Compact prefilled auto-disable device (CPAD)

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

Technology overview

Compact prefilled autodisable devices (CPADs) are prefilled syringes with design features that prevent their reuse and minimise the space required for storage and distribution. CPADs fall into two main subtypes based on their manufacturing method: (1) preformed CPAD and (2) blow-fill-seal (BFS) CPAD. Devices that do not fall into one of these categories were considered under a third subtype: (3) other types of CPADs (as described in detail below). CPADs are by definition small in size (compact), prefilled with the vaccine by the manufacturer, and contain an auto-disable mechanism. However, as described in this technical note, there are differences between the types such as with their vaccine filling process, number of components and assembly requirements.

The following devices were selected as examples to evaluate the three CPAD subtypes for this assessment.

- Preformed CPAD: Uniject™ (commercially available).
- BFS CPAD: ApiJect prototype (in development).
    - Pre-assembled (with integrated needle hub).
    - User-assembled (with separate needle hub).
- Other types of CPADs: INJECTO™ easyject (in development).

Summary of vaccine and innovation compatibility:

This innovation could be applied to any liquid parenteral vaccine. The innovation may be most useful with vaccines that would benefit from an easy-to-use single-dose presentation, for instance, for outreach settings.

The vaccines considered, or not considered for use with CPADs 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 CPADs are presented in Table 1. The key properties of CPADs that are relevant to these problem statements are:

- **Reduced acceptability due to painful administration:** Since CPADs are prefilled there is a perception by caregivers that the injection is less painful, which can improve acceptability.

- **Difficult preparation requiring trained personnel:** CPADs are prefilled and do not require preparation, which improves ease of use and training requirements.
- **Vaccine wastage or missed opportunities due to MDV presentation:** CPADs are a single dose presentation which reduces vaccine wastage and missed opportunities compared to a MDV.
- **Contamination risk due to use of multi-dose vial:** CPADs are a prefilled, single dose presentation, which reduces the contamination risk.
- **Needle-stick injuries:** There is a slight reduction in needlestick injury risk because CPADs do not require vaccine withdrawal from a vial.
- **Negative impact on the environment due to waste disposal practices:** CPADs have a smaller volume that is disposed in the safety box and result in a more complete burn through pit burning compared to glass.

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[d]	Comparator dose(s) per container
Licensed vaccines							
Pentavalent (Diphtheria tetanus pertussis hepatitis B haemophilus influenzae type B inactivated poliovirus; DTP, HepB, Hib)	Inactivated subunit plus polysaccharide-protein conjugated vaccine (PS-PCV)	Liquid	Yes	Yes	IM	• Vaccine ineffectiveness/wastage due to freeze exposure • Vaccine ineffectiveness/wastage due to heat exposure • **Reduced acceptability due to painful administration** • Cold-chain requirements during outreach • **Contamination risk due to multi-dose vials**	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S.

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

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

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

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Problem statements to be addressed[d]	Comparator dose(s) per container
Hepatitis B (birth dose)	Subunit	Liquid	Yes	Yes	IM	• Vaccine ineffectiveness/wastage due to freeze exposure • Vaccine ineffectiveness /wastage due to heat exposure • Cold-chain requirements during outreach • **Difficult preparation requiring trained personnel** • **Reduced acceptability due to painful administration**	Single-dose vial (SDV) or 10-dose vial; IM injection with an AD N&S.
Human papillomavirus (HPV)	Subunit	Liquid	Yes	No	IM	• Vaccine ineffectiveness /wastage due to freeze exposure • **Reduced acceptability due to painful administration** • 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.
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).

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	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 MDV presentation** • Difficult to deliver vaccine to the correct injection depth • **Difficult preparation requiring trained personnel** • Vaccine ineffectiveness/wastage due to freeze exposure	SDV or 5-dose vial.
Pipeline vaccines[e]							
Ebola (recombinant vesicular stomatitis virus, Zaire Ebola virus) (rVSV-ZEBOV)	Live vector	Liquid, frozen	No	No	IM	• *Cold-chain requirements during outreach (vaccine needs to be kept frozen)* • *Vaccine ineffectiveness/ wastage due to heat exposure*	Recently licensed as SDV vial
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)[f]	Heterologous live attenuated recombinant viral vector + recombinant protein booster	Liquid booster (gp120)	Yes (MF59 [oil-in-water emulsion]) (recombinant protein booster)	Not known	IM	• ***Difficult preparation requiring trained personnel*** • *Reconstitution-related safety issues*	As still in Phase 2b/3, assume SDV.

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

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

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

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

** Must be discarded after 6 hours

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Measles rubella (MR)	Live attenuated.	Lyophilised	No	No	SC	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs.
Meningitis A (MenAfriVac)	PS-PCV	Lyophilised	Yes, in diluent (Aluminum-salt based)	Yes**	IM	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs.
Rabies	Whole-inactivated.	Lyophilised	No	No	IM or ID	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs.
Rotavirus	Live attenuated virus	Liquid	No	No	Oral	A CPAD could be applicable to any liquid *parenteral* vaccine. Oral vaccines could be in similar types of prefilled containers, but do not require needles or AD features, so these presentations are categorized separately under VIPS.
Yellow fever	Live-attenuated	Lyophilised	No	No	SC or IM	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs.

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

Vaccine	Vaccine type	Formulation	Adjuvant	Preservative	Route	Rationale for exclusion
Enterotoxigenic *E. coli* (ETEC) (ETVAX)	Whole inactivated organism	Liquid vac, lyophilized buffer, lyophilized adjuvant	Yes (dmLT, double-mutant heat labile toxin [of ETEC])	No	Oral	A CPAD could be applicable to any liquid *parenteral* vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs. Oral vaccines could be in similar types of prefilled containers, but do not require needles or AD features, so these presentations are categorized separately under VIPS.
Human immunodeficiency virus (HIV) (ALVAC-HIV + bivalent Subtype C gp120)	Heterologous live attenuated recombinant viral vector + recombinant protein booster	Lyophilized prime	No	Not known	IM	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs
Malaria (RTS,S)	Recombinant protein	Lyophilized vaccine; adjuvant in diluent	Yes (AS01E [QS21 + MPL] in diluent)	Not known	IM	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs
Mycobacterium tuberculosis (M.tb) (Next generation BCG: VPM1002)	Live attenuated	Lyophilised	No	No	ID	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs
Respiratory syncytial virus (RSV) (pre-fusion F protein)	Subunit	Lyophilised	No	Not known	IM	A CPAD could be applicable to any *liquid* parenteral vaccine. Vaccines that require reconstitution or mixing of multiple components are not compatible with CPADs

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
Pentavalent (Liquid SDV or 10-dose vial)	All three CPAD subtypes (preformed, pre-and user-assembled BFS, and other), merely serve as the primary container and do not impact vaccine efficacy because the formulation of the vaccine remains unchanged. There are some efficacy data available for pentavalent vaccines in Uniject—in a phase 3, open label non-inferiority study, Quinvaxem in CPADs was demonstrated to be non-inferior to Quinvaxem in single-dose vials with respect to seroprotection/seroconversion rates for all antibodies (1).	**Neutral**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There are no vaccine efficacy data available for delivery of these vaccines in CPAD devices. All three CPAD subtypes (preformed, pre-and user-assembled BFS, and other), merely serve as the primary container and it is expected that vaccine efficacy would be no different than the comparators because the formulation of the vaccine remains unchanged.	**No data**
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)		

Vaccines	*Does the innovation improve vaccine efficacy based on clinical evidence using correlates of protection or a surrogate?*	Overall score
Ebola (rVSV-ZEBOV) (Liquid SDV)		
HIV (ALVAC-HIV + bivalent Subtype C gp120)		
Influenza (pandemic) (VAL 506440) (Liquid SDV)		

Indicator: Vaccine effectiveness

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

Table 4

Parameter assessment		
Vaccines	***Does the innovation improve vaccine effectiveness as per the following parameters based on field or other evidence?*** ○ ***Cases averted*** ○ ***Outpatient visits averted*** ○ ***Hospitalisations averted*** ○ ***Deaths averted*** ○ ***Vaccine doses given within the recommended age range (timeliness of vaccination)***	**Overall score**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	In a study in China, timely administration of HepB birth dose was significantly improved by out of cold chain distribution using Uniject compared with out of cold-chain distribution in vials.(2)	**Better**
All other vaccines assessed	For all three CPAD subtypes (preformed, pre-and user-assembled BFS, and other), it is expected that vaccine effectiveness will be the same for all products even though small differences in effectiveness may occur.	**No data**

Indicator: Ability of the vaccine presentation to withstand heat exposure[h,i]

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)?* [j]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
Pentavalent (Liquid SDV or 10-dose vial)	Routine	No. VVM 14	No data. Unlikely given the heat stability of current products.	No, unless other routine vaccines that it is co-administered with are also qualified for CTC use.	All three CPAD subtypes (preformed, pre-and user-assembled BFS, and other), do not impact the ability of the vaccine to withstand heat exposure. **Neutral**
Hepatitis B (birth dose) (liquid SDV or 10-dose vial)	Health facilities Outreach Home births	No. VVM30	Yes. CTC qualification in process for one or more vaccines.	Yes. For birth-dose outreach to homes and for storage at remote health facilities without cold chain.[k]	See assessment for pentavalent **Neutral**

[h] *Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing*
[i] *Improved heat stability can also be used to increase shelf life, hence no indicator on shelf-life extension is included in the framework.*
[j] *This parameter is not used for scoring purposes, it is contextual/background information.*
[k] World Health Organization, PATH. *Controlled Temperature Chain: Strategic Roadmap for Priority Vaccines 2017-2020.* Geneva: WHO; 2017. https://www.who.int/immunization/programmes_systems/supply_chain/ctc_strategic_roadmap_priority_vaccines.pdf?ua=1.

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)?* [j]	*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?*
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*	No. VVM30	Quadrivalent HPV vaccine (Merck) is qualified for CTC use (up to 3 days, below 42°C).[l]	Yes. For outreachto schools and communities.[m]	See assessment for pentavalent **Neutral**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No. VVM 7	No data. Unlikely given the heat stability of current products.	Yes, for use in campaigns	See assessment for pentavalent **Neutral**
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	No. VVM 30	Yes. Likely given the heat stability of current products.	Yes. For school and community based vaccination and outbreak response (3).	See assessment for pentavalent **Neutral**

[l] World Health Organization website. WHO Prequalified Vaccines page. Type: Human Papillomavirus (Quadrivalent). Commercial Name: Gardasil. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178. Accessed 21/10/2019.

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

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)?* [i]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
Ebola (rVSV-ZEBOV) (Liquid SDV)	Campaigns Outbreak response	Yes. Stored as frozen liquid at -80°C to -60°C for long term storage.[n] Can be stored at 2-8°C for no more than two weeks or at room temperature for four hours after thawing.[o]	No data, but unlikely.	Yes. for both use case scenarios.[p]	See assessment for pentavalent **Neutral**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	No data	No data.	Yes. For outreach and campaigns	See assessment for pentavalent **Neutral**

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

[o] 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.

[p] World Health Organization website. Immunization, Vaccines and Biologicals: WHO Ebola Vaccine Target Product Profile page. https://www.who.int/immunization/research/target-product-profile/ebolavaccine/en/. Accessed February 20, 2020.

Vaccines	*Assumed use case*	*Is the vaccine particularly heat sensitive (i.e. VVM2) and does it require special storage conditions (i.e. such as being kept frozen)?* [i]	*Is there evidence that this vaccine can be qualified for CTC use.*	*Would the context of use of the vaccine benefit from CTC use (state which use case scenario)?*	*Does the innovation paired with the vaccine improve heat stability?*
Influenza (pandemic)(VAL 506440) (Liquid SDV)	Campaigns Outbreak response	No data	No data.	Yes, for both use case scenarios	See assessment for pentavalent **Neutral**

Indicator: Ability of the vaccine presentation to withstand freeze exposure

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

Table 6

Parameter assessment		
Vaccines	***Does the innovation paired with the vaccine improve freeze exposure?***	**Overall Score**
All applicable vaccines	All three CPAD subtypes (preformed, pre-and user-assembled BFS, and other) do not impact the freeze stability of the vaccine.	**Neutral**

1.2 Criteria on coverage and equity

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

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

Table 7

Parameter assessment		
Vaccines	***Does the innovation improve the overall coverage for the vaccine within a target population for one or all doses?***	**Overall Score**
Hepatitis B (birth dose)	Preformed CPADs have been shown to increase coverage for hepatitis B (2)(4).	**Better**
All other applicable vaccines	No data are available on the ability of a CPAD to improve overall coverage.	**No data**

[q] *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[r]

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

Table 8

Vaccines	*Does the innovation avoid reconstitution and is that an improvement?*	*Does the innovation require fewer vaccine product components?*	*Does the innovation require fewer preparation steps and less complex preparation steps?*	*Does the innovation improve dose control?*	*Does the innovation improve targeting the right route of administration (accuracy in terms of route and/or depth of injection)?*	Overall score
All applicable vaccines	**Preformed CPAD** All CPAD devices are prefilled with liquid vaccine product and cannot be used with lyophilised vaccines. Therefore, there is no reconstitution and thus there is no difference with the comparators.	**Preformed CPAD:** Uniject™ is a fully assembled all-in-one integrated device, consisting of needle and vaccine dose. Thus, it requires fewer vaccine product components than the comparators.	**Preformed CPAD:** Uniject™ is a fully assembled all-in-one integrated device, consisting of needle and vaccine dose. Therefore, it has fewer preparation steps than the comparators. In general, HCWs have found the device to be easy and quick to use (5). Lay healthcare workers (LHWs) demonstrated the ability to effectively manage Uniject™ supplies and administer Uniject™ with technical ease following training and supervision. LHWs described Uniject™ as having the potential to reduce work load, increase coverage and facilitate the	**Preformed CPAD:** The Uniject™ device improve dose control since it is prefilled and the user does not have to measure and draw the correct dose. .Whereas, the comparators require withdrawing of vaccine from vials. Feedback from HCWs in Vietnam was that dosing preparation was more accurate and safer, minimizing human error (7). Vaccinators were concerned about the appropriate dose not being delivered due to residual vaccine remaining in the reservoir and whether this would have an impact on its effectiveness (7). This is an issue that would need to	**Preformed CPAD:** Use of the Uniject™ device has a similar likelihood as the comparators using AD needles and syringes (N&S) for targeting the right route for vaccine administration. In one study comparing the acceptability and feasibility of delivering a vaccine using preformed CPAD versus AD N&S, some vaccinators commented that the “handle part is too tight to maintain the device in the arm/leg,” which could have an impact on the ease of use and keeping the device in the appropriate layer of the skin (7).	**Better** **(Pre-formed CPAD)**

[r] *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
			ability of LHWs to conduct vaccinations (6).	be addressed in training as the Uniject™ device is slightly overfilled to compensate for the small amount of vaccine that remains in the blister.		
	Neutral	**Better**	**Better**	**Better**	**Neutral**	
	BFS pre-assembled: As above.	**BFS pre-assembled:** It is an all-in-one integrated device, consisting of a custom needle hub, needle, and blister containing the vaccine dose. This requires fewer vaccine product components than the comparators.	**BFS pre-assembled:** It would have fewer steps to prepare the vaccine than the comparators as it comes already prefilled with the vaccine. This makes it less complex.	**BFS pre-assembled:** It is prefilled with the vaccine whereas the comparators (using AD N&S) require the vaccinator to draw the dose from the vial. The squeeze force needs to be sufficient for expulsion of the entire dose volume, which has not yet been determined for this device. The appropriate overfill will need to be determined based on the required squeeze force to ensure that sufficient dose control can be reliably delivered.	**BFS pre-assembled:** It has a similar likelihood to the comparators for targeting the right route for vaccine administration.	**Better** **(BFS pre-assembled)**
	Neutral	**Better**	**Better**	**Better**	**Neutral**	

Vaccines	*Does the innovation avoid reconstitution and is that an improvement?*	*Does the innovation require fewer vaccine product components?*	*Does the innovation require fewer preparation steps and less complex preparation steps?*	*Does the innovation improve dose control?*	*Does the innovation improve targeting the right route of administration (accuracy in terms of route and/or depth of injection)?*	Overall score
	BFS user-assembled: As above	**BFS user-assembled:** It has a separate custom needle hub/needle which must be assembled to the blister by the vaccinator to administer the vaccine. The needle hub/needle can be stored separately in dry storage. The user-assembled BFS CPAD would have the same number of components as the AD N&S comparators.	**BFS user-assembled:** The user-assembled BFS CPAD requires assembly of the needle hub with needle and container, which is the same number of steps as the comparators.	**BFS user-assembled:** It is prefilled with the vaccine whereas the comparators (using AD N&S) requires the vaccinator to draw the dose from the vial. The squeeze force needs to be sufficient to ensure expulsion of the entire dose volume, which has not yet been determined for this device. The appropriate overfill will need to be determined based on the required squeeze force to ensure that sufficient dose control can be reliably delivered.	**For BFS user-assembled:** There is a potential risk that the blister could be mistaken for oral administration, which could impact effectiveness of the vaccine. This risk could be mitigated with training and visual cues on the device.	**Mixed** **(BFS user-assembled)**
	Neutral	**Neutral**	**Neutral**	**Better**	**Worse**	
	CPAD other type: As above	**CPAD other type:** The easyject is an integrated device with all the components for delivery packaged together.	**CPAD other type:** Although there is no test/field study data to directly support the scoring, technically the easyject device would be easier to handle as there are fewer and less complex steps, and no filling is required, whereas the comparators need to withdraw the vaccine.	**CPAD other type:** It is prefilled with the vaccine whereas the comparators (using AD N&S) require the vaccinator to draw the dosage from the vial. This device also uses a plunger which offers more control to successfully expel the full dose based on the design compared to the squeezing mechanism of the other CPAD subtypes.	**CPAD other type:** It has a similar likelihood to the comparators for targeting the right route for vaccine administration.	**Better** **(Other CPAD)**

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
	Neutral	**Better**	**Better**	**Better**	**Neutral**	

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

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

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Table 9

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	Routine	No, as this is a routine vaccine	Same assessment as Hep B.	For the preformed CPAD subtype, several studies have demonstrated that they enable self-administration of hormonal contraception (8)(9)(10). Training and practice injections were needed however, so this might not be suitable for vaccine injection. As a childhood vaccine, self-administration would also not be suitable for this vaccine.	**Better**

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
			Better	**N/A**	
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Health facilities Outreach Home births	Yes. It would be useful if the vaccine could be administered by midwives or traditional birth attendants.	All CPAD subtypes are intended to be simpler to use than vials with needle and syringe (N&S) delivery and are therefore potentially suitable for use by lesser trained vaccinators to enable alternative delivery scenarios. Use with lesser-trained vaccinators has been demonstrated for Uniject with HepB vaccine (5).	Not applicable. This is a birth dose vaccine so self-administration is not a possibility.	**Better**
			Better	**N/A**	
HPV (SDV or 2-dose vial)	Outreach to schools and communities *The initial MAC (typically 5 or 6 age cohorts rather than 1) may be special circumstance for CTC*	Yes. Could potentially be delivered by lesser trained personnel in these settings.	Same assessment as Hep B.	HPV could potentially be self-administered by adolescent vaccinees, however CPADs might not be appropriate for self-administration (see assessment for penta).	**Better**
			Better	**Neutral**	
Polio (IPV) (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	Routine Campaign	No, in the case of routine vaccine. Can be delivered as a co-formulation with other routine IM vaccines.[s] Yes, It would be beneficial if lesser trained personnel could deliver the vaccine in campaign/ outbreak settings	Same assessment as Hep B.	Not applicable. This is a childhood vaccine so self-administration is not a possibility.	**Better**
			Better	**N/A**	

[s] Polio Global Eradication Initiative website. IPV page.http://polioeradication.org/polio-today/polio-prevention/the-vaccines/ipv/. Accessed 21/10/2019.

Vaccines	*Assumed use case*	Would the context of use of the vaccine benefit from delivery by a lesser trained person and self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
Typhoid conjugate (Liquid SDV or 5-dose)	Catch up vaccination Outbreak response Routine	Yes. Delivery by lesser-trained personnel could facilitate catch-up vaccination and vaccination in response to confirmed outbreaks of typhoid fever and in humanitarian emergencies (11).	Same assessment as Hep B. **Better**	TCV could potentially be self-administered by older vaccinees, however CPADs might not be appropriate for self-administration (see assessment for penta). **Neutral**	**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.[t]	Same assessment as Hep B. **Better**	Ebola vaccine could potentially be self-administered by older vaccinees, however CPADs might not be appropriate for self-administration (see assessment for penta). **Neutral**	**Better**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Boost: liquid SDV)	Routine vaccine in areas of high endemicity Targeted outreach and campaigns to susceptible populations	Yes. For targeted outreach to susceptible populations and campaigns.	Same assessment as Hep B. **Better**	No. The innovation does not affect the delivery of the vaccine by injection. **Neutral**	**Better**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	Campaigns Outbreak response	Yes, for both use case scenarios	Same assessment as Hep B.	Pandemic influenza vaccines could potentially be self-administered by older vaccinees, however CPADs might not be appropriate for self-administration (see assessment for penta).	**Better**

[t] Health Policy Watch website. David Branigan. Evidence Shows Ring Vaccination Strategy Effective In Limiting Ebola Outbreak In DRC. 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 self-administration (state which setting/use case scenario)?	*Does the innovation enable a lesser trained person (e.g. volunteers/caregivers/parents/lesser trained personnel) to administer the vaccine?*	*Does the innovation enable self-administration?*	Overall score
			Better	**Neutral**	

Indicator: Ability to facilitate dose sparing

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

Table 10

Vaccines	*Does the innovation improve dose sparing of the vaccine?*	Overall score
All applicable vaccines	A CPAD device will have no impact on the ability to facilitate dose sparing of a vaccine as they do not change the delivery route nor the delivery volume.	**Neutral**

Indicator: Availability of the innovation in a single-dose presentation or multi-dose with preservative to avoid missed opportunities and reduce vaccine wastage.

*Score legend: Dark Green: **Considerably better,** The innovation is available in a much improved presentation from the perspective of missed opportunities and reducing vaccine wastage (for example, a single dose presentation compared to a multidose presentation without preservative); Green: **Better** than the comparator, The innovation is available in an improved presentation from the perspective of missed opportunities and reducing vaccine wastage (for example, a single dose presentation compared to a multidose presentation with preservative); White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator (The innovation is not*

available in an improved presentation from the perspective of missed opportunities and reducing vaccine wastage); N/A*: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

Note: **All SDV comparators will score neutral compared to an innovation that is a single-dose presentation**

Table 11

Parameter assessment		
Vaccines	***Is the innovation available in a single-dose presentation or multi-dose with preservative to avoid missed opportunities (e.g., due to reluctance to open a MDV) and reduce vaccine wastage?*** ***(State whether the comparator is SDV or MDV)***	**Overall score**
Pentavalent (Liquid SDV or 10-dose vial)	The comparator is a single- or 10-dose vial with preservative. All CPADs are expected to be a single-dose presentation and wastage and reluctance to open a MDV would be improved compared to the 10-dose vial comparator.	**Better (MDV)**
Hepatitis B (birth dose) (Liquid SDV or 10-dose vial)	The comparator is a single- or 10-dose vial with preservative. All CPADs are expected to be a single-dose presentation and wastage and reluctance to open a MDV would be improved compared to the 10-dose vial comparator.	**Better (MDV)**
HPV (Liquid SDV or two-dose vial)	The comparator is a single- or 2-dose vial without preservative. All CPADs are expected to be a single-dose presentation and wastage and reluctance to open a MDV would be substantially improved compared to the 2-dose vial comparator.	**Considerably better (MDV)**
IPV (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	The comparator is a single- or 10-dose vial for IM delivery with preservative. All CPADs are expected to be a single-dose presentation and wastage and reluctance to open a MDV would be improved compared to the 10-dose vial comparator	**Better (MDV)**
Typhoid conjugate (Liquid SDV or 5-dose)	The comparator is a single- or 5-dose vial with preservative. All CPADs are expected to be a single-dose presentation and wastage and reluctance to open a MDV would be improved compared to the 5-dose comparator especially since the vaccine should be discarded within 6 hours after opening.	**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**
Ebola (rVSV-ZEBOV) (Liquid SDV)	All CPADs are expected to be a single-dose presentation and as the comparator is available as a frozen liquid SDV without preservative[u] thus the reluctance to open a MDV is not a problem with current presentations.	**Neutral (SDV)**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	The comparator is a single-dose vial similar to the innovation. It is not known whether or not it will contain a preservative.	**Neutral (SDV)**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	The comparator is a single-dose vial similar to the innovation. It is not known whether or not it will contain a preservative.	**Neutral (SDV)**

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

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

Table 12

Parameter assessment				
Vaccines	***Does the innovation include features that may improve pain experienced by the recipient following vaccination?***	***Does the innovation include features that may improve perception of ease of administration (i.e. convenience for the vaccinees/caregivers)?***	***Does the innovation include features that may improve/impact any other benefit related to acceptability by vaccinees/caregivers?***	**Overall score**
	Preformed CPAD:	**Preformed CPAD:**	**Preformed CPAD:**	**Better**

[u] EMA. ERVEBO, INN-Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live) product information. Annex 1. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf. Accessed

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	In a study of mothers whose infants had been injected using Uniject, mothers expressed a strong preference for Uniject over a standard needle and syringe and considered Uniject less painful. Their perceptions of reduced pain may have been due to the sharpness of the single-use needle, although, the speed of injection may also have played a role in reducing anxiety and perceived pain (5). A study in Bolivia found that of women who received TT Uniject™ at antenatal home visits, 50% of women interviewed stated it was less painful that traditional injections, 10% stated it was similar, 7% found it more painful, and 33% could not compare (12). The assumption is that it would be no different for other vaccine types against the comparators.	Uniject™ prefilled with TT vaccine was successfully used in an outreach immunization program in Bolivia, the performance of the device and its acceptability by the vaccinators and recipients was high (5). The Uniject presentation has been shown to improve acceptability of HepB birth dose vaccination among caregivers. In a study of mothers whose infants had been injected using Uniject, 94% said they experienced no anxiety before the injection and 92% said they would agree to future injections with the device. Mothers expressed a strong preference for the Uniject device over a standard needle and syringe (5). Since Uniject is considered very easy to administer, it is also used for self-administration. Uniject has also been approved for self-administration of DMPA-SC.[v]	The assumption is it would be no different to the comparators as the device has a needle. However, there is no data available on this from the perspective of the recipient.	
	Better	**Better**	**No data**	
	BFS pre-assembled: The assumption is that it would be no different to Uniject™, thus would be better than the comparators. However, there are no data available on this from the perspective of the recipient.	**BFS pre-assembled:** There are no data on ease of administration as the device is still under development.	**BFS pre-assembled:** There are no data on other benefits as the device is still under development.	**Better**
	Better	**No data**	**No data**	

[v] Inject Sayana Press website. Available at http://www.injectsayanapress.org/. Accessed 02 October 2019.

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**
	BFS user-assembled: The assumption is it would be no different to Uniject™, thus would be better than the comparators. However, there are no data available on this from the perspective of the recipient.	**BFS user-assembled:** There are no data on ease of administration as the device is still under development.	**BFS user-assembled:** There are no data on other benefits as the device is still under development.	**Better**
	Better	**No data**	**No data**	
	Other type: The assumption is it would be no different to the comparators as the device has a needle. However, there are no data available on this from the perspective of the recipient.	**Other type:** There are no data on ease of administration as the device is still under development.	**Other type:** There are no data on other benefits as the device is still under development.	**Better**
	Neutral	**No data**	**No data**	

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

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

Table 13

Vaccines	*Does the innovation require fewer components?*	*Or does the innovation include labelling that facilitates product tracking?*	Overall score
All applicable vaccines	**Preformed CPAD**: Compared to AD needle and syringe (N&S) it will be better because the Uniject™ preformed CPAD is a fully assembled, all-in-one integrated device. HCWs in Senegal and Vietnam reported that the use of CPADs could reduce stock-outs, reduce risk of glass vials breaking. CPADs also eliminate shortages of either the vaccine or syringe as the CPAD is an all in one device (7).	All CPADs are expected to have the same labelling as the comparators. The innovation does not impact labelling that facilitates product tracking.	**Better**
	Better	**N/A**	
	BFS pre-assembled: It is an all-in-one integrated device consisting of the needle hub, needle, and blister with vaccine dose.	All CPADs are expected to have the same labelling as the comparators. The innovation does not impact labelling that facilitates product tracking.	**Better**
	Better	**N/A**	
	BFS user-assembled: It has a separate needle hub with needle which must be assembled with the blister at the point of use to administer the vaccine, so it has the same number of components as the comparators.	All CPADs are expected to have the same labelling as the comparators. The innovation does not impact labelling that facilitates product tracking.	**Neutral**
	Neutral	**N/A**	
	Other type: The Easyject is an integrated device with all the components for delivery packaged together.	All CPADs are expected to have the same labelling as the comparators. The innovation does not impact labelling that facilitates product tracking.	**Better**
	Better	**N/A**	

1.3 Criteria on safety

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

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

Table 14

Parameter assessment		
Vaccine	***Does the innovation reduce the frequency of serious AEFIs?***	**Overall score**
Pentavalent (Liquid SDV or 10-dose vial)	CPADs are not expected to impact the frequency of serious AEFIs compared with the comparators. **For preformed CPAD,** an open-label, randomized, phase 3 study in the Philippines found no serious adverse events and no difference in frequency of solicited or unsolicited AEs compared with N&S (1).	**Neutral**
Hepatitis B (birth dose) (Liquid SDV or 10-dose vial)	CPADs are not expected to impact the frequency of serious AEFIs compared with the comparators. **For preformed CPAD,** three hepatitis B studies in Indonesia found no serious adverse events following immunization (PATH unpublished data, 1996) (5)(13). Likewise, studies in India and China found no serious events linked to Uniject™ (2).	**Neutral**
All other applicable vaccines	CPADs are not expected to impact the frequency of serious AEFIs compared with the comparators. However, none of the **CPAD subtypes,** have been tested in humans with the vaccines listed, so there are no AEFI data.	**No data**

Indicator: Likelihood of contamination and reconstitution errors

(This indicator is further measured in Phase 2 only if the comparator is a MDV)

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

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

Table 15

Vaccines	*Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?*	*Does the innovation reduce the potential risk of reuse of delivery technology?*	*Does the innovation reduce the risk of use of nonsterile components?*	*Does the innovation reduce the risk of contamination while filling the delivery device?*	*Does the innovation require fewer preparation steps and less complex preparation steps)?*	*Does the innovation reduce the likelihood of using an incorrect diluent during reconstitution?*[x]	Overall score
All applicable vaccines	**Preformed CPAD** CPADs are prefilled with a liquid vaccine, and do not require reconstitution which is no different to the comparators.	**Preformed CPAD** The innovation is expected to have an autodisable feature so would have the same risk of reuse as the comparators.	**Preformed CPAD** All the equipment is manufactured and packaged under sterile conditions[y] which is similar to the comparators.	**Preformed CPAD** CPADs are prefilled reducing the risk of contamination in comparison to the comparators which require that the AD syringe be filled from a vial.	**Preformed CPAD** Since the innovation is prefilled it would have fewer preparation steps than the comparators.	**Preformed CPAD** CPADs are prefilled with a liquid vaccine, and do not require reconstitution which is no different to the comparators.	**Better (Preformed CPAD)**
	Neutral	**Neutral**	**Neutral**	**Better**	**Better**	**Neutral**	
	BFS pre-assembled CPAD As above	**BFS pre-assembled CPAD** BFS CPADs with AD features have yet to be developed but these features could potentially be added to the devices.	**BFS pre-assembled CPAD** As above	**BFS pre-assembled CPAD** As above	**BFS pre-assembled CPAD** As above	**BFS pre-assembled CPAD** As above	**Better (BFS pre-assembled CPAD)**
	Neutral	**Neutral**	**Neutral**	**Better**	**Better**	**Neutral**	

[y] *Note: For other type, the stopper is solid, which prevents contamination when inserting the plunger.*

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?*[x]	Overall score
	BFS user-assembled CPAD As above	**BFS user-assembled CPAD** BFS CPADs with AD features have yet to be developed but these features could potentially be added to the devices.	**BFS user-assembled CPAD** As above	**BFS user-assembled CPAD** For the user-assembled BFS CPAD, there is a possibility of contamination by the user while assembling the product.	**BFS user-assembled CPAD** The device requires assembly of the needle hub and container, which is the same number of steps as the comparators.	**BFS user-assembled CPAD** As above	**Worse (BFS user-assembled CPAD)**
	Neutral	**Neutral**	**Neutral**	**Worse**	**Neutral**	**Neutral**	
	Other CPAD types As above	**Other CPAD types** The innovation is expected to have an autodisable feature so would have the same risk of reuse as the comparators.	**Other CPAD types** As above	**Other CPAD types** Device is prefilled reducing the risk of contamination in comparison to the comparators which require that the AD syringe be filled from a vial.	**Other CPAD types** Although there is no test/field study data, the easyject device should be easier to handle as there are fewer and less complex steps, and no filling is required, whereas the comparators require that the AD syringe be filled from a vial.	**Other CPAD types** As above	**Better (other CPAD type)**
	Neutral	**Neutral**	**Neutral**	**Better**	**Better**	**Neutral**	

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?*[z]	*Does the innovation reduce the risk of injury after vaccine administration?*	Overall score
All applicable vaccines	No, all CPADs have the same number of sharps as the comparators.	For all CPADs, delivery of vaccine using the CPAD device requires one sharp. There is a slight reduction in needlestick injury risk compared to standard needle and syringe technique because vaccine withdrawal from a vial is not needed. An acceptability study in Vietnam with preformed CPADs identified a perceived risk by HCWs using CPAD (Uniject™) was that the needle could break in the arm or leg of restless children or that the needle could potentially "break bone" of children, due to its perceived length (7), although the needle length is the same as current AD N&S used for immunization.	By definition, all CPADs must have an AD feature to be considered CPADs, which prevents re-use of contaminated needles, though to date BFS CPADs with autodisable features have yet to be developed. It is no different than the comparators.	All CPADs do not currently include a SIP feature, which is the same as the comparators (AD N&S). Injury after vaccination could be reduced if a sharps injury protection (SIP) feature is incorporated into the device.	Similar risk as the comparators for all CPADs.	**Better**
	Neutral	**Better**	**Neutral**	**Neutral**	**Neutral**	

[z] *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 (per person vaccinated)

Notes for Table 17:

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

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

Table 17

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
All applicable vaccines	**Preformed CPAD SDV assessment:** The estimated cost of goods sold (COGS) is slightly higher for a preformed CPAD ($1.62) compared to a vaccine in a SDV ($1.55) (14). (Note: these estimates include an antigen cost of $0.99 which does not vary by technology and this does not impact the absolute cost differences; the COGS exclude regulatory and R&D costs). For the SDV this COGS estimate excludes the cost of the separate AD N&S that is needed for administration. Wastage rates for a CPAD and SDV would likely be the same. Therefore, based on COGS estimates, the purchase cost of the vaccine regimen would increase by approximately $0.07 per dose with a CPAD compared to a SDV.	**Preformed CPAD SDV assessment:** Compared to a SDV, a preformed CPAD would eliminate the need for a separate delivery device since the CPAD is an all-in-one device. For the comparator, an AD N&S is required and this costs approximately $0.04.[aa] Therefore, a preformed CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**Preformed CPAD SDV assessment:** The volume of preformed CPAD is 12 cm^3. The volume of an AD N&S used for vaccine administration is 42 cm^3. So the volume disposed in the safety box is smaller, reducing safety box purchase costs, but this cost savings would be <$0.01 per dose.	Overall score: **Worse** • Based on COGS data, estimated net increase of ~$0.03 per dose ($0.07 increase in vaccine purchase costs, $0.04 savings due to the elimination of a separate AD N&S and <$0.01 savings in safety box costs). • COGS estimates are preliminary as the CPADs are still under development and COGS do not account for mark-up (e.g. profit, regulatory costs, R&D costs etc.) and so the absolute cost differential may be larger. • For a vaccine such as Hep B costing $0.49 per dose in SDV for Gavi supported countries, this represents a 6% cost increase with a CPAD; while for a vaccine such as HPV costing $4.50 per dose this is <1% cost increase. So the innovation may be more suitable for use with relatively more expensive vaccines.
	Worse	**Better**	**Better**	

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

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
	Preformed CPAD MDV assessment: The estimated COGS is higher for a preformed CPAD ($1.62) compared to a vaccine in a MDV ($1.21) (14). (Note: these estimates include an antigen cost of $0.99 which does not vary by technology and this does not impact the absolute cost differences; the COGS exclude regulatory and R&D costs). For the MDV this COGS estimate excludes the cost of the separate AD N&S that is needed for administration. Wastage rates for a CPAD would likely be ~4% compared to ~9% for an MDV with preservative[bb] but the increase in wastage rate with MDV would not be high enough to overturn the increase in cost associated with CPAD. Therefore, based on COGS estimates, the purchase cost of the vaccine regimen would increase by ~$0.35 per dose with a CPAD compared to a SDV.	**Preformed CPAD MDV assessment:** Compared to a MDV, a preformed CPAD would eliminate the need for a separate delivery device since the CPAD is an all-in-one device For the comparator, an AD N&S is required and this costs approximately $0.04. Therefore, a preformed CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**Preformed CPAD MDV assessment:** Same assessment as for Preformed CPAD SDV.	Overall score: **Worse** • Based on COGS data, estimated net increase of ~$0.31 per dose ($0.35 increase in vaccine purchase costs, $0.04 savings due to the elimination of a separate AD N&S and <$0.01 savings in safety box costs). • COGS estimates are preliminary as the CPADs are still under development and COGS do not account for mark-up (e.g. profit, regulatory costs, R&D costs etc.) and so the absolute cost differential may be larger. • For a vaccine such as Hep B costing $0.25 per dose in 10-dose vials for Gavi supported countries, this represents a 124% cost increase with a CPAD; while for a vaccine such as IPV costing $2.00 per dose in 10-dose vials then this is a 16% cost increase. So the innovation may be more suitable for use with relatively more expensive vaccines.
	Worse	**Better**	**Better**	

[bb] *World Health Organization website. WHO vaccine wastage rates calculator page. https://www.who.int/immunization/programmes_systems/supply_chain/resources/tools/en/.*

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*
	BFS pre-assembled CPAD SDV assessment: There is no publicly available data on the likely purchase price or COGs of a BFS pre-assembled CPAD.	**BFS pre-assembled CPAD SDV assessment:** Compared to a SDV, a BFS pre-assembled CPAD would eliminate the need for a separate delivery device since the CPAD is an all-in-one device. For the comparator, an AD N&S is required and this costs approximately $0.04. Therefore, for a pre-assembled CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**BFS pre-assembled CPAD SDV assessment:** Same assessment as for Preformed CPAD SDV.	Overall score: **No data** • No data on COGS or purchase price of BFS pre-assembled CPAD. • ~$0.04 in saving would result from the elimination of separate AD N&S and reduction in safety box purchase costs. • In summary, it is possible that the overall assessment will be the same as for preformed CPAD.
	No data	**Better**	**Better**	
	BFS pre-assembled CPAD MDV assessment: There is no publicly available data on the likely purchase price or COGs of a BFS pre-assembled CPAD but it is likely that a BFS preassembled CPAD will cost more than a MDV.	**BFS pre-assembled CPAD MDV assessment:** Compared to a MDV, a BFS pre-assembled CPAD would eliminate the need for a separate delivery device since the CPAD is an all-in-one device. For the comparator, an AD N&S is required and this costs approximately $0.04. Therefore, a preassembled CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**BFS pre-assembled CPAD MDV assessment:** Same assessment as for Preformed CPAD SDV.	Overall score: **No data** • No data on COGS or purchase price of BFS pre-assembled CPAD. • ~$0.04 in saving would result from the elimination of separate AD N&S and reduction in safety box purchase costs. • In summary, it is possible that the overall assessment will be the same as for preformed CPAD.
	No data	**Better**	**Better**	

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
	BFS user-assembled SDV assessment: The estimated COGS is lower for a BFS user-assembled CPAD (~$1.38) compared to a vaccine in a SDV ($1.55). (Note: these estimates include an antigen cost of $0.99 which does not vary by technology and this does not impact the absolute cost differences; the COGS exclude regulatory and R&D costs). The BFS user assembled CPAD would have the needle co-packaged with the vaccine and the needle price is included in the COGS. price. For the SDV this COGS estimate excludes the cost of the separate AD N&S that is needed for administration. Wastage rates for a CPAD and SDV would likely be the same. Therefore, based on COGS estimates, the purchase cost of the vaccine regimen would decrease by approximately $0.17 per dose with a CPAD compared to a SDV.	**BFS user-assembled SDV assessment:** Compared to a SDV, a BFS user assembled CPAD would have the needle co-packaged with the vaccine and the needle price is included in the vaccine price and so there would be no separate delivery devices that need to be purchased. For the comparator, an AD N&S is required, and this costs approximately $0.04. Therefore, a BFS user assembled CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**BFS user-assembled SDV assessment:** Same assessment as for Preformed CPAD SDV.	Overall score: **Better** • Based on COGS data, estimated net decrease of ~$0.21 per dose ($0.17 decrease in vaccine purchase costs, $0.04 savings due to the elimination of a separate AD N&S and <$0.01 savings in safety box costs). • COGS estimates are preliminary as the CPADs are still under development and COGS do not account for mark-up (e.g. profit, regulatory costs, R&D costs etc.) and so the absolute cost differential may be smaller. • For a vaccine such as Hep B costing $0.49 per dose in SDV for Gavi supported countries, this represents a 43% cost decrease with a CPAD; while for a vaccine such as HPV costing $4.50 per dose this is 5% cost decrease. So the savings with the innovation may be larger with relatively less expensive vaccines.
	Better	**Better**	**Better**	

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
	For BFS user-assembled MDV assessment: The estimated COGS is higher for a BFS user-assembled CPAD (~$1.38) compared to a vaccine in a MDV ($1.21) (14). (Note: these estimates include an antigen cost of $0.99, which does not vary by technology and this does not impact the absolute cost differences; the COGS exclude regulatory and R&D costs). The BFS user assembled CPAD would have the needle co-packaged with the vaccine and the needle price is included in the COGS. price. For the MDV this COGS estimate excludes the cost of the separate AD N&S that is needed for administration. Wastage rates for a CPAD would likely be ~4% compared to ~9% for a MDV with preservative, but the increase in wastage rate with MDV would not be high enough to overturn the increase in cost associated with CPAD. Therefore, based on COGS estimates, the purchase cost of the vaccine regimen would increase by ~$0.11 per dose with a CPAD compared to a SDV.	**For BFS user-assembled MDV assessment:** Compared to a MDV, a BFS user assembled CPAD would have the needle co-packaged with the vaccine and the needle price is included in the vaccine price, so there would be no separate delivery devices that need to be purchased. For the comparator, an AD N&S is required, and this costs approximately $0.04. Therefore, a BFS user assembled CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**For BFS user-assembled MDV assessment:** Same assessment as for Preformed CPAD SDV.	Overall score: **Worse** • Based on COGS data, estimated net increase of ~$0.07 per dose ($0.11 increase in vaccine purchase costs, $0.04 savings due to the elimination of a separate AD N&S and <$0.01 savings in safety box costs). • COGS estimates are preliminary as the CPADs are still under development and COGS do not account for mark-up (e.g. profit, regulatory costs, R&D costs etc.) and so the absolute cost differential may be larger. • For a vaccine such as Hep B costing $0.25 per dose in 10-dose vials for Gavi supported countries, this represents a 28% cost increase with a CPAD; while for a vaccine such as IPV costing $2.00 per dose in 10-dose vials then this is a 4% cost increase. So the innovation may be more suitable for use with relatively more expensive vaccines.
	Worse	**Better**	**Better**	

Vaccines	*Does the innovation reduce the purchase cost of a vaccine regimen, accounting for wastage?*	*Does the innovation reduce the purchase cost of delivery devices (injection syringes or other components needed for vaccine preparation and administration), accounting for wastage?*	*Are the safety box costs reduced because of a change in the waste disposal volumes and / or types of sharps waste generated?*	*Overall score*
	Other type SDV assessment: There is no publicly available data on the COGs or potential price of other types of CPADs.	**Other type SDV assessment:** Compared to a SDV, other types of CPAD would be an all-in-one device and so there would be no separate delivery devices to be purchased. For the comparator, an AD N&S is required, and this costs approximately $0.04. Therefore, other type BFS CPAD would reduce the purchase cost of delivery devices by $0.04 per dose.	**Other type SDV assessment:** There is no publicly available information on the volume of other types of CPADs .	Overall score: **No data** • No data on COGS or purchase price of other type CPAD. • ~$0.04 saving per dose would result from the elimination of separate AD N&S. • No data on impact on safety box purchase costs but these are typically insignificant. • In summary, it is possible that the overall assessment will be the same as for preformed CPAD.
	No data	**Better**	**No data**	
	Other type MDV assessment: Same as SDV assessment above.	**Other type MDV assessment:** Same as SDV assessment above.	**Other type MDV assessment:** Same as other type CPAD SDV assessment above.	Overall score: **No data** • No data on COGS or purchase price of other type CPAD. • ~$0.04 saving per dose would result from the elimination of separate AD N&S. • No data on impact on safety box purchase costs but these are typically insignificant. • In summary, it is possible that the overall assessment will be the same as for preformed CPAD.
	No data	**Better**	**No data**	

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

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

Note: ***PATH VTIA model analyses[cc] have shown than the cold chain storage and transport costs per cm³ are much higher than the costs of storage and transport out of the cold chain.***

Table 18

Vaccines	*Does the innovation reduce the economic costs of cold chain storage and transport for a vaccine regimen?*	*Does the innovation reduce the economic costs of out of cold chain storage and transport for a vaccine regimen including delivery technology(ies)?*	*Does the innovation reduce the economic costs of time spent by the vaccinators when preparing and administering the vaccine?*	*Does the innovation reduce the economic costs of time spent by staff involved in stock management*	Overall score
All applicable vaccines	**Preformed CPAD SDV assessment:** The volume of preformed CPAD is 12 cm^3. The volume of SDV differ by vaccine and manufacturer: for example, a SDV of Hep B the volumes for the two SDV procured by UNICEF for Gavi are 14.53[dd] and 14.06 cm^3[ee] , while for HPV the volume is 18.4 cm^3 [ff] and for IPV it is 17.5cm^3 [gg]. Therefore, a preformed CPAD would slightly reduce the economic costs of cold chain storage and transport, though because the difference in	**Preformed CPAD SDV assessment:** Compared to a SDV, a preformed CPAD would eliminate the need for a separate delivery device since the CPAD is an all-in-one device. Therefore, a preformed CPAD would remove any economic costs of out of cold chain storage and transport. As a reference point for the magnitude of these costs, out of cold chain storage and transport	**Preformed CPAD SDV assessment:** Vaccine is pre-filled, thus no need for preparation. A time and motion study conducted by PATH showed it took 7.3 seconds for a provider to deliver a dose when using Uniject compared to 19.3 seconds for a liquid vaccine in a SDV (15). Program officers, medical officers, nurses, HCWs, and vaccinators expressed how	**Preformed CPAD SDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	Overall score: **Better** • Total delivery costs will decline by <$0.02 per dose with a preformed CPAD compared to SDV. • As a reference point, a costing study estimated that delivery costs for IPV in SDV were ~$0.13 per dose (16). A ~$0.02 reduction in delivery costs would be a 15% cost reduction.

[cc] *Vaccine Technology Impact Assessment (VTIA). PATH internal document.*
[dd] *World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial Name: Euvax B. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=68*
[ee] *World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial Name: Hepatitis B Vaccine (rDNA) (Paediatric). https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=133*
[ff] *World Health Organization website. WHO Prequalified Vaccines page. Type: Human Papillomavirus. Commercial Name: Gardasil 9. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=306*
[gg] *World Health Organization website. WHO Prequalified Vaccines page. Type: Polio vaccine – Inactivated (IPV). Commercial Name: Poliomyelitis Vaccine (Inactivated). https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=325*

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
	volume is so small, the cost savings would be ~$0.01 per dose.	costs for injection devices would be ~$0.01 for an AD N&S.	simple it is to prepare a CPAD– it is time saving (7). Some indication that time to immunise using CPAD is reduced: In Senegal, CPAD reduced administration time by 27-35%, while in Vietnam it was reduced by 40-61% compared to AD syringes. The timing included all the steps starting from the child being present to the disposal of the device (7). Average human resource costs per minute were estimated at ~$0.03 per minute by PATH's VTIA model. So that savings in vaccinator time would be likely be <$0.01 per dose.		
	Better	**Better**	**Better**	**Neutral**	
	Preformed CPAD MDV assessment: The volume of a preformed CPAD is 12 cm^3. The volume of MDV differ by vaccine and manufacturer: As an example, for a MDV of Hep B the volumes for the two MDV procured by UNICEF for Gavi are 2.109[hh] and 2.86 cm^3 [ii] per	**Preformed CPAD MDV assessment:** Same assessment as Preformed CPAD SDV.	**Preformed CPAD MDV assessment:** A time and motion study conducted by PATH showed it took 7.3 seconds for a provider to deliver a dose when using Uniject compared to 15.2 seconds for a liquid vaccine in a MDV (15).	**Preformed CPAD MDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	Overall score: **Worse** • Total delivery costs will increase by ~$0.02 per dose ($0.03 increase in cold cain storage and transport costs, ~$0.01 decrease in out of cold chain storage and transport costs, and <$0.01 decrease in

[hh] *World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial Name: Hepatitis B Vaccine (rDNA) (Paediatric).* https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=132

[ii] *World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial Name: Euvax B.* https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=71

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
	dose, 3.38 cm^3 for IPV in 10-dose vials[jj] and 2.1 cm^3 for pentavalent[kk]. Therefore, a preformed CPAD would increase the economic costs of cold chain storage and transport compared to a MDV. Using estimates from PATH's VTIA model, cold chain costs would increase by ~$0.03 per dose when volume increases from 3 cm^3 to 12 cm^3.		Same reference point as Preformed CPAD SDV assessment and conclusion that costs savings would be <$0.01 per dose.		vaccinator time costs) with a preformed CPAD compared to MDV. • As a reference point, a costing study estimated that delivery costs for IPV in 10-dose vials were ~$0.06 per dose (16). A ~$0.02 increase in delivery costs would be a 33% cost increase.
	Worse	**Better**	**Better**	**Neutral**	
	BFS pre-assembled SDV assessment: The targeted volume for a BFS pre-assembled CPAD would be the same or less than that of a preformed CPAD. Similar to a preformed CPAD, a BFS pre-assembled CPAD would slightly reduce the economic costs of cold chain storage and transport by ~$0.01 compared to a SDV.	**BFS pre-assembled SDV assessment:** Same assessment as Preformed CPAD SDV.	**BFS pre-assembled SDV assessment:** Given that this would be a similar mechanism and activation procedure as the Uniject, this is ranked better than the comparator assuming a similar assessment as the preformed CPAD. Further time and motion studies should be conducted to verify this assumption. Same reference point as Preformed CPAD SDV assessment and conclusion that	**BFS pre-assembled SDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	Overall score: **Better** • Same rationale as for the preformed CPAD versus a SDV.

[jj] *World Health Organization website. WHO Prequalified Vaccines page. Type: Polio vaccine – Inactivated (IPV). Commercial Name: Poliomyelitis Vaccine (Inactivated).* https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=372

[kk] *World Health Organization website. WHO Prequalified Vaccines page. Type: Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b. Commercial Name: Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae type b Conjugate Vaccine Adsorbed.* https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=225

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
			costs savings would be <$0.01 per dose.		
	Better	**Better**	**Better**	**Neutral**	
	BFS pre-assembled MDV assessment: The targeted volume for a BFS pre-assembled CPAD would be the same or less than that of a preformed CPAD, but likely larger than the volume per dose in a MDV. The BFS pre-assembled CPAD would increase the economic costs of cold chain storage and transport in comparison to a MDV. We assume similar savings as for the preformed CPAD.	**BFS pre-assembled MDV assessment:** Same assessment as Preformed CPAD SDV.	**BFS pre-assembled MDV assessment:** Given that this would be a similar mechanism and activation procedure as the Uniject, this is ranked better than the comparator assuming a similar assessment as the preformed CPAD. Further time and motion studies should be conducted to verify this assumption. Same reference point as Preformed CPAD SDV assessment and conclusion that costs savings would be <$0.01 per dose.	**BFS pre-assembled MDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	Overall score: **Worse** • Same rationale as for the preformed CPAD versus a SDV
	Worse	**Better**	**Better**	**Neutral**	
	BFS user-assembled SDV assessment: The targeted volume for a BFS user-assembled CPAD would be the same or less than that of a preformed CPAD given that the needle is not co-packaged with the vaccine. The BFS pre-assembled CPAD would	**BFS user-assembled SDV assessment:** Compared to a SDV, a BFS user assembled CPAD would have a separate needle stored in dry storage which is expected to be smaller than an AD N&S. But we have no volume data for the	**BFS user-assembled SDV assessment:** No data. Since this is a prefilled device, the only required step for administration is assembly of the needle. With the SDV the vaccinator has to take time to draw and calibrate the dose	**BFS user-assembled SDV assessment:** There are no features on this innovation that impact the time spent by staff	Overall score: **No data** • No data on the costs for storage and transport in and out of the cold chain or the impact on vaccinator time costs. • In summary, it is possible that the delivery costs will decline, similar to a

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
	therefore likely reduce the economic costs of cold chain storage and transport in comparison to a SDV. But we have no volume data to estimate these costs.	separate needle to estimate these costs.	which is not required for prefilled container (PATH, internal data, 2019). Time and motion studies should be conducted to verify this assumption.	involved in stock management.	preformed CPAD compared to a SDV.
	No data	**No data**	**No data**	**Neutral**	
	BFS user-assembled MDV assessment: The targeted volume for a BFS user-assembled CPAD would be the same or less than that of a preformed CPAD given that the needle is not co-packaged with the vaccine. But the volume is likely larger than the per dose volume in a MDV. The BFS user-assembled CPAD would increase the economic costs of cold chain storage and transport in comparison to a MDV. But we have no volume data to estimate these costs.	**BFS user-assembled MDV assessment:** Compared to a MDV, a BFS user assembled CPAD would have a separate needle hub stored in dry storage which is expected to be smaller than an AD N&S. But we have no volume data for the separate needle to estimate these costs.	**BFS user-assembled MDV assessment:** No data. Since this is a prefilled device, the only required step for administration is assembly of the needle. With the SDV the vaccinator has to take time to draw and calibrate the dose which is not required for prefilled container (PATH, internal data, 2019). Time and motion studies should be conducted to verify this assumption.	**BFS user-assembled MDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	Overall score: **No data** • No data on the costs for storage and transport in and out of the cold chain or on the impact on vaccinator time costs. • In summary, it is possible that the delivery costs will increase, similar to a preformed CPAD compared to a MDV.
	No data	**No data**	**No data**	**Neutral**	

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
	Other type SDV assessment: There is no publicly available information on the volume of other types of CPADs to estimate these costs.	**Other type SDV assessment:** Same assessment as Preformed CPAD SDV.	**Other type SDV assessment:** No data. However, since this is a prefilled device, the only required step for administration to place the needle shield/plunger rod into the barrel of the device. With the SDV the vaccinator has to take time to draw and calibrate the dose, which is not required for prefilled container (PATH, internal data, 2019). Further time and motion studies should be conducted to verify this assumption.	**Other type SDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	**Overall score: No data** • No data on the costs for storage and transport in the cold chain or on the impact on vaccinator time costs. • The costs for storage and transport out of the cold chain will decline. • The magnitude of the volume stored and transported in the cold chain for the other type of CPAD versus SDV will drive the overall change in costs.
	No data	**Better**	**No data**	**Neutral**	
	Other type MDV assessment: There is no publicly available information on the volume of other types of CPADs to estimate these costs but they are likely larger than MDV.	**Other type MDV assessment:** Same assessment as Preformed CPAD SDV.	**Other type MDV assessment:** No data. However, since this is a prefilled device, the only required step for administration to place the needle shield/plunger rod into the barrel of the device. With the SDV the vaccinator has to take time to draw and calibrate the dose, which is not required for prefilled container (PATH, internal data, 2019). Further time and motion studies should be conducted to verify this assumption.	**Other type MDV assessment:** There are no features on this innovation that impact the time spent by staff involved in stock management.	**Overall score: No data** • No data on the costs for storage and transport in the cold chain or on the impact on vaccinator time costs. • The costs for storage and transport out of the cold chain will decline. • In summary, it is possible that the delivery costs will increase, similar to a preformed CPAD compared to MDV.

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
	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 CPADs. **Worse** Other costs: There are no upfront costs for hardware, recurrent or ongoing costs for CPADs. **Neutral**	Overall score: **Worse** • Vaccinators will need to be trained on how to use CPADs. There are no other upfront or recurrent costs with CPADs.

1.5 Criteria on environmental impact

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

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

Table 20

Vaccine	*Does the innovation reduce the volume of medical (biohazard) disposal waste?*	*Does the innovation reduce sharps waste disposal?*	*Is the innovation, and its packaging, composed of more sustainable materials that improves waste disposal?*	Overall score
All applicable vaccines	For all types of CPADS, the volume of medical waste (other than sharps) is expected to be reduced since the entire CPAD device is thrown in the sharps waste. For the comparators, vials are disposed of with medical waste.	CPAD's small size compared to a standard AD needle and syringe could positively impact disposal practices by decreasing the sharps waste volume.[mm]	All types of CPADs are made from plastic (other type is also available in glass). Glass, including vials used with standard needles and syringes do not burn easily and can explode and shatter. However, pit burning of plastic containers is easier and could result in a more complete burn though there is concern regarding the pollution created from burning plastic (17). The volume of plastic burned is less for a CPAD than a syringe, which improves waste disposal. **For other type,** the CPAD may be made of glass and therefore also neutral.	**Better**
	Better	**Better**		

[ll] *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).*
[mm] *PATH. A HealthTech Historical Profile: The Uniject Device. Seattle: PATH; 2005. https://path.azureedge.net/media/documents/TS_hthp_uniject.pdf*

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

1.6 Criteria on technology readiness

Indicator: Clinical development pathway complexity[nn]

Notes:

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

- These are based on published data and input from regulatory consultants.
- Only endpoints related to efficacy have been considered.
- For pipeline vaccines, we have assumed that the vaccine will NOT be licensed using needle and syringe (or other standard delivery device) prior to licensure with the new device. The complexity rating assumes that the vaccine is used with the innovation for initial licensure.

*Score legend: **High complexity:** Lacks a clear licensure pathway; **Moderate complexity**: Will likely require a phase III efficacy study and it should be possible to run a trial with a clinical endpoint (as case definitions and clinical endpoints have been agreed upon, there is sufficient disease burden to evaluate the effect of the vaccine, and trial sites and capacity are available); **Low complexity**: Will likely require a non-inferiority trial (as there is an available metric of potency (surrogate or correlate of protection (CoP)) to compare with the existing vaccine); **No complexity:** Will likely not require a phase III efficacy study or non-inferiority trial (as there is no change in formulation, route of administration, or delivery mechanism); N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 21

Vaccines	*Is the clinical development pathway complex?*	Overall score
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	Immunological endpoints (serum antibody titres) have been used for non-inferiority trials and approval of pentavalent vaccine in new delivery devices in the past (18). It is assumed that similar endpoints could be used to assess all types of CPADs.	**Low complexity**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	Seroprotection against hepatitis B is defined as having anti-HBs concentration of ≥ 10 mIU/ml (13). 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) (18) and also initial studies of HepB vaccine in Uniject (13). It is assumed that similar endpoints could be used to assess all types of CPADs.	**Low complexity**
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 (19). It is assumed that similar endpoints could be used to assess all types of CPADs.	**Low complexity**

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

Vaccines	*Is the clinical development pathway complex?*	Overall score
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 (20) or IPV containing hexavalent vaccine (21). It is assumed that similar endpoints could be used to assess all types of CPADs.	**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 (22).[oo] It is assumed that similar endpoints could be used to assess all types of CPADs.	**Low complexity**
Ebola (rVSV-ZEBOV) (Liquid SDV)	Immunological correlates of protection have not been established for Ebola virus (23)(24), and it has only been possible to demonstrate efficacy of the most advanced candidate rVSV-ZEBOV) using ring vaccination trials (25). Demonstration of efficacy of an Ebola vaccine in a CPAD is likely to require an efficacy trial and as such, only be possible during an outbreak. Efforts are underway to expedite the approval process for Ebola vaccines.[pp]	**Moderate complexity**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	Ongoing phase III clinical trials of HIV vaccines have prevention of HIV acquisition as the primary endpoint,[qq] and it seems likely that this will be the case for other new HIV vaccines. Attempts to define immunological correlates of protection based on data from earlier phase III trials are ongoing (26).	**High complexity**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	WHO guidelines refer to three different types of pandemic vaccines: vaccines against novel inter-pandemic influenza strains; vaccines for stockpiling; vaccines developed following the outbreak of a pandemic.[rr] 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.[rr]	**Low complexity**

[oo] World Health Organization. *Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines.* Geneva: World Health Organization; 2013. https://www.who.int/biologicals/areas/vaccines/TYPHOID_BS2215_doc_v1.14_WEB_VERSION.pdf.

[pp] World Health Organization website. Essential medicines and health products page: *African regulators' meeting looking to expedite approval of vaccines and therapies for Ebola.* *https://www.who.int/medicines/news/AFR_reg_meet/en/.* Accessed 21/10/2019.

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

[rr] World Health Organization. Proposed Guidelines: Regulatory Preparedness for Human Pandemic Influenza Vaccines. Presented at: Expert Committee on Biological Standardization, October 8 – 12, 2007; Geneva, Switzerland. *https://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf*

Indicator: Technical development challenges

The WHO Delivery Technologies Working group[ss], which is comprised of industry members and global health stakeholders, was invited to complete a survey following a consultation on CPADs. 12 member organizations responded to the survey and 9 member organizations responded to the question on technical challenges. The following challenges were identified as the most important technical challenges facing the development of CPADs (most frequently identified challenges first):

- Compatibility of CPAD materials with vaccine (5/9)
- Production with alternative filling methods, such as blow-fill-seal (5/9)
- Cost of goods (4/9)
- Moisture vapor/gas barrier properties of materials (4/9)
- Device size (4/9)

Score legend: ***High complexity*** *of technical development challenges that are unlikely to be overcome;* ***Moderate complexity*** *of technical development challenges that might be overcome with longer development time and/or more funding;* ***Low complexity*** *of technical development challenges, e.g. applying an existing barcode; N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

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
All vaccines assessed	**For preformed CPAD,** technical feasibility has been demonstrated and one device (BD; Uniject™) is commercially available. Key technical considerations CPADs include stability, leakage, moisture vapor/gas barrier properties of materials, and flexibility and deformability properties of the CPAD material (i.e. squeezability).	**Low complexity**
	For BFS CPAD (pre-assembled and user-assembled), the device is still in the design phase and technical feasibility has yet to be demonstrated. Further design work and evaluation is needed to address issues previously identified with current prototypes including incorporation of an autodisable feature, fluid path leakage, and container squeezability. Concerns have also been raised with exposure to heat during the vaccine filling process of BFS containers several vaccines have been demonstrated to be stable when filled in BFS, including live attenuated rotavirus (6), live attenuated influenza (27), and respiratory syncytial virus vaccines (28). Studies would be required to show that the formulation was compatible with, and stable in the CPAD.	**Moderate complexity**
	For other CPADs, since they most closely resemble a traditional N&S, technical development is expected to be less complex. However, the one known device is still in the development phase. All chosen materials for the components are also known and accepted as primary packaging for biologics and pharmaceuticals.	**Low complexity**

[ss] *Survey carried out after DTWG telecons on CPADs held on October 17 and 18, 2019*

Indicator: Complexity of manufacturing the innovation

The WHO Delivery Technologies Working group,[tt] which is comprised of industry members and global health stakeholders, was invited to complete a survey following a consultation on CPADs. 12 member organizations responded to the survey and 9 member organizations responded to the question on manufacturing challenges. The following challenges were identified as the most important manufacturing challenges facing the development of CPADs (most frequently identified challenges first):

- Filling and sealing (6/9)
- Aseptic production (4/9)
- Quality control and inspection (4/9)
- Filling line capacity (3/9)

Score legend: ***Very high complexity:*** *Novel manufacturing processes not yet under development;* ***High complexity****: Novel manufacturing processes under development;* ***Moderate complexity****: Novel processes demonstrated at pilot scale ;* ***Low complexity****: Established manufacturing processes, but cannot leverage current capacity ;* ***No complexity:*** *Established manufacturing processes available at commercial scale and access to production facilities if relevant.*

Table 23

Vaccines	*How complex is the manufacturing process? (Specify if special materials are used)*	Overall score
All vaccines assessed	**For preformed CPAD,** the CPAD typically requires specialized filling equipment that will need to be purchased and validated by vaccine manufacturers requiring time and investment/resources as well as regulatory and WHO prequalification for each vaccine packaged in a CPAD. Vaccine manufacturers need to establish a new filling line to use Uniject™ but there are precedents for this being successful. Vaccine manufacturers will need to ensure that have a sufficient and guaranteed supply of preformed CPAD from the manufacturer for filling, and that supply of 'empty' devices is not a bottleneck	**Low complexity**
	For user assembled BFS CPADs, the CPAD container is manufactured using BFS–a continuous, automated and aseptic process which means the filling and finishing process is completed in one production line as opposed to separate manufacturing stages. BFS filling technology is widely available, but commercial-scale BFS facilities capable of filling biologic products are limited and capacity may need to be established.	**Low complexity**
	For pre-assembled BFS CPADs, custom automated assembly equipment is needed for aseptic assembly of the needle hub to the BFS container. This technology is in the process of being developed and will likely be specific to each CPAD design.	**Moderate complexity**
	For other type, the known device most closely resembles a traditional N&S; therefore, it has the potential to align with current prefilled syringe manufacturing facilities and to simplify training. Injecto is in the planning process of establishing the first validated industrial production line of the easyject device.	**Low complexity**

[tt] *Survey carried out after DTWG telecons on CPADs held on October 17 and 18, 2019*

Indicator: Robustness of the innovation-vaccine pipeline

Notes:

In table 24, it has been assumed throughout that:

- The developers of CPAD technology are (see phase I TN for details):
  - Preformed CPADs (e.g., Uniject): Becton Dickinson
  - BFS CPADs (pre- and user-assembled): ApiJect and Brevetti Angela.
  - Other CPAD types: Injecto.
- The 'suppliers/manufacturers of the vaccine' parameter focuses on WHO prequalified products (see WHO Prequalified Vaccines Database for details).[uu]
- Therefore, on a non-vaccine-specific basis, the number of developers would be assessed as 'moderately robust'. However, the pipeline is less robust when considered at the vaccine-specific level.
- Developers have been assessed as to whether or not they have a programme on the specific vaccine in question.
  - Where possible only products that are in 'full' preclinical development (i.e. with a clear path and intention to enter clinical trials) or clinical development have been listed.
  - In cases where studies have been published, and it is possible, but not clear whether the programme will progress to clinical studies, the key publications have been listed.
  - Exploratory, preclinical studies, especially by academic groups have not been included.

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

Table 24

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	**Preformed CPAD.** Tetanus toxoid vaccine (PT-Biofarma) in Uniject is WHO prequalified.[vv] Pentavalent (Crucell, Quinvaxem) was previously prequalified in Uniject, but was not made commercially available. **BFS (pre-assembled and user-assembled) subtype.** No known development programmes **For other CPAD types** No known development programmes.	There are multiple producers of liquid pentavalent or other DTP-containing vaccines. There are six WHO PQ manufacturers of pentavalent vaccine.

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

[vv] World Health Organization website. WHO Prequalified Vaccines page. Type: Tetanus toxoid. Commercial name: TT vaccine. *https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=16*

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
	Not robust	**Highly robust**
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	**For preformed CPAD (Uniject).** Hepatitis B vaccine (PT-Biofarma) in Uniject is WHO prequalified.[ww] **For BFS (pre-assembled and user-assembled) subtype:** No known development programmes. **For other types** No known development programmes.	There are multiple producers of hepatitis B vaccine; five different manufacturers have WHO PQ hepatitis B vaccine.
	Not robust	**Highly robust**
HPV (SDV or 2-dose vial)	**All CPAD types:** No known development programmes.	There are two manufacturers of three licensed HPV vaccines. Both have WHO PQ products. Several other manufacturers are developing HPV vaccines. UNICEF does not expect any new HPV vaccines to be WHO PQ'ed before 2021.[xx]
	No data	**Moderately robust**
Polio (IPV) (IM: Liquid SDV or 10-dose) (ID: Liquid SDV or 5-dose)	**All CPAD types:** No known development programmes.	There are several manufacturers of IPV and Sabin IPV vaccines. Four vaccine manufacturers produce WHO PQ IPV. There are however supply constraints[yy] and only two suppliers to UNICEF (29). New manufacturers of PQ IPV are expected to enter the market from 2020.[yy]
	No data	**Not robust**
Typhoid conjugate (Liquid SDV or 5-dose)	**All CPAD types:** No known development programmes.	There is only one manufacturer of typhoid conjugate vaccine that is WHO PQ.
	No data	**Not robust**
Ebola (rVSV-ZEBOV) (Liquid SDV)	**All CPAD types:** No known development programmes.	There is only one manufacturer of this particular candidate Ebola vaccine. Other Ebola vaccines have different characteristics.
	No data	**Not robust**
	All CPAD types: No known development programmes.	There is only one manufacturer of this particular candidate HIV vaccine. However, a similar candidate vaccine using a different virus vector and

[ww] World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial name: Hepatitis B Vaccine Recombinant. *https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=9*

[xx] UNICEF. *Human Papillomavirus Vaccine Supply and Demand Update.* Copenhagen: UNICEF; 2018. https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf. Accessed 21/10/2019.

[yy] UNICEF. *Inactivated Polio Vaccine: Supply Update.* Copenhagen: UNICEF; 2019. https://www.unicef.org/supply/files/ipv-inactivated-polio-vaccine-supply-update.pdf. Accessed 21/10/2019.

Vaccines	*Are there multiple developers of the technology?*	*Are there multiple suppliers/manufacturers of the vaccine?*
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)		recombinant protein in a heterologous prime-boost regimen is in late-stage trials.[zz]
	No data	**Not robust**
Influenza (pandemic) (VAL 506440) (Liquid SDV)	**All CPAD types:** No known development programmes.	There are a few developers of mRNA vaccines against pandemic flu: Moderna;[aaa] Curevac (universal flu vaccine)[bbb] and Vir (universal flu vaccine).[ccc] Other pandemic influenza vaccines have different characteristics.
	No data	**Moderately robust**

1.7 Criteria on commercial feasibility[ddd]

The WHO Delivery Technologies Working group[eee], which is comprised of industry members and global health stakeholders, was invited to complete a survey following a consultation on CPADs. 12 member organizations responded to the survey and 9 member organizations responded to the question on commercial feasibility challenges. The following challenges were identified as the most important commercial feasibility challenges facing the development of CPADs (most frequently identified challenges first):

- Cost/willingness to pay (8/9)
- Establishing partnerships to support development and commercialization (6/9)
- Investment in manufacturing scale up (6/9)

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

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

[bbb] Curevac website. Our Pipeline page. https://www.curevac.com/our-pipeline. Accessed 10/10/2019.9

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

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

[eee] *Survey carried out after DTWG telecons on CPADs held on October 17 and 18, 2019*

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

Summary feedback from country consultation:

- CPADs were ranked #5 useful innovation.
- Immunisation staff ranked CPADs as 5th out of 9 VIPS innovations that would have the greatest impact in helping address their immunisation programme's challenges and decision-makers 4th - based on weighted scores approach.
- Both groups mentioned the benefits of ease of use and logistics, reduced vaccine wastage and risk of contamination, saved health care worker time, improved delivery of the correct dose amount, increased acceptability due to less pain, improved waste disposal and possibility of reducing missed opportunities.
- Both groups also mentioned other benefits such potential of improving coverage, and ability to enable delivery outside health facility/less trained personnel.
- Both groups raised concerns about the impact on cold chain volume and overall cost, complexity of the technology use, time requirement of administering CPADs, packaging/integrity of the seals and waste disposal.
- Immunisation staff reported need for community sensitisation, risk of reduced acceptability and possibility of not delivering full dose as possible challenges.
- Decision makers were also concerned about the price per dose - though 21 out of 28 decision makers interviewed expressed interest in purchasing CPADs, 5 stated potential interest, 2 participants said they would not be interested.
- Decision makers provided feedback to combine CPADs with heat-stable vaccines.
- Immunisation staff suggested that CPADs should be combined with sharps injury prevention features.

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.*

[fff] *As part of VIPS phase II activities, in-depth country consultations were conducted in 6 countries (Ethiopia, Mozambique, Nepal, Senegal, Uganda, Nigeria) gathering information from X respondents representing immunisation staff and decision makers/purchasers on vaccine specific delivery challenges faced by immunization programme and which innovations they perceived could address these challenges and provide additional benefits. The interviews were conducted between November 2019 and February 2020 by PATH and CHAI using semi-structured and open-ended questions.*

Table 25

Vaccines	*Have countries expressed interest to suggest demand for the vaccine-innovation pairing and potential country uptake?*	Overall score
Hep B	Country demand may be limited since the per unit cost of vaccine in CPADs are likely higher than in multidose vials.[ggg] Governments occasionally changed policies to increase uptake. For example, the Indonesian Ministry of Health established a policy stating that all hepatitis B (birth dose) vaccine in Indonesia's public health programs is to be given with Uniject.[hhh]	**Mixed country interest**
All other applicable vaccines	No data are available on country interest to suggest demand for CPADs paired with all other applicable vaccines.	**No data**

Indicator: Potential breadth of the target market

Notes:

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

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

Table 26

Vaccines	*How broad is the potential target market?*	Overall score
Pentavalent (DT-containing) (Liquid SDV or 10-dose vial)	Global demand for wP containing pentavalent vaccines has been estimated to be between 300–350 M doses per year between 2015–2035[iii]. Most HICs and upper-middle income countries use aP, rather than wP-containing vaccines. This should not impact the feasibility of use with the innovation however, but this would need to be confirmed.	**Large**

[ggg] *Gilchrist S. Pull Mechanisms for Value-Added Technologies for Vaccines: An Evaluation of the Issues Influencing Vaccine Producer Willingness to Advance, Adopt, and Commercialize Value-Added Technologies for Vaccines for Low-Income and Lower-Middle-Income Country Markets. Seattle: PATH; 2009.*

[hhh] *PATH. A HealthTech Historical Profile: The Uniject Device. Seattle: PATH; 2005. https://path.azureedge.net/media/documents/TS_hthp_uniject.pdf*

[iii] *Gavi 2017. Pentavalent vaccine supply and procurement roadmap. Available at* https://www.gavi.org/sites/default/files/document/penta-roadmap-public-summarypdf.pdf- *Accessed 21/10/2019*

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 (30). Adoption of birth dose by national immunization programmes has not matched the implementation of 3-dose hepatitis B vaccination starting later in infancy (30).	**Large**
HPV (SDV or 2-dose vial)	The WHO recommends that all countries should introduce HPV vaccination into national immunization programmes (31). 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).[jjj] 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.[jjj]	**Large**
Polio (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.[kkk]	**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.[lll] 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 (32).	**Small / 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.[mmm] Presumably primarily for stockpiling to control outbreaks, (e.g., by ring vaccination with rVSVΔG-ZEBOV).	**Small**
HIV (ALVAC-HIV + bivalent Subtype C gp120) (Prime: lyo. SDV. Boost: liquid SDV)	The estimated market size for an HIV vaccine will depend on whether it prevents infection only, or also decrease viral load in those who acquire infection. One model study estimated that demand for vaccines that would prevent infection only was 22–61 million annual doses. Depending on the model inputs, HICs represented ~30% of the market size, but 70% of the value, whereas LICs were ~45% of the market size (17M doses), but only 10% of the value (33).	**Large**

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

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

[lll] Gavi. *TCV Supply and Procurement Roadmap* July 2018. https://www.gavi.org/sites/default/files/document/typhoid-conjugate-vaccine-roadmap--public-summarypdf.pdf. Accessed 11/10/2019.

[mmm] Gavi. *Ebola Vaccine Supply and Procurement Roadmap* March 2018. https://www.gavi.org/sites/default/files/document/ebola-roadmap---public-summarypdf.pdf. Accessed 11/10/2019.

Vaccines	*How broad is the potential target market?*	Overall score
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 (34). 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**

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

*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 (current presentations)	*Is there current donor/stakeholder support for the vaccine-innovation pairing?*	*Do partnerships exist between at least one of the technology developers and a vaccine manufacturer or have vaccine manufacturers expressed interest?*	Overall score
Pentavalent (Liquid SDV or 10-dose vial)	There has been interest and donor support for pentavalent vaccine in a CPAD in the past; the Gates Foundation supported PATH's efforts to assist a vaccine manufacturer with development of pentavalent vaccine in a CPAD, but there is no known current interest.	Quinvaxem (Crucell) was previously prequalified but was not made commercially available.	**Moderate interest**

[nnn] *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 (current presentations)	*Is there current donor/stakeholder support for the vaccine-innovation pairing?*	*Do partnerships exist between at least one of the technology developers and a vaccine manufacturer or have vaccine manufacturers expressed interest?*	Overall score
	Moderate interest	**Moderate interest**	
Hepatitis B (birth dose) (Liquid SDV or 10-dose MDV)	There has been interest from WHO, UNICEF, the US CDC, the Burnet Institute, and the Gates Foundation in expanding use of Hep B vaccine in Uniject for birth dose outreach. The Foundation also supported the development of Total Systems Effectiveness R&D Use Cases for HepB CPADs. However, no entities are currently providing sufficient support to bring new products to market or to expand Biofarma's product availability beyond their current markets (i.e., mostly the national market in Indonesia).	Hepatitis B vaccine (Biofarma) is WHO prequalified in Uniject.[ooo]	**Moderate interest**
	Moderate interest	**Moderate interest**	
All other applicable vaccines	There have been UNICEF tenders for vaccines in Uniject in the past, but none recently. Similarly, donors have not *fully* supported CPADs for a variety of reasons, including the higher per unit cost when compared to a standard syringe and multidose vial. The Bill & Melinda Gates Foundation is currently supporting the development of BFS CPADs that may be lower cost. There has been interest from WHO, UNICEF, and the Gates Foundation in tetanus-containing Uniject (though this is not a vaccine under evaluation by VIPS) and expanding use of Hep B Uniject for birth dose outreach. The Foundation also supported the development of Total Systems Effectiveness R&D Use Cases for tetanus toxoid and HepB CPADs.	No known partnerships	**Mixed interest**
	Moderate interest	**No interest**	

[ooo] World Health Organization website. WHO Prequalified Vaccines page. Type: Hepatitis B. Commercial name: Hepatitis B Vaccine Recombinant. *https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=9*

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	**For preformed CPAD,** Uniject™ was developed by PATH Seattle, WA, USA based on a concept licensed to PATH from Merck. PATH then worked with a private medical device packaging company called Horizon Medical, Inc. for piloting production and development of automated filling systems.[ppp] Later, the technology was transferred and licensed to BD, which currently manufactures and supplies the device to vaccine and pharmaceutical companies per the terms of their licensing agreement with PATH. Original Unject patents have expired, so development of alternative preformed CPAD technologies should not encounter blocking issues.	**No**
	For BFS (pre-assembled and user-assembled) and other type CPAD, there are no data as the products are still under development.	**No data**

SECTION FOUR: Summary

ABILITY OF THE INNOVATION TO ADDRESS IMMUNIZATION ISSUES

CPADs have several useful features including being prefilled, ready-to-use, and AD. They can potentially address several immunization challenges including: reduced acceptability due to painful administration; difficult preparation requiring trained personnel; vaccine wastage or missed opportunities due to MDV presentation; contamination risk due to use of multi-dose vial; needlestick injuries; and negative impact on the environment due to waste disposal practices.

It should be technically feasible to combine many of the VIPS priority vaccines (existing and pipeline) with CPADs, potentially all liquid injectable vaccines. However, they typically require specialized filling equipment. The innovation may be most useful with vaccines that would benefit from an easy-to-use single-dose presentation, for instance, for outreach settings.

[ppp] *PATH. A HealthTech Historical Profile: The Uniject Device. Seattle: PATH; 2005.* https://path.azureedge.net/media/documents/TS_hthp_uniject.pdf

SYNERGIES WITH OTHER VIPS INNOVATIONS

CPADs could be compatible with several other innovations under evaluation in VIPS:

- **Heat stable/CTC qualified vaccines**: If new liquid formulations with improved heat-stability are used in these devices, they could reduce vaccine wastage due to damage caused by accidental exposure to high temperatures. If these vaccines are also CTC qualified, they could lessen the cold chain requirements for storage and transport prior to administration and facilitate outreach.
- **Vaccine vial monitors with threshold indicators**: If the products are CTC qualified, they would also benefit from the application of a VVM-TI label to improve temperature monitoring during CTC use.
- **Freeze-damage resistant vaccines:** If the vaccine is freeze-sensitive, then a freeze resistant liquid formulation could help to prevent freeze damage and wastage due to suspected freeze damage. Single dose vaccine containers like CPADs are particularly susceptible to freeze damage.
- **AD sharps injury protection:** Sharps injury protection features could be added to the needles of these devices to protect health workers after injections are given.
- **Barcodes:** Lastly, barcodes on these devices would improve patient record keeping and inventory once health systems have the requisite equipment to use them.

References

(1) Capeding MR, Alberto E, Versteilen A, Rauscher M, Bagchi P, Palacios PI. Comparison of the immunogenicity and safety of pentavalent vaccine Quinvaxem in a compact prefilled auto-disabled (cPAD) injection system versus single-dose vials in healthy infants: a phase 3, open-label, randomized, parallel-group, non-inferiority study. Int J Infect Dis. 2016 May;46:71-8. doi: 10.1016/j.ijid.2016.02.015.

(2) Wang L, Li J, Chen H, Li F, Armstrong GL, Nelson C, et al. Hepatitis B vaccination of newborn infants in rural China: evaluation of a village-based, out of cold chain delivery strategy. *Bulletin of the World Health Organization*. 2007;85:688–694.

(3) Typhoid vaccines: WHO position paper – February 2008. *Weekly Epidemiological Record*. 2008;83(6):49-60. https://www.who.int/wer/2008/wer8306.pdf.

(4) Hennessey K, Mendoza-Aldana J, Bayutas B, Lorenzano-Mariano KM, Diostista S. Hepatitis B control in the World Health Organization's Western Pacific Region: targets, strategies, status. *Vaccine*. 2013;31S:J85–92.

(5) Sutanto A, Suarnawa I, Nelson C, Stewart T, Soewarso TI. Home delivery of heat-stable vaccines in Indonesia: outreach immunization with a prefilled, single-use injection device. *Bulletin of the World Health Organization*. 1999;77(2):119–126

(6) Glenton C, Khanna R, Morgan C, Nilsen ES. The effects, safety and acceptability of compact, pre-filled, autodisable injection devices when delivered by lay health workers. Tropical Medicine and International Health. 2013 Aug;18(8):1002–1016. doi: 10.1111/tmi.12126.

(7) Guillermet E, Dicko HM, N'Diaye M, Hane F, Ba SO, Gomis K, et al. Acceptability and feasibility of delivering pentavalent vaccines in a compact, prefilled, autodisable device in Vietnam and Senegal. *PLoS One*. 2015;10(7):e0132292.

(8) Kaplan I, Ross D, Hilton F, Morgenstern D, Wolter K. The role of training in effective simulated self-injection of subcutaneous depot medroxyprogesterone acetate: observations from a usability study. *Contraception*. 2016 Oct;94(4):314-20. doi: 10.1016/j.contraception.2016.05.006.

(9) Bahamondes L, Marchi NM, Nakagava HM, de Melo ML, Cristofoletti Mde L, Pellini E, Scozzafave RH, Petta C. Self-administration with Uniject of the once-a-month injectable contraceptive Cyclofem. *Contraception* 1997;56:310–304.

(10) Binanga A, Bertrand JT. Pilot Research as Advocacy: The Case of Sayana Press in Kinshasa, Democratic Republic of the Congo. *Glob Health Sci Pract*. 2016 Dec 28;4(4):542-551. doi: 10.9745/GHSP-D-16-00236.

(11) Typhoid vaccines: WHO position paper – February 2008. *Weekly Epidemiological Record*. 2008;83(6):49-60. *https://www.who.int/wer/2008/wer8306.pdf.*

(12) Quiroga R, Halkyer P, Gil F, Nelson C, Kristensen D. A prefilled injection device for outreach tetanus immunization by Bolivian traditional birth attendants. Rev Panam Salud Publica. 1998 Jul;4(1):20–25.

(13) Otto BF, Suarnawa IM, Stewart T, Nelson C, Ruff TA, Widjaya A, Maynard JE. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. *Vaccine*. 1999 Oct 14;18(5-6):498–502.

(14) Sedita J, Perrella S, Morio M, Berbari M, Hsu JS, Saxon E, Jarrahian C, Rein-Weston A, Zehrung D. Cost of goods sold and total cost of delivery for oral and parenteral vaccine packaging formats. *Vaccine*. 2018 Mar 14;36(12):1700–1709. doi: 10.1016/j.vaccine.2018.01.011.

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

(16) 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.

(17) PATH. *Programmatic and Human Factors Evaluation of Three Blow-Fill-Seal Parenteral Vaccine Container Designs*. Seattle: PATH; 2018. https://www.dcvmn.org/IMG/pdf/180331_rommelag_-_path_-_gates_foundation_grant_bfs_final_report_20180330_sm.pdf

(18) 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 Sep 28;30(44):6241–8.

(19) 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. doi:10.1001/jama.2011.407.

(20) 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. Doi:10.1016/S2214-109X(16)30075-4.

(21) 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. doi:10.1080/21645515.2017.1294294.

(22) Vaccines and vaccination against yellow fever. WHO position paper – June 2013. Wkly Epidemiol Rec 2013;88:269–83.

(23) 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. doi:10.1016/S0140-6736(18)31710-0.

(24) Medaglini D, Santoro F, Siegrist C-A. Correlates of vaccine-induced protective immunity against Ebola virus disease. Seminars in Immunology. 2018;39:65–72.

(25) 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. Doi:10.1016/S0140-6736(16)32621-6.

(26) 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. *Annual Review of Medicine*. 2015;66:423–37.

(27) Sheldon EA, Jeanfreau R, Sliman JA, Charenkavanich S, Rousculp MD, Dubovsky F, Mallory RM. Immunogenicity of a quadrivalent Ann Arbor strain live attenuated influenza vaccine delivered using a blow-fill-seal device in adults: a randomized, active-controlled study*. *Influenza Other Respir Viruses*. 2013 Nov;7(6):1142-50. doi: 10.1111/irv.12027.

(28) Lin YH, Orvisky E, Hau R, et al. Feasibility evaluation of blow fill seal process and compatibility with aluminum phosphate adjuvanted recombinant RSV F nanoparticle vaccine [poster online]. Presented at: 11th International Respiratory Syncytial Virus Symposium. Ashville, NC; 2017. https://novavax.com/download/files/posters/11th-International-RSV-Symposium/YHLin_RSV_2018_Poster_FINAL.pdf

(29) Sutter RW, Cochi SL. Inactivated Poliovirus Vaccine Supply Shortage: Is There Light at the End of the Tunnel? *Journal of Infectious Diseases*. 2019 Oct 8;220(10):1545–6.

(30) Hepatitis B vaccines: WHO position paper—July 2017. *Weekly Epidemiological Record*. 2017 Jul 7;92(27):369-392.

(31) Human papillomavirus vaccines: WHO position paper, May 2017. *Weekly Epidemiological Record*. 2017 May 19;92(19):241-268.

(32) 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. doi:10.1080/21645515.2017.1333681.

(33) 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 Jul 5;28(30):4786–97.

(34) McLean KA, Goldin S, Nannei C, Sparrow E, Torelli G. The 2015 global production capacity of seasonal and pandemic influenza vaccine. *Vaccine*. 2016 Oct 26;34(45):5410–3.