Vaccines for Preventive Indications: A Case Study of A Vaccine Against Rabies. Vaccines (Basel) 2019;7. https://doi.org/10.3390/vaccines7040132.

[65] World Health Organization null. BCG vaccine: WHO position paper, February 2018 - Recommendations. Vaccine 2018;36:3408–10. https://doi.org/10.1016/j.vaccine.2018.03.009.

[66] Schwarz TF, McPhee RA, Launay O, Leroux-Roels G, Talli J, Picciolato M, et al. Immunogenicity and safety of 3 formulations of a respiratory syncytial virus candidate vaccine in non-pregnant women: a phase II, randomized trial. J Infect Dis 2019. https://doi.org/10.1093/infdis/jiz395.

[67] Poirier D, Renaud F, Dewar V, Strodiot L, Wauters F, Janimak J, et al. Hepatitis B surface antigen incorporated in dissolvable microneedle array patch is antigenic and thermostable. Biomaterials 2017;145:256–65. https://doi.org/10.1016/j.biomaterials.2017.08.038.

[68] Sutter RW, Cochi SL. Inactivated Poliovirus Vaccine Supply Shortage: Is There Light at the End of the Tunnel? J Infect Dis 2019;220:1545–6. https://doi.org/10.1093/infdis/jiy739.

[69] Bekker L-G, Moodie Z, Grunenberg N, Laher F, Tomaras GD, Cohen KW, et al. Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial. Lancet HIV 2018;5:e366–78. https://doi.org/10.1016/S2352-3018(18)30071-7.

[70] Nieuwenhuizen NE, Kaufmann SHE. Next-Generation Vaccines Based on Bacille Calmette-Guérin. Front Immunol 2018;9:121. https://doi.org/10.3389/fimmu.2018.00121.

[71] Peyraud N, Zehrung D, Jarrahian C, Frivold C, Orubu T, Giersing B. Potential use of microarray patches for vaccine delivery in low- and middle- income countries. Vaccine 2019;37:4427–34. https://doi.org/10.1016/j.vaccine.2019.03.035.

[72] World Health Organization null. WHO position paper, Meningococcal A conjugate vaccine: Updated guidance, February 2015. Vaccine 2018;36:3421–2. https://doi.org/10.1016/j.vaccine.2017.07.063.

[73] Meningococcal vaccines: WHO position paper, November 2011. Wkly Epidemiol Rec 2011;86:521–39.

[74] Vuocolo S, Balmer P, Gruber WC, Jansen KU, Anderson AS, Perez JL, et al. Vaccination strategies for the prevention of meningococcal disease. Hum Vaccin Immunother 2018;14:1203–15. https://doi.org/10.1080/21645515.2018.1451287.

[75] Ives A, Dieuzy-Labaye I, Abela-Ridder B. Global characteristics of the rabies biologics market in 2017. Vaccine 2019;37 Suppl 1:A73–6. https://doi.org/10.1016/j.vaccine.2018.10.012.

[76] Mogasale V, Ramani E, Park IY, Lee JS. A forecast of typhoid conjugate vaccine introduction and demand in typhoid endemic low- and middle-income countries to support vaccine introduction policy and decisions. Hum Vaccin Immunother 2017;13:2017–24. https://doi.org/10.1080/21645515.2017.1333681.

[77] Jácome R, Carrasco-Hernández R, Campillo-Balderas JA, López-Vidal Y, Lazcano A, Wenzel RP, et al. A yellow flag on the horizon: The looming threat of yellow fever to North America. Int J Infect Dis 2019;87:143–50. https://doi.org/10.1016/j.ijid.2019.07.033.

[78] Marzetta CA, Lee SS, Wrobel SJ, Singh KJ, Russell N, Esparza J. The potential global market size and public health value of an HIV-1 vaccine in a complex global market. Vaccine 2010;28:4786–97. https://doi.org/10.1016/j.vaccine.2010.04.098.

[79] McLean KA, Goldin S, Nannei C, Sparrow E, Torelli G. The 2015 global production capacity of seasonal and pandemic influenza vaccine. Vaccine 2016;34:5410–3. https://doi.org/10.1016/j.vaccine.2016.08.019.

[80] Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics 2013;132:e341-348. https://doi.org/10.1542/peds.2013-0303.