Intradermal (ID) syringes

(not including prefilled ID syringes or ID Disposable Syringe Jet Injectors)

Comparator: Bacille Calmette-Guerin (BCG) autodisable (AD) needle and syringe (N&S)[a], using Mantoux technique

Section 1: Summary of innovation

1.1 Examples of innovation types:

Syringe-adapter (without needle): ID adapter

Image source: (1)

Needle-hub: MicronJet 600

Image source: [b]

Syringe adapter with needle: Vax-ID (classified as a needle-hub in this assessment)

Image source: [c]

1.2. Description of innovation:

ID vaccination uses inexpensive and widely available BCG N&S. To achieve the correct depth of injection the needle is inserted at an acute angle to the skin to deposit the vaccine just below the surface (Mantoux technique). The volume administered is less than for subcutaneous (SC) or intramuscular (IM) injection, typically 0.05 ml or 0.1 ml. This technique is widely used in lower and middle income countries (LMICs) as BCG is given at birth to all infants in LMICs (2).

Relatively few vaccines are given ID compared with the IM and SC routes. In recent years, there has been interest in using the ID route with other vaccines because the epidermal and dermal layers of the skin are rich in immune cells, so delivery of vaccines to these sites could increase vaccine immunogenicity, resulting in the same immune response being induced with less antigen ('dose-sparing') (3). This can be important for vaccines that are supply-constrained, or expensive, or that have sub-optimal immunogenicity in hard-to-immunise subgroups. ID delivery does not result in dose-sparing for all vaccines however, and in some cases (e.g. yellow fever), dose-sparing is possible without changing the route of the injection (4).

Inactivated poliovirus vaccine (IPV) (5–7) and rabies virus vaccines (8), are administered ID to large numbers of people in some settings to take advantage of dose-sparing, and are given using the Mantoux technique. Experience with these vaccines has shown that it is feasible to implement an immunization campaign using BCG N&S to deliver ID IPV (9), and to switch from IM to ID administration of rabies vaccine for post-exposure prophylaxis (10).

Some researchers however consider the Mantoux technique to have several drawbacks including:

[a] The N&S used for ID vaccination is referred to using several names including: 1 ml, 0.1 ml, BCG, insulin or allergy syringes. For clarity, these are all referred to as BCG syringes in this report. The technique used for ID injection is referred to as the Mantoux technique.
[b] https://www.nanopass.com/technology/
[c] Vax-ID spec sheet https://novosanis.com/delivery-solutions/vax-id

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- The need for trained vaccinators and the perceived difficulty of the technique (1,9,11,12)
- Perception that incorrect administration can lead to adverse events (11) or reduced vaccine immunogenicity (13)
- Unacceptable pain on or after ID injection (14)

Consequently, a number of devices have been, or are being developed to improve the ease, accuracy and reproducibility of ID injections. These can be grouped into several sub-types:

- Prefilled syringes (not included in this technical note)
- Needle-hubs and syringe-adapter (both with ID needles), to be used with separate syringes. These are hubs or larger adapters that fit onto the end of a standard BCG or insulin syringe. They have an integrated short needle or needles (typically less than 1.5 mm) that only penetrate the skin to the depth of the dermis.
- Syringe-adapters (no needle); to fit separate syringes with needles, to facilitate ID injection. These devices fit a standard BCG or insulin syringe that already has a needle. They are a 'hockey-stick' shape and are designed to control the angle and depth of needle penetration.
- Field-filled ID syringes. These devices resemble a standard syringe but incorporate some form of needle (e.g. plastic needle) for filling and a short (less than 1.5 mm) needle for injection.

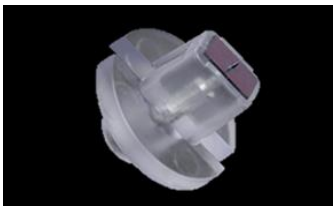
For this Technical Note, the assessment has been conducted by categorising the ID syringes into the following three subtypes: (1) needle-hubs, (2) adapters and (3) syringes.

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Bella-mu intradermic needle  	**Uneedle**, Enschede, The Netherlands.[e] **Status**: CE marked. Working towards 510K approval. The version with the 1.8 mm needle is currently available and used for cosmetic applications.[f] No partnerships or collaborations with vaccine companies are listed on their website.	**Syringe-hub** with single ID needle fabricated from silicon that enables a sharper point and smaller bevel than steel.[f] Two needle lengths in development: 1.4 and 1.8 mm. The 1.4 mm version is for vaccine use.[f] Dead-space has not been optimized yet, so is the same as a standard Luer lock needle.[f] The device is not autodisable (AD), but this could be considered in the future.[f] **Use:** Needle hub is fitted to a standard Luer-lock syringe (after filling); insert the needle perpendicular to the skin; inject.

[e] https://www.uneedle.com/home
[f] Teleconference with Gerd Velduis (and JH), 19 February 2019

Product name; Image	**Developer (place); website**	**Brief description, notes**
Image source: [d]		**Claims:** Needles are produced by 'innovative manufacturing processes', and are low cost.[d] **Device size**: "the same as any Luer-lock needle hub and determined by the size of the needle-shield." [f]
DebioJect™ (formerly NanoJect)   Image source: [g]	**Debiotech** Lausanne, Switzerland. [h] **Status**: CE marked in 2014.[i] No partnerships or collaborations with vaccine companies are listed on their website.	**Syringe-hub** with one or several hollow microneedles (MNs, 350 to 900 microns length), with a side protected delivery hole.[i,j] The MNs are produced by micro-electro mechanical systems (MEMS) technology.[i] The hubs can be attached to a syringe or to a 'reservoir' with a spring-powered inserter. The device is not AD. **Claims:** By placing the hole on the side of the needle at a precise depth, the skin can be punctured without coring and without removing any tissue. This minimises leakage and improves healing.[i] **Clinical studies, vaccines:** • Phase 1, rabies vaccine (15).
MicronJet 	**Nanopass Technologies Ltd,** Nes Ziona Israel.[l] **Status**: MicronJet 600 is registered in the US (11) with FDA clearance as an ID delivery device for substances approved for delivery below the	**Syringe-hub.** Sterile single-use 'hollow MN hub that can be attached to a Luer syringe following filling with a separate needle' (11). The MNs are 0.6 mm long, and 'are based on MEMS technology and are made of pure silicon crystal'.[s]

[d] https://www.uneedle.com/needle/bella-mu
[g] https://debiotech.com/file/pdf/news_Issue_49_Hi_Res_debioject.pdf
[h] https://debiotech.com/page/index.php?page=product_01&id=1&id_prod=47 Video is use: https://www.youtube.com/watch?v=CdK-Ljzzxwc
Factsheet: http://www.cea.fr/cea-tech/leti/PublishingImages/Materiels%20pour%20LID/Debiotech.pdf
https://www.electronicsweekly.com/news/design/silicon-needle-injects-drugs-without-pain-2017-07/
https://www.debiotech.com/file/pdf/news_PR2014MDEA_silverAward.pdf
[i] https://www.debiotech.com/page/index.php?page=product_01&id=1&id_prod=47
[j] http://www.ondrugdelivery.com/publications/Injectable%20Formulations%202012/Debiotech.pdf
[l] https://www.nanopass.com
[s] https://www.nanopass.com/technology/

Product name; Image	**Developer (place); website**	**Brief description, notes**
Image source: [k]	surface of the skin'[m]; 'also CE certified'; ISO 13485 certified.[l] Licensed for marketing in China, Brazil, Kong-Kong, Korea, Russia, Canada and Israel. 'Has been used for 264,000 injections to approximately 4,900 patients in more than 45 completed and ongoing clinical trials.'[n] **Partnerships**: 2017: IDRI for RNA Zika vaccine ID;[o] . 2016: West Pharmaceutical services. Strategic investment by West in Nanopass.[p] 2009: IDRI for use with vaccines, including H5-VLP influenza [q]; and skin tests (they are developing a *M. leprae* test based on PPD)[r]	The device (i.e. the hub) is not AD. It would need to be paired with an AD syringe with removable needle (for filling) and be redesigned to make the hub AD.[t] Nanopass doesn't have plans to make an AD version at present but would consider this if funding was available.[u] **Use:** Apply hub to syringe after filling; need to have blue line facing the vaccinator, hold at 45°, inject on deltoid or forearm, until see wheal.[v] **Clinical studies, vaccines:** • Influenza H5N1 VLP (16); • Influenza, seasonal (Inflexal) (17) • Zoster vaccine (Zostavax), (18) • IPV (19,20) • Influenza, seasonal (21–23) **Ongoing clinical trials, vaccines:** • Zostavax, transplant donors (phase 1);[w] • HepB vaccine, Sci-B-Vac[x] (phase 2/3);[y] • Pandemic flu (phase 1).[z] Clinical studies have been completed or are ongoing for allergy, oncology, and autoimmunity applications.[n]

[k] https://d2cax41o7ahm5l.cloudfront.net/cs/speaker-pdfs/brian-k-meyer-merck-co-usa.pdf
[m] https://www.accessdata.fda.gov/cdrh_docs/pdf9/K092746.pdf
[n] https://www.nanopass.com/clinical/
[o] https://www.nanopass.com/idri-nanopass-sign-agreement-to-develop-an-intradermal-rvrna-based-zika-virus-vaccine/
[p] https://www.nanopass.com/west-makes-investment-in-nanopass-technologies-2/
[q] https://clinicaltrials.gov/ct2/show/NCT01657929?term=IDRI&rank=5
[r] http://www.idri.org/idri-use-nanopass-micorneedle-technology/
[t] Courtney Jarrahian, PATH. Personal communication (email), 14 February 2019
[u] Yotam Levin, Nanopass. Personal communication (email), 27 February 2019
[v] https://www.nanopass.com/product/
[w] https://clinicaltrials.gov/ct2/show/NCT02329457?term=02329457&rank=1
[x] https://www.vbivaccines.com/sci-b-vac/
[y] https://clinicaltrials.gov/ct2/show/NCT03307902
[z] https://www.clinicaltrials.gov/ct2/show/NCT03472976

Product name; Image	**Developer (place); website**	**Brief description, notes**
Microdermics  Image source: [aa]	**Microdermics**, Vancouver, BC, Canada.[aa] May 2017. Strategic partnership with Vetter.[bb]	**Syringe-hub.** A variety of formats. Most are attachable adapters with hollow metallic microneedles. It is not known whether these are AD or not. Use a mould for MN fabrication on metallic sheets which speeds up production time.[cc] Tested for drug applications to date and will investigate vaccines in the future.[cc]
ID Adapter  Image source: [dd]	**West Pharmaceutical Services**, Exton, PA, USA.[dd] Originally developed by SID Technologies, Newton, PA, USA and PATH. This was designed to work with one specific type of AD syringe (Helm Medical) (1). A Helm Medical 0.1 ml AD syringe is World Health Organization (WHO) prequalified; [ee] Helm Medical is now part of Sanavita (Germany). **Status**: The ID adapter has FDA 510K and CE Mark clearance and is 'marketed in USA and Europe' by West Pharma (1) and globally by Helm Medical. **Global health use**: In November 2015, 'the Global Polio Eradication Initiative (GPEI) endorsed the procurement of the ID adapter	**Syringe-adapter.** A polycarbonate, sterile, disposable, injection-moulded, injection aid that snaps on (sideways) on the end of a 1 ml or 0.1 ml AD fixed needle syringe with 12.5 mm needle, to guide 'the angle and limiting the depth of needle insertion'.[gg] It is intended for one-time use only, as it could be contaminated by bodily fluids. It could however, be removed from the syringe and reused (1). SID Technologies, West, and PATH previously explored the feasibility of ID adapter designs that prevent the reuse of the adapter (24). Designs have not been identified to date that are likely to meet AD standards for WHO prequalification. [hh] **Use:** The AD syringe is filled, and then the ID adapter fitted. The instructions include the need to make sure the needle is straight in the adapter, also need to wait 3–5

[aa] https://www.microdermics.com
[bb] https://www.microdermics.com/news/2017/5/30/microdermics-enters-strategic-agreement-with-vetter-pharma
[cc] https://drug-dev.com/intradermal-delivery-new-technology-brings-simplicity-scalability-to-intradermal-drug-delivery/
[dd] https://www.westpharma.com
[ee] http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=37
[gg] http://investor.westpharma.com/news-releases/news-release-details/study-demonstrates-benefit-wests-id-adapter-improving-0
[hh] Courtney Jarrahian, PATH. Personal communication (email), 14 February 2019.

Product name; Image	Developer (place); website	Brief description, notes
	produced by West Pharmaceuticals and the Tropis (PharmaJet) disposable-syringe jet injector for the WHO IPV stockpile for polio outbreak response' (11). A stock of 4.1 million 'West ID adapters with Helm AD syringe' has been purchased by GPEI for use with ID IPV.[ff]	seconds after injection before removing the needle slowly [ii]. **Clinical trials, vaccines:** • IPV, field-study, Pakistan (9) • IPV, campaign trial, Gambia[jj] No data with vaccines other than IPV (11). **Clinical studies, no vaccines** • Saline delivery to assess ID injection quality (1,24). **Packaging:** The ID adapter has been produced to date in a rigid, form-fill-seal package and has not been optimized for mass production. Future optimized packaging strategies to reduce costs and storage volume could include co-packaging with the AD syringe in a soft blister.
Vax-ID  Image source: [kk]	**Novosanis**, Wijnegem, Belgium.[ll] **Status**: Started development in 2010. Currently, 'in development stage'. Patent in US, China and Hong Kong. Currently seeking CE mark approval for field-filled version. No partnerships or collaborations with vaccine companies are listed on their website but the company has ongoing collaborations with vaccine manufacturers.[mm]	**Syringe adapter (field-filled) and pre-filled ID syringe.** The prefilled syringe is not reviewed in this technical note)**.** The field-filled device is a large 'adapter or hub' (medical grade polypropylene) that fits onto a syringe. The current version will be re-designed to be smaller. Contains a 31G double-pointed needle; several needle lengths (0.6 – 2.0 mm length) and gauges are being developed.[mm] Because of its design it is reviewed as a 'needle-hub' in this assessment. **Use.** Fill syringe and remove needle. Fit Vax-ID and activate by rotating the foot; this controls depth and force of

[ff] Jarrahian C. Innovations in technologies and tools for delivery and evaluation of fIPV. Presentation 8 June 2018.
[ii] https://www.youtube.com/watch?v=8GNdiWR69uY
[jj] https://clinicaltrials.gov/ct2/show/NCT02967783
[kk] Vax-ID spec sheet https://novosanis.com/delivery-solutions/vax-id
[ll] https://novosanis.com
[mm] Teleconference with Timothi Van Mulder (and JH), 22 February 2019

Product name; Image	Developer (place); website	Brief description, notes
		injection, ensuring sufficient force is applied. (25).[nn] Penetration depth of needle for different age-groups was based was based on a survey of skin thickness (26). The device is not AD. The foot can be removed and re-used. This will be redesigned, including to incorporate automatically retracting needle.[mm] To minimise dead-space, a 'low dead-space' syringe (e.g. from B-Braun) is used in which the plunger fills some of the space within the Luer fitting.[mm] **Clinical trials, vaccines:** • Phase 1, hepatitis B vaccine (25). • Ongoing undisclosed trials comparing Vax-ID with Mantoux. [nn] **Device size, field-filled adapter:** *Current version*: 50 x 18 mm approx. *Next generation:* 20 x 12 mm approx. [nn]
Intradermal safety device (IDSD)  Image source: [oo]	**Star Syringe,** Pippingford, UK.[pp] **Status:** Developed as far as prototypes for use in clinical studies. Not listed on developer's website. Development on hold but could be re-started if funding was available.[qq] No partnerships or collaborations with vaccine companies are listed on their website.	**ID syringe,** field-filled. AD syringe with a plastic-spike for filling and a separate hub with an ID needle that fits over the plastic spike to minimise dead-space. Two needle lengths, 1.2 and 1.5 mm. Narrow barrel for accurate measuring of the dose. **Use:** Uncap the plastic spike; draw dose into the syringe; place the needle-hub over the plastic spike and lock in position; flip back the needle cover; inject perpendicular to the arm; recover needle and discard.

[nn] https://novosanis.com/delivery-solutions/vax-id
[oo] https://www.cugh.org/sites/default/files/TS01.2_Zehrung.D.pdf
[pp] https://www.starsyringe.com
[qq] Graham Madin, Star Syringe. Personal communication (email), 4 March 2019

Product name; Image	**Developer (place); website**	**Brief description, notes**
		'Meets or exceeds WHO global public health standards for AD technology and US standards for needle-stick protection' (9). **Clinical trials, vaccines** • IPV, field-study, Pakistan (9) **Clinical usability studies,** no vaccine. • Prototype devices NCT02556047 [rr].

[rr] https://www.clinicaltrials.gov/ct2/show/NCT02556047

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- **The shorter, less obvious needle may improve acceptability** for caregivers and recipients.
- There are **limited data indicating less pain or greater acceptability** for specific devices.
- The devices are designed to improve ease of use and therefore their use could potentially expand the number of HCWs available to deliver ID injections in a campaign setting.

2.2 Key challenges:

- While the devices are designed to **improve the ease of use and accuracy of ID injections** potentially improving immunization effectiveness, the existing data do not verify this**.**
- **Most devices lack an AD feature.**
- There is **limited applicability** as there are relatively few vaccines that are delivered ID (BCG, IPV, rabies), though the ID route might be used with more vaccines in the future.
- The devices require **additional components** and have **more complex preparation steps** increasing health care worker preparation time and risk of contamination.

2.3 Additional important information:

- Some ID devices have received **regulatory clearance as medical devices** e.g. 510(k) in the USA or CE mark in Europe. The devices are **not combination products** and should not need to be approved with a specific vaccine from a named manufacturer.
- All ID syringes should facilitate **dose-sparing** of vaccine, as does the comparator.
- Most of the devices are **not AD** and are unlikely to meet any future WHO Performance, Quality, and Safety (PQS) performance specification requirements.
- Some devices **have more dead-space** than the comparator, **increasing vaccine wastage.**
- **Timeline to availability**: At least one device has been discontinued. Several of the others are very early in development. Most/all of the devices in development are **not AD.** One ID adapter and one needle-hub are available commercially, but are **not AD.**
- **Clinical data**: While clinical studies are generally not required for ID device regulatory clearance, it is likely that stakeholders and purchasers will **expect data from non-inferiority trials** with the vaccine to be used prior to programmatic introduction for ID vaccine delivery**.**
- Changing to the ID route to facilitate dose-sparing can result in **higher vaccine wastage rates** if the vial-size is not changed accordingly to reduce the number of possible doses per vial (this also applies to the comparator).
- All the devices are highly likely to be **more expensive** than the comparator, particularly when first introduced. Several of the devices are used with the comparator or with another injection syringe, so will be an **additional cost**.

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SECTION 3: Evaluation criteria

3.1 Health impact criteria

Indicator: Ability of the vaccine presentation to withstand heat exposure

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

Table 2.

Ability of the vaccine presentation to withstand heat exposure	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	Neutral	Neutral	The innovations are intended to be used with current vaccine formulations and presentations. They do not have any features that will improve (or reduce) heat stability.
		Neutral	*Neutral*	*Neutral*	***No difference** to the comparator for all subtypes*

Indicator: Ability of the vaccine presentation to withstand freeze exposure

*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 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral	Neutral	Neutral	The innovations are intended to be used with current vaccine formulations and presentations. They do not have any features that will improve (or reduce) freeze resistance.

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Neutral	*Neutral*	*Neutral*	***No difference*** *to the comparator for all subtypes*

3.2 Coverage and equity criteria

Indicator: Ease of use[ss]

*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 4.

Ease of use	**Parameters to measure against a comparator**	**ID needle-hub Sub-type**	**ID adapter Sub-type**	**ID syringes sub-type**	**Assessment**
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation avoid reconstitution and is that an improvement?**	Neutral	Neutral	Neutral	The innovations are intended to be used with current vaccine formulations and presentations.
	Does the innovation require fewer vaccine product components?	Worse	Worse	Worse	All the device formats have more components than the comparator; e.g. additional needles for filling, or separate syringe hubs, or separate adapters for fitting onto a syringe.
	[tt]**Does the innovation require additional components or equipment (such as scanners or label readers)?**	NA	NA	NA	

[ss] Ease of use can prevent missed opportunities resulting from the complexity of preparation and administration procedures. It could also impact the ability for lesser trained personnel to administer the vaccine (incl. self-administration). It can be assessed based on usability data from field studies (or based on design of innovation if field studies not available).
[tt] This parameter is only assessed for RFID/barcodes, for all other innovations it is not applicable (N/A).

Ease of use • *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Parameters to measure against a comparator**	**ID needle-hub Sub-type**	**ID adapter Sub-type**	**ID syringes sub-type**	**Assessment**
	Does the innovation require fewer preparation steps and less complex preparation steps?	Worse	Worse	Worse	All the formats require more steps than the comparator. In most cases this is fitting an adapter or hub onto a syringe.
	Does the innovation improve dose control?	Neutral	Neutral	Neutral	The devices are all syringe-based and not prefilled. Therefore, no improvement in dose-control over the comparator is expected. It is assumed that any ID syringe used for immunization will be fixed-dose (PQ requirement). Some AD ID syringes are fixed-dose, and give more accurate dose delivery than variable-dose syringes (27). The ID adapters and needle-hubs should be compatible with fixed-dose BCG syringes.
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	Neutral	There are no data to suggest that any of the devices significantly improve the immunogenicity of ID delivery relative to the comparator (9,13,15,25). The quality of ID injections is usually assessed by bleb-size sometimes combined with a measure of vaccine 'leakage'. One study with the ID adapter found 71% injections produced blebs, vs. 44% with the comparator (24). An earlier study however found that approximately 10% of injection attempts with ID adapters failed to penetrate the skin (1). A study in pigs reported similar accuracy for the ID adapter and comparator (BCG N&S) (28). A study with the IDSD found that it gave significantly fewer 'successful' injections than the comparator BCG N&S (9). Immunogenicity might not be related to bleb size and injection site leakage however. A correlation between bleb

					size and immune response was reported in one study (13). Another found that the IDSD gave a lower frequency of blebs and induced lower immune responses, but this could have been due to incomplete delivery of the dose (9). Other studies have not found a correlation between size of bleb and immunogenicity (12,22).
		Worse	*Worse*	*Worse*	***Worse*** *than the comparator for all sub-types*

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

*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 5.

Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • *Assessment of the potential to reduce stock outs based on the innovation's features*	**Parameters to measure against a comparator**	**ID needle-hub Sub-type**	**ID adapter Sub-type**	**ID syringes sub-type**	**Assessment**
	Does the innovation require fewer components?	Worse	Worse	Worse	All the formats of ID syringe have more components than the comparator; e.g. additional needles for filling, or separate syringe hubs, or separate adapters for fitting onto a syringe.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	Neutral	None of the devices have any features that would facilitate labelling or product tracking, similar to the comparator.

Worse	*Worse*	*Worse*	***Worse*** *than the comparator for all sub-types*

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

*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 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Parameters to measure against a comparator**	**ID needle-hub Sub-type**	**ID adapter Sub-type**	**ID syringes sub-type**	**Assessment**
	Painful or not painful	Better	No data	Better	ID injections are generally perceived as painful (14). There are few data however on pain felt with the innovations relative to the BCG N&S comparator. No difference in pain scores with the device vs the comparator when syringe adapter with needle (Vax-ID) was used to deliver a hepatitis B vaccine (25). Less pain at needle insertion and vaccine injection for a needle hub (Debioject) compared with ID N&S (15). There was less crying by infants with the IDSD compared with BCG N&S (9). The MicronJet600 needle hub is claimed to be less painful than BCG N&S, but the only data comparing the two devices are for tuberculin skin testing rather than vaccine delivery. In this case, the Micronjet was significantly less painful than the comparator (29). Although the data suggests the score could be better or neutral, we have used better for the final scoring of the indicator.

	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Perception of ease of administration (i.e. convenience for the vaccinees/ caregivers)**	No data	No data	Better	Star IDSD was preferred by caregivers because their children cried less (9). It is not clear whether this could be attributed to less pain or perceived ease of the process. There are no data from any of the studies on the vaccinees' perception of ease of administration.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers				
		Better	*No data*	*Better*	***Better*** *(taking the optimistic view) for both ID needle-hub and syringe sub-types* ***No data*** *available for ID adapter*

3.3 Safety criteria

Indicator: Likelihood of contamination

*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.*

Category: *Delivery technology (not prefilled)*

Innovation: *ID syringes*

Comparator: *BCG AD N&S, using Mantoux technique*

Table 7.

Likelihood of contamination • *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?	Neutral	Neutral	Neutral	None of the innovations remove the need for reconstitution.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Worse	Worse	Worse	All of the devices, with the exception of the ID adapter, require the needle used for filling the device to be discarded and replaced with a new hub with the mini-needle, or for the syringe to be inserted into an injection device. The ID adapter has to be fitted to the syringe after filling. These extra steps, close to the needle and open end of the syringe increase the risk of contamination.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Worse	Worse	Worse	All of the innovations involve additional steps relative to the comparator; either replacing the filling needle with a new hub or fitting the adapter.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Worse	Worse	Worse	Only the IDSD and the non-commercialised AD version of the ID adapter are AD. As such all versions of the innovation in development increase the potential for re-use relative to the comparator.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Neutral	Neutral	No non-sterile components are involved in the use of the innovation or the comparator.
		Worse	*Worse*	*Worse*	***Worse*** *than the comparator for all sub-types*

Indicator: Likelihood of needle stick injury

*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.

Likelihood of needle stick injury	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Worse	Neutral	Neutral	None of the innovations reduce the number of sharps. With the exception of the ID adapter and IDSD syringe, the needle hub subtype involves more sharps (one needle for filling and one for injection) than the comparator.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Worse	Neutral	Neutral	All the innovations involve sharps, either in the ID-needle hub and ID syringe, of in the case of the ID adapter, the needle on the BCG syringe. In some cases, the innovations require more needles than the comparator as in the case of ID needle hubs which require an extra needle (one needle for filling the syringe plus the micro needle on the hub for the actual injection (see row above).
	Does the innovation include an auto disable feature and is that better than the comparator?	Worse	Worse	Neutral	The ID hub designs (Micronjet, Bella-mu), do not have AD features.[uu],[vv] The version of the ID adapter subtype that is assessed for this parameter does not have an AD feature. Some of the innovations include AD features: the ID adapter (syringe component only); Vax-ID (syringe component only; and Star IDSD.

[uu] Teleconference with Gerd Velduis (and JH), 19 February 2019
[vv] Yotam Levin, Nanopass. Personal communication (email), 27 February 2019

Likelihood of needle stick injury • *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Parameters to measure against a comparator**	**ID needle-hub Sub-type**	**ID adapter Sub-type**	**ID syringes sub-type**	**Assessment**
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Neutral	Neutral	The comparator does not currently have a SIP, although they could be fitted. None of the innovations include a SIP.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Neutral	Neutral	Some of the devices might reduce the risk of injury by virtue of their short needle length (1–1.5 mm) or partial coverage of the needle (eg, ID adapter), but this is only theoretical. There are no data on this point.
		Wore	*Worse*	*Neutral*	***Worse*** *for both ID needle hub and ID adapter* ***No difference*** *to ID syringes*

3.4 Economic costs criteria

Indicator: Total economic cost of storage and transportation of commodities per dose[ww]

*Legend: Dark Green: **Considerably better** than the comparator: Reduces the volume per dose for applicable parameters; Green: **Better** than the comparator: Reduces the volume per dose for either of the applicable parameter, and there is no difference for the other; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the volume for one of the parameter, and increases the volume for the other parameter compared to the comparator; Red: **Worse** than the comparator: Increases the volume per dose for either of the applicable parameters, and there is no difference for the other; Dark Red: **Considerably worse** than the comparator: Increases the volume per dose for both parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[ww] The assessment of the indicator is volume-related and builds upon PATH's VTIA analysis. A directional estimation is made at this stage, and a better evaluation will be done in Phase II with more antigen-specific data.

Table 9.

Total economic cost of storage and transportation of commodities per dose	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Worse	Neutral	Neutral	Hubs that fit onto a BCG syringe are likely to have a larger dead-space relative to a BCG syringe with a fixed needle. Consequently, fewer doses will be obtained from a vial, increasing vaccine purchase volumes (and therefore cold-chain volume) by 30-40% (27). This is not a consideration for the ID adapter and ID syringe. For these two innovations there is no impact on cold chain volume since for all ID-enabling innovations, none of the components are stored together with the vaccine vial in the cold chain.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Worse	Neutral	Neutral	All of the devices (except the IDSD) are additional components to be used in conjunction with the comparator or another syringe. The packaged volume of the comparator is 37cm^3. [xx] Using the ID needle hub attached to the BCG syringe would increase the volume stored and transported out of the cold chain. The volume of the 0.1 ml Helm syringe is approximately 30 cm^3. [yy] The additional volume of the ID adapter would be small and hence the total volume of the Helm syringe with ID adapter would be smaller than the comparator, but only if an optimized co-packaging approach was developed (hence the neutral score) We do not have information on the volume of the ID syringe and assume that it would be the same size as the comparator.

[xx] http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/LinkPDF.aspx?UniqueID=bde91130-e9bf-46b8-b9a2-84c6ade326e9&TipoDoc=DataSheet&ID=0
[yy] http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/LinkPDF.aspx?UniqueID=f80a6583-ef0b-4c8a-9e95-95e923ea024b&TipoDoc=DataSheet&ID=0

Considerably Worse	*Neutral*	*Neutral*	***Considerably*** *worse for ID needle-hub* ***No difference*** *for ID adapter and ID syringe*

Indicator: Total economic cost of the time spent by staff per dose

*Legend: Dark Green: **Considerably better** than the comparator: Reduces time for all applicable parameters; Green: **Better** than the comparator: Reduces time for either, and there is no difference for the other one; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the time for one of the parameters, and increases the time for the other parameter; Red: **Worse** than the comparator: Increases the time for either of the applicable parameters; and there is no difference for the other one; Dark Red: **Considerably worse** than the comparator: Increases time for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 11.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Neutral	Neutral	Neutral	The injection time has been described as being perceived as faster for the Vax-ID than N&S, but the difference in time for preparation and delivery was not recorded (14). In a feasibility study in Pakistan, the IDSD was found to be the fastest compared with the ID adapter or BCG syringe. The ID adapter was the preferred device overall however (9). Because of the lack of data, we score them as not different from the comparator.
	Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Neutral	Neutral	ID syringes have no attributes that save time for staff involved in stock management.

Neutral	*Neutral*	*Neutral*	***No difference*** *to the comparator for all sub-type*

VIPS is a Vaccine Alliance project from Gavi, World Health Organization, Bill & Melinda Gates Foundation, PATH and UNICEF

Indicator: Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)

*Legend: White: **Neutral**: NO there are no one-time/upfront or recurrent costs and this is not different than the comparator; Red: **Worse** than the comparator: YES there are one-time/upfront or recurrent costs.*

Table 11.

Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)	Parameters to measure against a comparator	ID needle-hub Sub-type	ID adapter Sub-type	ID syringes sub-type	Assessment
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	Neutral	Neutral	Similar to the comparator, there are no upfront or recurrent costs required with this innovation (other than training costs which would be required with any innovation).
		Neutral	*Neutral*	*Neutral*	***No difference** to the comparator for all sub-types*

3.5 Secondary criteria on potential breadth of innovation use

Indicator: Applicability of innovation to one or several types of vaccines

Table 12.

Applicability of innovation to one or several types of vaccines *To what types of vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could be applied to any vaccine that can be delivered intradermally. Examples of currently available vaccines that have been demonstrated to be compatible with ID delivery include: BCG, rabies, yellow fever, meningococcal conjugate vaccines and IPV. The live recombinant BCG 'next-generation' TB vaccine should also be suitable. The innovation may be most relevant as a dose-sparing strategy, to reduce the impact of supply or cost constraints.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate vaccine combination *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	No. ID syringes do not have any features that facilitate novel combinations.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	The majority of the data has come from manufacturers' websites or presentations. For some of the devices there are one or two peer-reviewed studies that include some information on usability, although these usually did not include the comparator used in this Technical Note. This has been combined with expert opinion.
Inconsistency of results	There are too few comparable studies to assess inconsistency of results.
Indirectness of comparison • *Indicate the setting in which the study was conducted (low, middle or high income setting);* • *Comment if the data is on non-vaccine application of the innovation*	All the data assessed has been for vaccine applications

Overall assessment:	*Low to Moderate*	*Some ID syringes are at a very early stage of development, and the only available data are manufacturers' claims. The most advanced devices have been used in a small number of feasibility studies.*

4.2 List of technical experts, manufacturers and/or technology developers interviewed for inputs:

Table 15.

Expert/type	Organisation/contact details	Notes
Paul Mallins	WHO PQ mallinsp@who.int	Telecon on 17 December 2018.

Expert/type	Organisation/contact details	Notes
Gerd Velduis, CBDO, Business Development and General Management	U-Needle BV, Enschede, The Netherlands www.uneedle.com gerd.veldhuis@uneedle.com	Telecon on 19 February 2019
Timothi Van Mulder	Novosanis, Wijnegem, Belgium www.novosanis.com timothy.vanmulder@novosanis.com	Telecon on 22 February 2019
Contacted via website	Microdermics, Vancouver, BC, Canada www.microdermics.com	JH sent emails on 15 February and 21 February 2019. No reply
Paul Vescovo	Debiotech, Lausanne, Switzerland www.debiotech.com p.vescovo@debiotech.com	JH sent emails on 15 February and 21 February 2019. No reply
Yotam Levin, CEO	Nanopass, Nes Ziona, Israel www.nanopass.com yotam@nanopass.com	JH sent email, 27 February 2019. Reply 27 February 2019
Graham Madin	Star Syringe, Pippingford, UK www.starsyringe.com grahammadin@mac.com	JH sent email, 1 March 2019. Reply 4 March 2019

4.3 List of technical experts, manufacturers and/or technology developers that have reviewed and provided feedback/input to the technical notes (TN):

Table 16.

Reviewers	Organisation/contact details	Notes
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Developed TN
PATH Medical Device and Health Technology Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH dkristensen@path.org	Reviewed TN

Reviewers	Organisation/contact details	Notes
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Reviewed TN

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