Programmatic and human factors evaluation of three blow-fill-seal parenteral vaccine container designs

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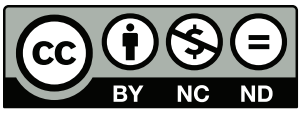

All photos in this report are by PATH.

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Annex list

This report, *Programmatic and human factors evaluation of three blow-fill-seal parenteral vaccine container designs*, contains the following annex:

Annex: Personas

- 1.1: Nursing officer persona
- 1.2: District EPI officer persona
- 1.3: National EPI program officer persona

Abbreviations

AD	autodisable
BCG	bacillus Calmette-Guérin
BFS	blow-fill-seal
bOPV	bivalent oral polio vaccine
CPAD	compact, prefilled, autodisable
DPC	dose per container
DTP	diphtheria-tetanus-pertussis
DTP3	third dose of diphtheria-tetanus-pertussis vaccine
DTP-HepB-Hib	diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenza*e type b
EPI	Expanded Programme on Immunization
FGD	focus group discussion
Gavi	Gavi, the Vaccine Alliance
GOU	Government of Uganda
HCW	health care worker
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
IPV	inactivated polio vaccine
ISO	International Organization for Standardization
JE	Japanese encephalitis
LMIC	low- and middle-income country
MMD	multi-monodose
MOH	Ministry of Health
MR	measles-rubella
NA	not applicable
NEPI	National Expanded Program on Immunization (of Vietnam)
OPV	oral polio vaccine
PCV	pneumococcal conjugate vaccine
RUP	reuse prevention
TT	tetanus toxoid
UNEPI	Uganda National Expanded Program on Immunisation
UNICEF	United Nations Children's Fund
VVM	vaccine vial monitor
WHO	World Health Organization

Background

Vaccines save millions of lives each year and are among the most cost-effective health interventions that have been developed. However, vaccines can be cost and price sensitive for low- and middle-income countries (LMICs), especially given the other cost and implementation challenges they face. In low-resource settings, vaccines are typically packaged and supplied in multidose glass ampoules and vials, and there is limited availability and access to low cost single-dose presentations that are programmatically suitable for use. When providing routine immunization services, health care workers (HCWs) may feel pressure to maximize the use of vaccine doses in multidose containers and may, therefore, be reluctant to open a vial if only a few eligible children show up at an immunization session.[1,2] This may negatively impact coverage and result in high immunization dropout rates, especially when using large, multidose vial presentations (e.g., greater than five doses per container [DPCs]) and when working to access hard-to-reach populations. Multidose vials may come with increased risk of contamination and adverse events. In comparison, smaller-dose vials may reduce wastage of open vials of vaccine, increase access, and reduce adverse events caused by contamination. However, the benefits of smaller-dose vials come at a higher vaccine price per dose. Additionally, smaller-dose vials can negatively impact cold chain storage and distribution capacity. Therefore, alternative packaging and delivery options for single-dose presentations are being evaluated that could minimize costs of manufacturing, transport, and storage, thus reducing the cost of vaccine delivery in LMICs.

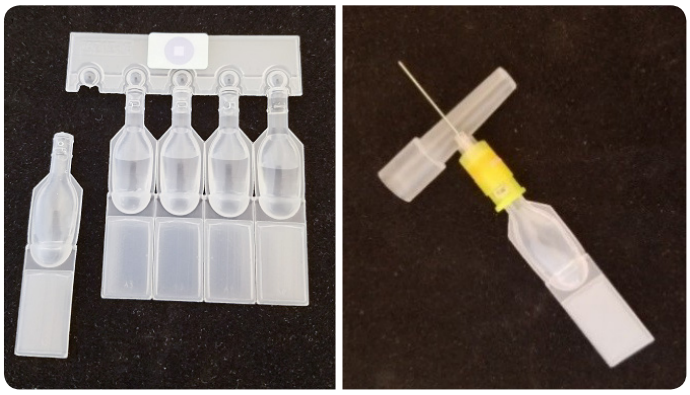
"Blow-fill-seal" (BFS) is a manufacturing process and packaging format platform widely used in packaging and delivery of aseptic pharmaceutical products, but the manufacturing process has not yet been validated for packaging and delivery of parenteral vaccines. BFS manufacturing offers flexibility in container and integrated-closure design that can be customized to attain a desired product presentation. The US Food and Drug Administration guidance on *Applying Human Factors and Usability Engineering to Medical Devices* states that assessments should be conducted to "demonstrate that the device can be used by the intended users without serious use errors or problems, for the intended uses and under the expected use conditions."[3] An evaluation conducted in the target environments of use is a recommended best practice. In addition to evaluating prototypes via a heuristics evaluation and bench testing in a laboratory, this enables a thorough exploration of potential failure modes and insights into usability, acceptability, and operational fit.

PATH conducted a formative usability assessment of three prototype containers produced via the BFS manufacturing process to characterize the usability of the designs and the potential acceptability and operational fit of single-dose BFS containers for delivery of parenteral vaccines in LMICs. This evaluation represents the first formative evaluation of BFS technology designed for parenteral vaccination to identify unanticipated use errors and mitigations. Vaccines that could potentially be candidates for packaging in BFS for use in LMICs are those that are currently in liquid single-dose or multidose presentations, including human papillomavirus (HPV), inactivated polio vaccine (IPV), pneumococcal conjugate vaccine (PCV), and the pentavalent vaccine protecting against diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b (DTP-HepB-Hib), as well as new vaccines in development that fit these criteria. Beyond vaccines, BFS containers could also be appropriate for other applications in low-resource settings, such as injectable contraceptives or antiretroviral drugs. The results presented here will identify functionality and design factors that could affect the future uptake, acceptability, and safety of BFS container designs in LMIC immunization programs. Furthermore, the proposed design recommendations are intended to improve programmatic suitability of the current prototype designs, characterized as operational fit in this evaluation, which is part of the World Health Organization (WHO) prequalification process to ensure the "suitability of the vaccine for the immunization services where it is intended to be used."[4]

PRODUCTS TO BE EVALUATED

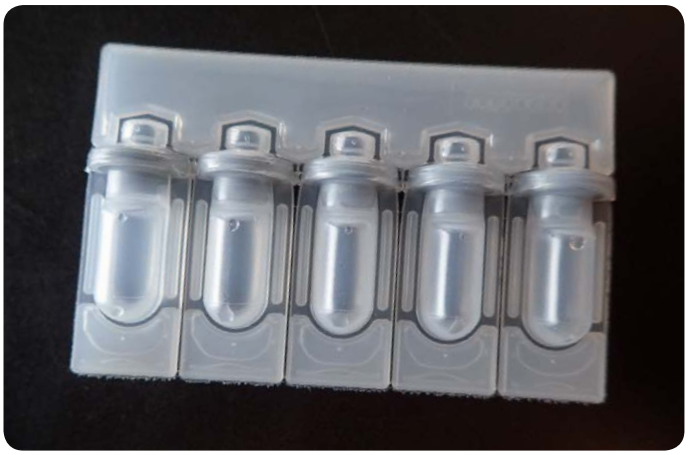
Rommelag Engineering,[5] based in Germany, designs and manufactures BFS filling equipment for a variety of products, including pharmaceuticals. Rommelag identified the following three BFS container designs (Table 1) for a PATH evaluation of usability and operational fit for delivery of parenteral vaccines in LMICs:

The compact, prefilled, autodisable (CPAD) delivery system designed by Apiject,[6] referred to as the "CPAD" in this report.[4] The CPAD is presented in the multi-monodose (MMD) format so that once a container is removed from the strip of five, the seal is broken and the container "open," requiring immediate use (analogous to a filled syringe drawn from a multidose vial). The design is a BFS container with a separate, custom needle hub that the user must attach at the time of use.



The compact, prefilled, autodisable (CPAD) delivery system.

NOTE: Although the device used in this evaluation is intended to have an autodisable (AD) feature, further design iterations would be required to bring it into compliance with international standards for autodisabling (International Organization for Standardization [ISO] 7886), as is required for WHO prequalification.



A strip of five single-dose blow-fill-seal vials.

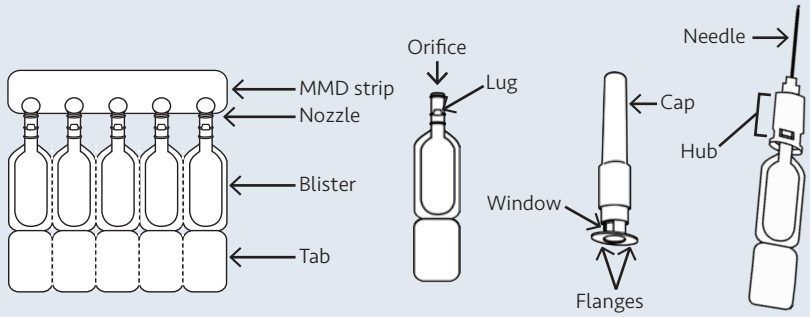
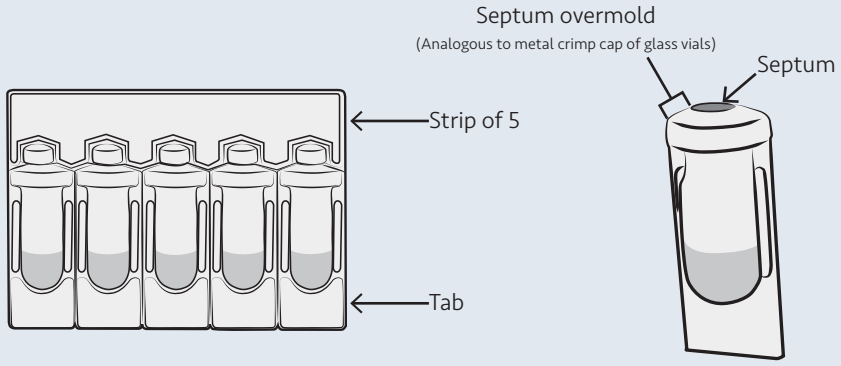
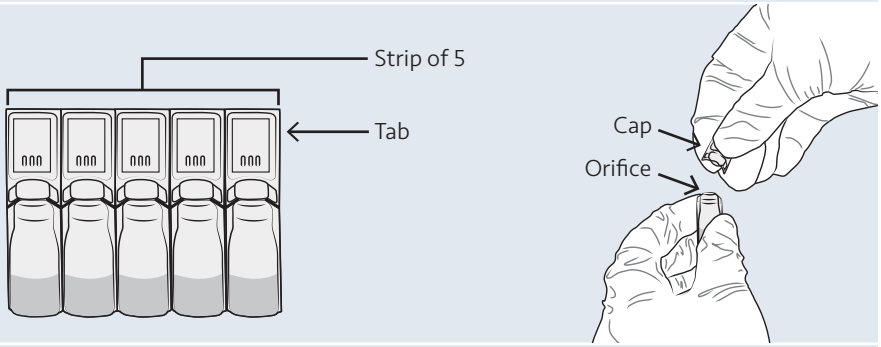
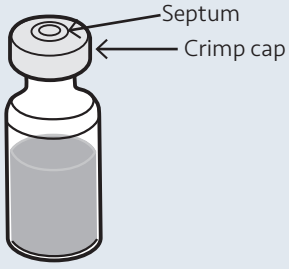
The single-dose BFS vial with a rubber septum designed by Rommelag, referred to as the "vial" in this report. A user must remove a single vial from the strip of five and use a standard AD needle and syringe to withdraw the vaccine for a parenteral injection (similar to the way one would with a standard glass vial).

The single-dose BFS ampoule designed by Global Good (made by Intellectual Ventures),[7] referred to as the "ampoule" in this report. Global Good designed the ampoule to achieve the smallest possible container size by using an "accordion" configuration that folds down to reduce overall bulkiness. A user must remove a container from the strip of five, twist the ampoule to remove the cap, and then use a standard AD needle and syringe to withdraw the vaccine for a parenteral injection.

A strip of five single-dose blow-fill-seal ampoules.

These prototype BFS container designs illustrate a range of features and demonstrate what BFS technology can produce in terms of container size, flexible packaging, and ease of delivery.

TABLE 1. **Design components of the blow-fill-seal devices.**

DEVICE	DESIGN COMPONENTS
CPAD	
Vial	
Ampoule	
Glass vial (standard vaccine container)	

Abbreviations: CPAD, compact, prefilled, autodisable; MMD, multi-monodose; mL, milliliter.

PROJECT OBJECTIVES

The objective of this programmatic and human factors evaluation was to assess the usability, acceptability, and operational fit of the three BFS container designs for packaging and delivery of parenteral vaccines, as described above, among Expanded Programme on Immunization (EPI) HCWs and other key stakeholders in Uganda and Vietnam. Results from this evaluation will identify functionality and design features that could affect the future uptake, acceptability, and safety of BFS container designs in LMIC immunization programs and are intended to help guide further product development efforts. Moreover, the results inform potential design iterations so that the final version of the BFS containers are suitable for programmatic use in LMICs. Bench testing in PATH's product development shop was also conducted to evaluate the container functionality and provide context for the programmatic study results.

Specific objectives of the evaluation included the following:

- **Usability—the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use.**[7]
  - Evaluate *usability* among target users.
  - Assess the ability of users to perform critical tasks, confirm predicted user errors, and identify unanticipated use errors of the three container designs.
  - Identify training requirements among target users.
- **Acceptability—acceptance of the device by users and stakeholders.**
  - Evaluate *acceptability*, including potential issues, perceived utility, and statements of like and dislike, among target users and stakeholders.
- **Operational fit—suitability within current routine practices and programmatic suitability within LMIC EPIs.**
  - Understand *operational fit* in target environments of use.
  - Assess alignment with priorities of country immunization programs, vaccine manufacturers, and global suppliers.

Immunization session at Commune Health Station in Vietnam.

Villagers waiting at a community outreach session in Uganda.

BENCH TESTING

PATH conducted bench testing to provide quantitative measurements to support the qualitative data generated during the programmatic and human factors evaluation. For each of the prototype BFS container designs, PATH measured (1) cold chain volume, (2) container removal force, (3) delivery performance, and (4) shake test repeatability. This bench testing was intended to provide an initial characterization of device performance, rather than verify compliance with set requirements.

HUMAN FACTORS AND PROGRAMMATIC EVALUATION

The programmatic and human factors evaluation focused on the usability, acceptability, and operational fit of the prototype BFS containers. The evaluation included (1) mock-use and product demonstrations and (2) individual interviews and focus group discussions (FGDs).

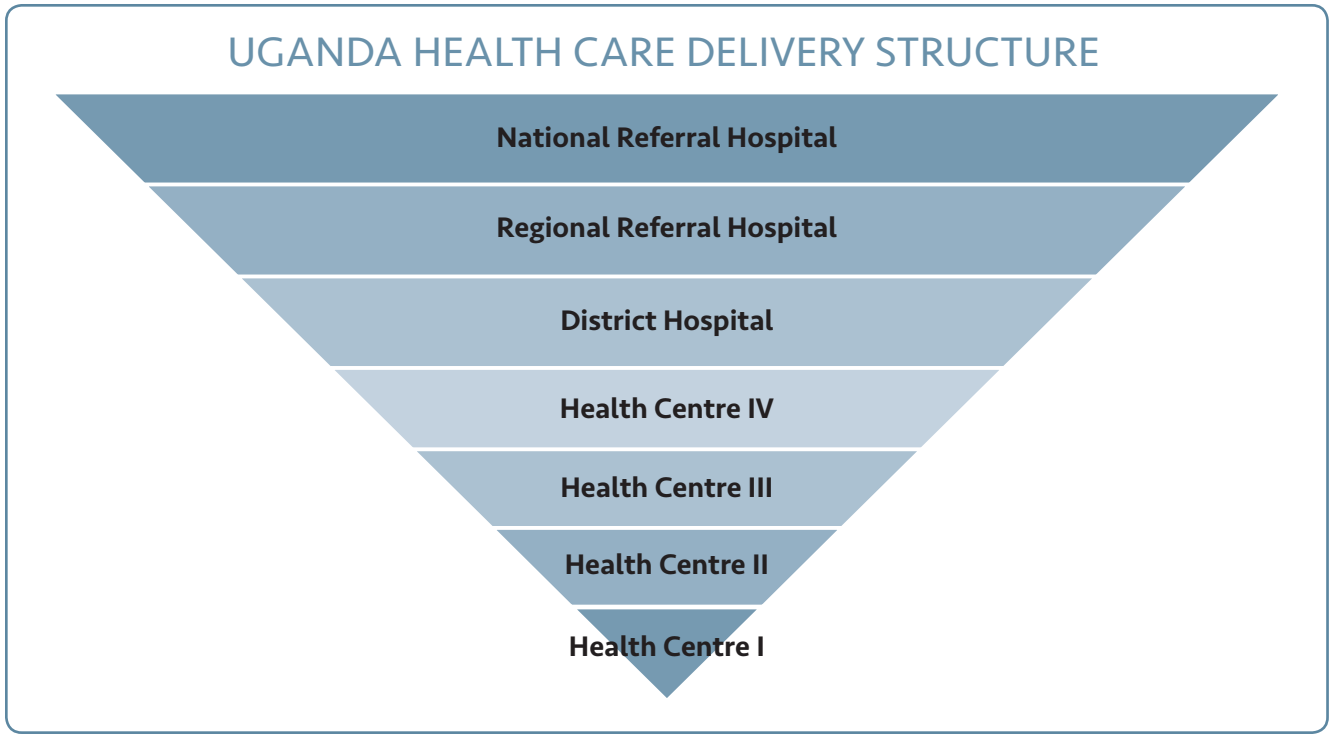
Ethical considerations

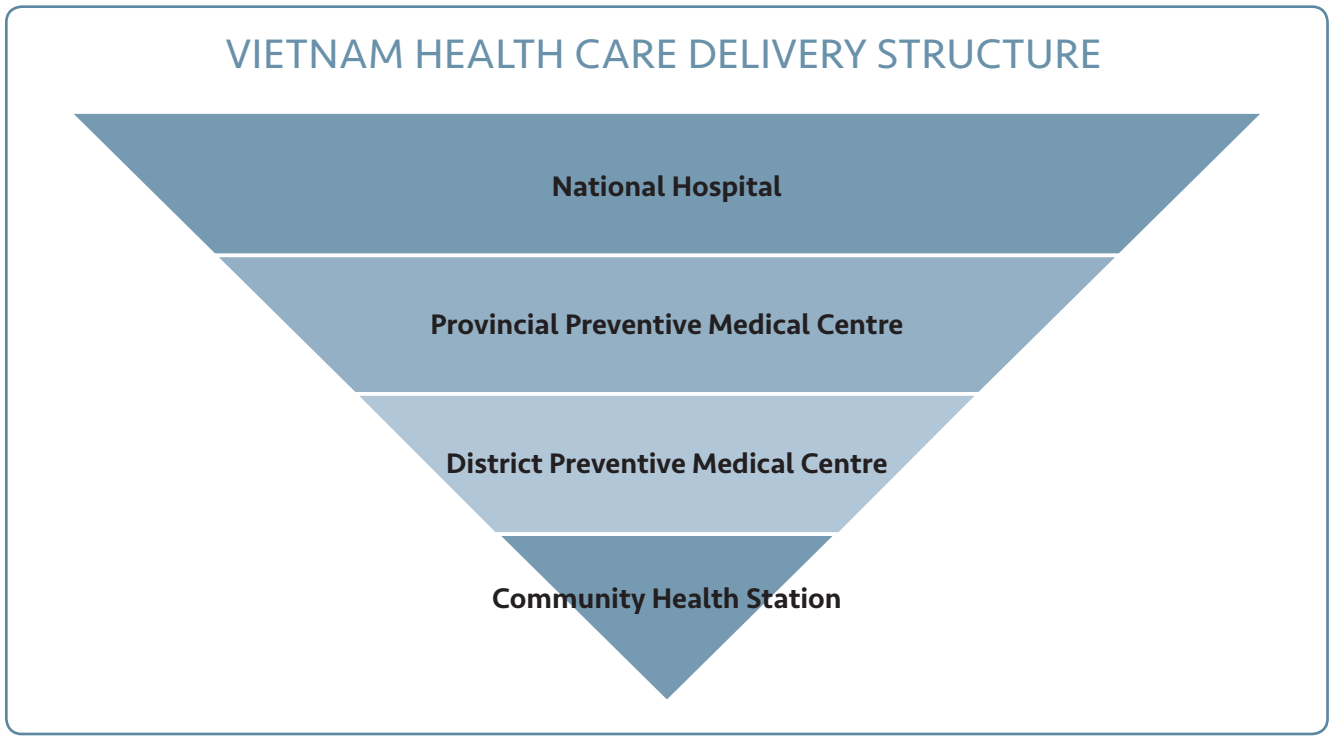
The programmatic and human factors evaluation was reviewed by PATH's Research Determination Committee and determined not to be human subjects research, meaning the study did not require PATH Research Ethics Committee review. The Uganda-specific protocol was then submitted to and approved by the Mbarara University of Science and Technology Research Ethics Committee and approved by the Uganda National Council for Science and Technology. Permission was also obtained from the Uganda National Expanded Program on Immunisation (UNEPI) within the Uganda Ministry of Health (MOH). The Vietnam-specific protocol was submitted to and approved by the Vietnam National Institute of Hygiene and Epidemiology's institutional review board. Informed consent to participate in the study and record interviews was obtained from all participants. In addition to consenting to participate in the evaluation, a subset of participants in Uganda who participated in the usability testing signed media permission forms, enabling use for reporting purposes of video and photos taken during the evaluation.

Country context and site selection

PATH selected Uganda and Vietnam for this evaluation because the countries represent different WHO regions with regional variations in health care systems, immunization programs, and cultural diversity. Along with local research partners and district health officials, the country study teams identified relevant clinics or hospitals and gained the necessary approvals to visit the clinics to observe routine immunization care and conduct data collection activities. To participate, health facilities needed to regularly provide immunization services in a routine or outreach setting.

The facilities selected for the evaluation represent different levels in the health care delivery system in each of the two countries. In Uganda, Health Centre II, Health Centre III, Health Centre IV, and Regional Referral Hospital facilities were included. In Vietnam, both Commune Health Stations, District Preventive Medical Centres, and Provincial Preventive Medical Centres were included. In both countries, vaccine storage facilities and EPI offices at different levels of the health system were also included. Also in both countries, purposive sampling was used to select facilities representing different contexts of use, such as vaccine storage conditions (with or without refrigeration), ease of access (in terms of road infrastructure and transport options), clinic throughput (average number of patients per immunization session), and vaccine coverage rates.





Methodology

Sampling for usability data

This qualitative evaluation did not include statistical analysis of data. Therefore, the sample size reflects a purposive sampling strategy based on qualitative sampling theory. The robustness of data generated by a sample of this size is demonstrated by Faulkner's 2003 meta-analysis of usability data, which demonstrates

that a sample size of 15 users will generate data reflecting 97 percent of all usability problems, with diminishing returns from larger sample sizes.[9] This sample size is also consistent with recommendations from the US Food and Drug Administration guidance document for human factor considerations of medical devices, which recommends 10 to 15 participants as the optimal sample size for varying types and targets of user testing.[3] Therefore, the target sample size for the usability testing was 15 participants.

Sampling for acceptability and operational fit data

In addition to the usability testing in Uganda, individual interviews and FGDs were conducted with HCWs and stakeholders in both countries to further understand acceptability and operational fit. Purposive sampling was used in both countries. In Uganda, a subset of HCWs who participated in the usability data collection also participated in the acceptability evaluation (a convenience sample was used). To allow for a more in-depth assessment of product impact on supply chains and to give better perspective on the ultimate program feasibility and value proposition considerations, we targeted 15 interviews/FGDs per country, with a total target sample size of 30 interviews/FGDs.

To describe the typical potential users of the BFS containers, personas were developed for a Ugandan nursing officer, a Vietnamese district EPI officer, and a Vietnamese national EPI program officer (see the Annex). The personas are representations of real users, including their behaviors, typical daily tasks, and limitations. The intent of the personas is to guide user-centered product development and design a product that meets user needs. Their environment of use is also characterized to explore the types of conditions BFS containers would be exposed to in the field during transport, storage, and usage.

Study design

This evaluation used a mix of qualitative data-collection methods, including (1) mock use of the BFS prototypes (giving water injections to a salt-filled condom or an orange, a procedure which has been previously shown to be a good medium for practicing injections); (2) direct observation of simulated use (checklists as well as audio, video, and photo formats); and (3) individual interviews and FGDs.

Usability data collection

The mock-use activity was conducted with HCWs who provide immunizations. Data collection focused on preparation, usability, form factors (shape, size, materials rigidity, ergonomic fit), and intuitiveness of the BFS containers. A usability checklist was used to guide direct observation of the mock-use activity, reflecting evaluation endpoints.

The usability testing followed a "Do-See-Do" format. Participants were first asked to try to use the prototype devices to prepare and deliver the placebo vaccine (water) into a salt-filled condom without receiving any coaching or instructions. Participants then watched a demonstration by the researcher, received instructions for use (see the Appendix), and were given the opportunity to use the prototypes a second time. Participants were also provided the option to try the prototypes a third time, especially if they were still experiencing difficulties with using the devices. The prototype devices were presented in randomized order to control order bias. During mock use, data were collected using observation checklists and video recording. In conjunction with the mock-use activity, individual interviews were conducted to collect additional information on acceptability and operational fit.

Use errors

Usability data were evaluated to identify (1) use errors (both hazard-related and other use errors); (2) close calls; and (3) use difficulties (Table 2).

TABLE 2. **Usability definitions.**

OBSERVATION TYPE	DEFINITION AND EXAMPLES
Use error	An act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.[9] There are two types of use errors:
	Hazard-related use error An error that results in a potential source of harm to the user or patient. For example, the user could spill some of the contents of the vaccine container, which could result in an incomplete dose being delivered.
	Other use error An error that results in incorrect use but does not pose a harm or safety risk. For example, the user could incorrectly remove the container according to the product information sheet.
Close call	A user almost commits a use error while performing a task but recovers in time to avoid making the use error.[10] For example, the user is about to puncture the side of the vial to draw liquid, but they realize that is incorrect and remove the vial from the strip and draw through the septum.
Use difficulty	A user has difficulty performing a task, including fumbling or difficulty manipulating the device. A use difficulty could become a use error, which could lead to harm, especially in conditions of stress, time constraint, or poor lighting. Although a use difficulty may not necessarily be observable, they can be identified during the debrief with the user. For example, the user could spend a lot of time inspecting the device or re-reading instructions because they are not sure how to perform the next task.

Acceptability data collection

Acceptability questionnaires distributed to vaccinators in Uganda and vaccinators, clinical managers, and program staff in Vietnam informed the device preference rankings. Interviews with users and stakeholders in both countries informed qualitative descriptions of acceptability. Individual interviews/FGDs included probes on perceived utility, advantages, disadvantages, and recommendations for improvement for each of the container designs.

Commune Health Station in Vietnam.

Operational fit data collection

Information on the patient flow; infrastructure; layout of the clinic, including the immunization area; staffing structure; and resources used in the facility were documented through direct observation and during the interviews and FGDs. In addition, interviews included prompts on perceived training requirements, potential supply-chain impacts, other programmatic considerations, and potential benefits and challenges for introduction of BFS containers.

Dry immunization supplies storage area at a Health Centre III in Uganda.

Data analysis

Video, photo, and audio data collected during mock-use activities were reviewed and coded according to pass/fail of critical tasks based on the usability checklist. In addition, further usability and operational fit codes were developed in vivo. Acceptability and operational fit data were translated as needed and then entered into MAXQDA (VERBI GmbH, Berlin, Germany), a qualitative data analysis software package for initial data cleaning and analysis, and were then exported to Excel (Microsoft, Redmond, Washington, USA) for final analysis. Where appropriate, data were entered directly into Excel. Data were then coded according to a codebook developed in advance and expanded with in vivo analysis.

Bench testing characterization

Prior to the country evaluation, bench testing was conducted to characterize each container prototype. The following user interface characteristics were evaluated:

- **Cold chain volume.** To approximate the cold chain volume required for transport and storage of the BFS containers, five strips of five single-dose containers of each device were used to determine the stacking configuration with the minimum volume per unit. Overwrap (foil packaging to prevent moisture vapor and gas transmission through the polymer container) was not included in this calculation because whether an overwrap is required is dependent on the vaccine.
- **Removal force.** BFS container presentations in a strip format require that the individual units be removed from the strip prior to use by (1) breaking away the unit from its adjacent containers and then (2) twisting the unit off from the tab. The force required for breaking the unit away from its neighbors depends upon the direction of separation. Containers were preconditioned to 2°C to simulate realistic use conditions following removal from cold chain storage. Removal force was then measured in two different directions for in-plane and out-of-plane separation. The torque to remove the container from the labeling tab also was measured.
- **Dose-delivery completeness.** To determine the delivery performance of the CPAD delivery system, it was weighed before delivery and after the first and second squeezes to assess the volume of liquid delivered from the device. The average force required to fully squeeze the CPAD container (as defined by the force required to make the two container walls touch) was measured.
- **Shake test.** Freeze damage in aluminum-adjuvanted, freeze-sensitive vaccines is assessed by visualizing how quickly the particulate contents settle out in the container compared to a known frozen sample used as a control. As BFS containers have a lower transparency than glass vials, testing was conducted to see if technicians could reliably identify which BFS containers had been freeze damaged using the standard shake test method.[12]

Results of these analyses are summarized below (Table 3), and the significance of these observations is discussed in the context of the programmatic evaluations in the following sections.

TABLE 3. Bench-testing results.

	ATTRIBUTE	SAMPLE SIZE	GLASS VIAL	CPAD	VIAL	AMPOULE
COLD CHAIN VOLUME	Volume per unit, excluding overwrap (cm^3)	n=25 (BFS)	~15 (single-dose vial) ~3 (ten-dose vial)	5.5	9.0	2.6
AVERAGE REMOVAL FORCE	In-plane separation (N)	3	NA	7.5	6.0	4.9
	Out-of-plane separation (N)	3	NA	2.6	5.6	0.7
	Tab twist-off torque (oz)	3	NA	3.0	20.0	21.0
AVERAGE DOSE DELIVERY	Dose delivered after first/second squeeze (mL)	30	NA	NA	NA	0.27/0.45
	Maximum squeeze force (N)	n=3	NA	NA	NA	62.8
SHAKE TEST	% false positives	n=100 (glass vial) n=150 (BFS)	0.0%	0.0%	0.0%	0.0%
	% false negatives		2.0%	1.3%	0.0%	2.0%

Abbreviations: BFS, blow-fill-seal; cm, centimeter; CPAD, compact, prefilled, autodisable; mL, milliliter; N, newton; NA, not applicable; oz, ounce.

Human factors and programmatic evaluation

SAMPLE/PARTICIPANTS

HCWs recruited for the study were typically nurses and midwives (job titles varied, but education/experience were comparable) who provide immunizations as part of their normal job duties in a clinic or outreach setting. Stakeholders included managers or decision-makers involved with immunizations, including those from the MOH, EPI, vaccine supply chain, or cold chain (Table 4).

TABLE 4. Sample size.

	UGANDA	VIETNAM
USABILITY TESTING		
Nurses and midwives providing EPI services	16	0
ACCEPTABILITY AND OPERATIONAL FIT		
Health care workers/vaccinators	32 (individual interviews)	15 (focus groups)
EPI program staff (National, provincial, regional, district)	9 (individual interviews)	3 (individual interviews) 10 (focus groups)

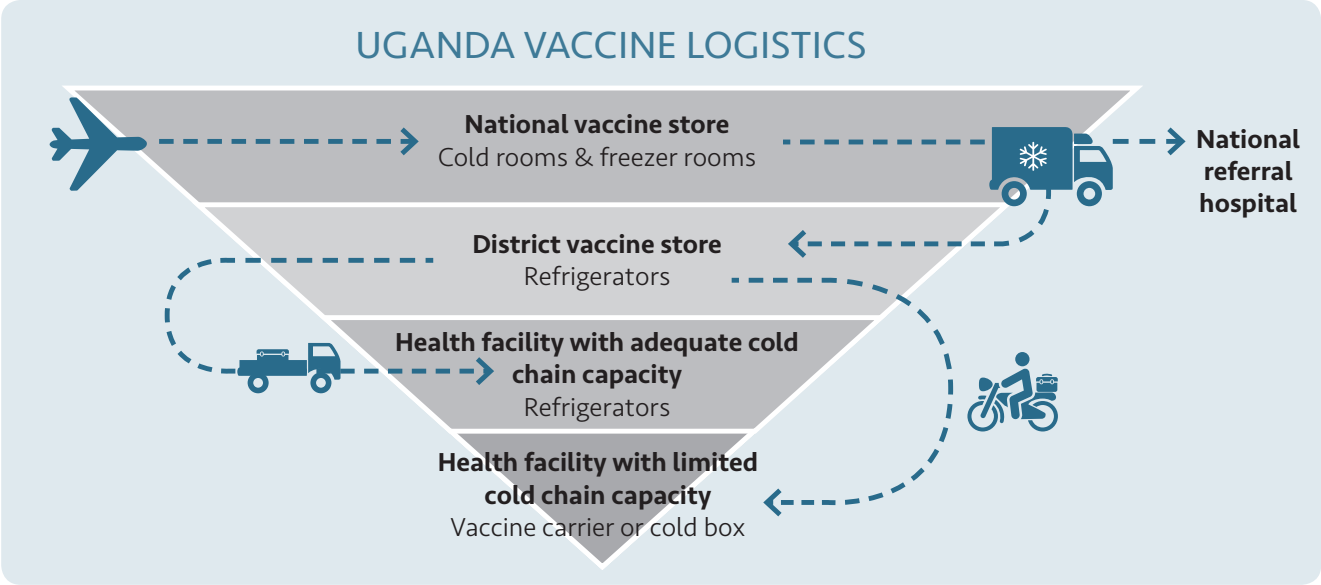
Abbreviation: EPI, Expanded Programme on Immunization.

A total of 50 sites (23 in Uganda; 27 in Vietnam) participated in the country evaluations. In Uganda, individual interviews were conducted with a total of 41 participants. Participants in the mock-use activity included registered midwives and nurses (diploma and bachelor's degree), enrolled nurses and midwives (certification), and one clinical medical officer (diploma in clinical medicine and community health). The acceptability and operational fit interviews included HCWs/vaccinators (usability participants and 16 additional participants), in addition to national-, regional-, and district-level EPI and cold chain managers. In Vietnam, HCWs/vaccinators participated in 15 FGDs. Ten additional FGDs were conducted with provincial-, regional-, and district-level EPI officers, managers, pharmacists, storekeepers (cold chain technicians), and physicians. Individual interviews were conducted with one national and two regional EPI managers. In Vietnam, vaccine manufacturers were also consulted to better understand the business drivers for the decision-making on how many DPCs of vaccines are packaged for use by Vietnam's National Expanded Program on Immunization (NEPI).

IMMUNIZATION PROGRAM DESCRIPTIONS

Uganda

It is estimated that in 2016, 93 percent of children in Uganda were vaccinated with the third dose of diphtheria-tetanus-pertussis (DTP3) vaccine, and 90 percent of districts achieved greater than 80 percent DTP3 coverage.[13] However, there are still challenges with implementation.[14,15] Only 22 of Uganda's 112 districts have good access to and utilization of immunization services, which is defined as reaching over 80 percent of children with all recommended doses of vaccine, according to district-specific targets[16,17] The Ugandan immunization program relies on a network of primary health centers to deliver vaccines, and these facilities function semiautonomously, forecasting demand and procuring vaccine supplies in a "pull" mechanism from the district-level supply stores.[18,19] UNEPI's decentralized structure, and the barriers to access that impact Uganda's immunization coverage rates, offered a challenge-test for novel vaccine delivery technologies, such as the parenteral BFS containers.



The immunization supply chain in Uganda is structured in a cascading hierarchy. Following arrival at the airport, vaccines are stored for two to four days and then transferred to the national vaccine store, which is part of the National Medical Stores. Shipments of vaccines arrive at the national cold room quarterly and are largely funded by Gavi, the Vaccine Alliance (Gavi) and the Government of Uganda (GOU). Five traditional vaccines—DTP-HepB-Hib, meningococcal conjugate vaccine, bivalent oral polio vaccine (bOPV), bacillus

Calmette-Guérin (BCG), and tetanus toxoid (TT)—are exclusively funded by the GOU. IPV, PCV, and HPV are cofunded by Gavi (80 percent) and the GOU (20 percent). All procurement processes are handled by the United Nations Children's Fund (UNICEF), which charges the GOU a 15 percent handling fee.

On a monthly basis, the national vaccine store delivers vaccines to each district vaccine store using refrigerated trucks, according to the schedule provided. The district vaccine stores also include storage facilities for non-cold chain supplies such as needles and syringes, diluent, and safety boxes. At the district level, vaccines and supplies are then bundled and delivered to health facilities through two mechanisms: (1) the district delivers supplies directly to clinics with functional refrigerators and adequate cold chain capacity using cold boxes, typically District Hospital, Health Centre IV, and Health Centre III facilities; (2) HCWs from facilities with nonfunctional refrigerators or limited cold chain capacity pick up supplies from the district vaccine store using vaccine carriers, typically Health Centre II and Health Centre II facilities. Regional Referral Hospitals receive their vaccine supplies directly from the national vaccine store or a district vaccine store depending on their location.

Cold room at the national vaccine store in Uganda.

Primary health centers offer services at static facilities and in outreach settings at the village level and may also serve as hubs for teams of HCWs during immunization campaigns. At the health facilities, vaccines are typically stored in refrigerators. Primary health centers with refrigerators resupply from the district stores monthly. Clinics that do not have refrigerators top off their one-month supply of vaccines from their district vaccine store or a nearby higher-level health facility that has a refrigerator. Vaccines that are not used during an immunization session must be returned to either the district facility for reallocation or a nearby higher-level health facility for storage, whenever possible. During both static and outreach immunization sessions, vaccines are stored in vaccine carriers.

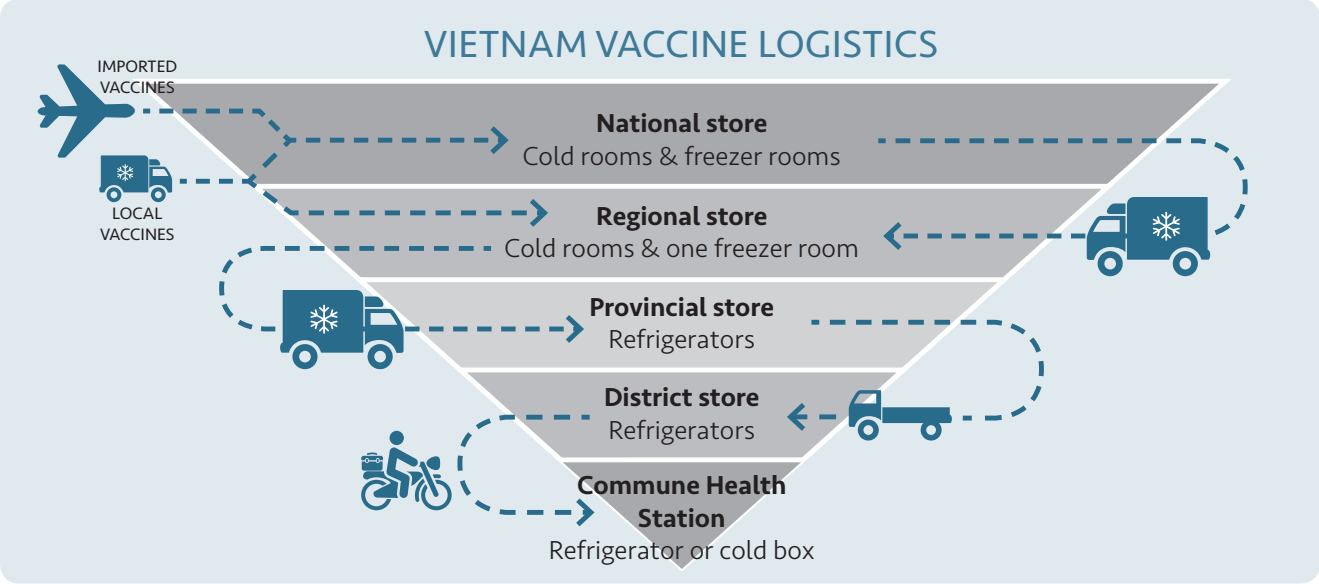
Refrigerated vehicle used to transport vaccines from the national vaccine store to the district vaccine store in Uganda.

Using the currently procured vaccines and vial sizes, HCWs estimate that a vaccine carrier can hold approximately 100 doses of vaccine (maximum volume of 1 liter), depending on the type of vaccine and how it is packaged. Each vaccine is accounted for and recorded in a vaccine and injection materials control book at each facility, and tally sheets are used during outreach to count how many vaccines are delivered in the community. These logs are carefully maintained to keep an ongoing record of the number and types of vaccine administered by each facility.

Vaccine refrigerator at a Health Centre IV in Uganda.

Vietnam

NEPI is structured around its geopolitical framework. The Commune Health Station is the basic unit for provision of health services in Vietnam. Commune Health Stations are generally staffed by four to six commune health workers, including nurses, an assistant doctor, and a doctor.[20,21] It is estimated that in 2016, 96 percent of children were vaccinated with DTP3 and that 97 percent of districts achieved greater than 80 percent DTP3 coverage.[22] Vietnam's highly centralized health system provides a unique counterpoint to Uganda's immunization program structure.



Cold rooms at regional store in Vietnam.

The immunization supply chain in Vietnam consists of one national vaccine store, four regional vaccine stores, 63 provincial stores, 712 district stores, and 11,160 Commune Health Stations. Local manufacturers produce all vaccines used in the routine immunization program—including diphtheria-tetanus-pertussis BCG, bOPV, Japanese encephalitis, measles, measles-rubella (MR) (beginning in 2018), TT, and hepatitis B (HepB)—and deliver them either to the national cold store or directly to the four regional cold stores. Typhoid and cholera vaccines are also produced locally but are not included in routine immunization at the national level. Imported vaccines (DTP-HepB-Hib and IPV) are received at the national store before being transported to regional stores. Vaccines are moved from the regional level to the provincial, district, and, finally, commune levels. Generally, vaccines are only supplied to the commune level for use during immunization activities (one to three days per month). Only 5 percent of Commune Health Stations conduct outreach activities. Vaccine carriers and cold boxes are used for transporting and storing vaccines during immunization days; during the rest of the month, vaccines are not stored at the commune level, except in some remote communes where vaccine refrigerators have been provided.

Cold chain capacity is a challenge in Vietnam. In 2016, the cold chain capacity appeared to be sufficient even after introduction of IPV and MR. However, additional vaccines have been introduced since then and the existing cold chain capacity is no longer sufficient to accommodate all the vaccine doses required in-country. For example,

there is insufficient cold chain volume to accommodate storage for vaccines like IPV (initially introduced in 2016, still ongoing in 2018), Japanese encephalitis (currently only used in campaign settings; routine immunization introduction planned for 2018), and rotavirus (planned, but no introduction date set). There are also needs for extra cold chain storage capacity for different scenarios for new vaccine introduction (i.e., Japanese encephalitis alone, Japanese encephalitis + rotavirus, rotavirus + IPV).

Table 5 (on the next page) summarizes the vaccines and vial sizes that are stocked for routine immunization use in Uganda and Vietnam. Larger, multidose vials are the most common presentation, but smaller-dose vials are also being purchased as new vaccines are introduced that are only available in smaller DPCs.

Health care worker traveling from the district store to a Commune Health Station with a vaccine carrier.

Reception table during immunization session at a Commune Health Station in Vietnam.

USABILITY RESULTS

In total, 16 users in Uganda completed mock-use activities of the three BFS containers during this evaluation. Usability data were not collected in Vietnam. Based on the usability testing, both the vial and ampoule—which are more similar to currently available vaccine containers—were the most intuitive to use. Even without instructions, all participants were able to complete the injections with the vial without coaching, and all but one could do so for the ampoule (one person attempted to deliver the contents orally). However, while 12 naïve (first-time) users were able to achieve perfect use on the first try with the vial, only 2 did so with the ampoule. The primary use error in this circumstance was the absence of tapping the ampoule to knock trapped liquid out of the cap before removing it, which frequently resulted in liquid spilling onto the fingers of the user. Further details are provided in each of the device-specific results sections below.

CPAD usability

For the CPAD device, only two of the naïve users were able to complete the injection without prompting, and none of the users delivered the injection correctly without committing a use error. The CPAD design was unfamiliar. Even users that had previous experience with CPAD devices—in particular, Sayana® Press (Sayana Press is a registered trademark of Pfizer Inc.)—did not realize that the device was a CPAD until instructions for use were provided. Following the product demonstration and receiving the instructions for use, all users successfully completed the injection with the CPAD; however, only five were able to do so without use errors as defined by the established criteria (see the Appendix).

The CPAD was not intuitive for most users, and they were unable to assemble it without instructions. Once instructions were given, users were able to assemble the needle hub, but assembly often deviated from correct use—in particular, proper alignment of the needle hub with the blister. Common observations for the CPAD are summarized in Table 6.

TABLE 5. Vaccines and vial sizes stocked for routine immunization in Uganda and Vietnam.

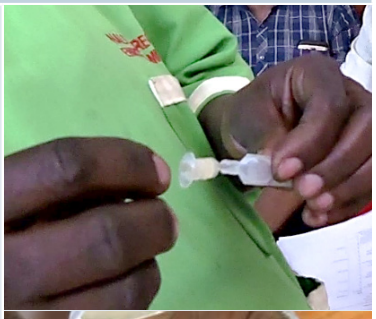
VACCINE	UGANDA		VIETNAM	
	SCHEDULE	PRESENTATION	SCHEDULE	PRESENTATION
BCG	Birth or on first contact	20-dose vial with diluent ampoule	Within first 30 days of birth	10-dose vial with diluent ampoule
DTP	NA	NA	18 months	20-dose vial
DTP-HepB-Hib	6, 10, 14 weeks	10-dose vial	2, 3, 4 months	1-dose vial
HepB	NA	NA	Birth	1-dose vial
HPV	10 years, +6 months	1-dose vial	NA	NA
IPV	14 weeks	5- or 10-dose vial	5 months	10-dose vial
Japanese encephalitis (inactivated)	NA	NA	12 months, +2 weeks; 2 years	5 mL vial (<3 years 0.25 mL dose, ≥3 years 0.5 mL dose)
Measles-containing vaccine	9 months (measles only)	10-dose vial with diluent ampoule	9 months (measles only); 18 months (MR)	10-dose vial with diluent ampoule
OPV	Birth; 6, 10, 14 weeks	20-dose vial	2, 3, 4 months	20-dose vial
PCV	6, 10, 14 weeks	2-dose vial	NA	NA
Rotavirus	6, 10 weeks	1-dose tube (Introduction ongoing, to be completed in 2018)	NA	NA
TT	15 years, +4 weeks, +6 months, +1 year, +1 year	20-dose vial	Women of reproductive age (15-45 years), +1 months, +6 months, +1 year, +1 year	20-dose vial
Typhoid conjugate vaccine	6 months	5-dose vial	NA	NA

Note: Data provided by the Uganda National Expanded Program on Immunisation for Uganda and the National Expanded Programme on Immunization for Vietnam.
Abbreviations: BCG, bacillus Calmette-Guérin; DTP, diphtheria-tetanus-pertussis; DTP-HepB-Hib, diphtheria, tetanus pertussis, hepatitis B, *Haemophilus influenzae* type b; HepB, hepatitis B; HPV, human papillomavirus; IPV, inactivated polio vaccine; MR, measles-rubella; NA, not applicable; OPV, oral polio virus; PCV, pneumococcal conjugate vaccine; TT, tetanus toxoid.

Several potential use errors that were identified during bench testing did not occur during the mock-use activity. These include needlestick injuries and puncturing the container with the needle; although users commented that both errors could occur. Users also did not attempt to prepare multiple devices ahead of time by removing more than one container from the CPAD strip (naïve users were provided five needle hubs with the MMD strip during the mock-use activity and not explicitly told to deliver a single dose). However, given the format of the evaluation, with a single use observed at a time, this practice would not offer any benefit to the user. During interviews, many users indicated that a vaccinator might prepare multiple devices before use, as right-sizing the number of doses per vaccine carrier to the anticipated size of the

immunization session is standard practice among all HCWs who participated in this evaluation. Likewise, HCWs indicated they would prefer to prepare the devices in advance of going to the community for an outreach session, storing the assembled devices in the vaccine carrier. Like prefilling syringes for use later in the day, this practice is not recommended due to the absence of a vaccine vial monitor (VVM), potential for contamination, and potential for reduced stability of the vaccine.[23]

TABLE 6. Common compact, prefilled, autodisable device usability observations.

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
HAZARD-RELATED USE ERRORS		
Inserting needle through nozzle. **Observed during naïve use only.** **POTENTIAL HARM:** Needlestick injury, dose-volume loss, contamination of hub.	On first (naïve) use, participants inserted the needle into the CPAD nozzle because they did not realize that it was a CPAD device. Users assumed that they needed to draw the liquid from the orifice of the container to deliver the vaccine, thus treating the container as an ampoule. Users also tried to use the needle hub to draw liquid from the container by attempting to draw the hub away from the tabs as if they were the tabs at the base of a syringe and the hub were the plunger. This error was recorded exclusively during naïve use. In some instances, an RUP* needle and syringe was used to draw the liquid from the container as if it were an ampoule and then administered the vaccine. In another case, after using an RUP needle and syringe to draw vaccine, the user tried to attach the CPAD needle hub to the luer of the RUP needle and syringe stating that the RUP needle hub was for drawing and the CPAD needle hub was for delivery. *Although RUP syringes were used for this evaluation, autodisable syringes are used for immunization in Uganda.	  (Video)
Multiple squeezes. **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Pain, air in the muscle, muscle injury.	Multiple squeezes (ranging from 1–8 squeezes) were often required to expel the full dose volume. Multiple squeezes were observed both during naïve use and after instructions were provided. Bench testing confirmed this result, finding that one squeeze expelled only 54 percent of the intended dose volume on average. Users commented that the material was hard and difficult to squeeze and that a significant amount of squeeze force was required to expel all the liquid.* Users also repositioned to try different angles/grips to expel all the liquid on subsequent squeezes; they seemed surprised when, after several squeezes, there was still liquid remaining in the container. Multiple squeezes pose significant risk of injury to the recipient and is not permissible for vaccination. In addition, this has ergonomic risks for the user. *Through bench testing, it was determined that the CPAD requires on average 63 N of force.	 (Video)

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
Squirting/spilling from blister orifice. **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Risk of incomplete dose being delivered.	Squirting/spilling occurred during removal of the container from the MMD strip due to liquid being suspended in the top of the nozzle (and the user forgetting to tap the liquid down) or using too much force to remove the container so that the liquid spilled. In some instances, the user also separated the nozzle from the MMD strip before separating the blister tab.	 (Video)
Needle hub and blister misalignment and poor seating on the lugs led to the following observations: **1. Leaking from side of needle hub.** **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Leaking from joint, incomplete dose being delivered. **2. Needle pulling off nozzle when user attempted to remove cap.** **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Needlestick injury.	If the needle hub and blister were not secured properly (by pushing to attach needle hub into the lugs on the blister until a click is observed) due to needle hub and blister misalignment and/or poor seating on the lugs, sometimes (1) the needle was pulled off the nozzle when the user attempted to remove the cap prior to injection or (2) leaking occurred from the needle hub/blister joint during injection. Typically, users were not able to correctly secure the needle hub to the blister because the components were not in proper alignment. Intuitively, users thought that the wings should be perpendicular to the lugs like the wings on an autodisable needle and syringe and turned the needle hub accordingly. In this position, it was difficult to seat the hub onto the container. It is assumed this error typically occurred because it was not obvious to users how the lugs on the nozzle were supposed to click into the corresponding gaps and wings on the needle hub. Many users spent a significant amount of time trying to push the needle hub until they heard a click and often gave up waiting for a click and delivered the vaccine because assembling the device was taking too long. For some users, they were not using enough force and when they pushed harder they were able to secure the needle hub. Some users also rushed through the assembly process and did not confirm that they observed a click before continuing with administration.	 Leaking from side of needle hub (Video).  Needle pulling off nozzle during uncapping (Video).
Using the CPAD as an oral dropper. **Observed during naïve use only.** **POTENTIAL HARM:** Reduced vaccine efficacy, increased local adverse reactions.	Several participants assumed that the CPAD was an oral vaccine dropper, due to the similar shape of the CPAD and oral vaccine droppers like OPV and oral rotavirus vaccine. One participant stated that, "[the container] was very good for OPV" and then proceeded to squeeze the blister to expel a few drops of liquid, mimicking OPV administration. This error was recorded exclusively during naïve use. In some instances of naïve use, the participants did not intuit that they would need to assemble the needle hub with the blister, so they attempted to deliver the vaccine without using the needle.	 (Video)

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
OTHER USE ERRORS		
Twisting to attach needle hub to lugs on blister. **Observed during naïve use and second use after instructions.**	It was intuitive for users to twist the needle hub in place, which is standard for luer-lock needle and syringes but is contraindicated for CPAD assembly. This use error persisted even after a demonstration and instructions were provided. In some instances, users did initially push, and alignment appeared to be correct. However, when users did not hear a click after pushing and using force, they would twist until the needle appeared to be secure.	(Video)
CLOSE CALLS		
Administered using a different route of administration. **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Reduced vaccine efficacy.	The dose was delivered intradermally instead of intramuscularly (as observed by injection technique and user feedback). This error was due to the perception of the dose volume in the blister. Although the containers were filled with roughly 0.5 mL, which is the standard volume for intramuscular vaccines, the size of the container gave users the perception of a smaller dose volume. Therefore, users assumed the container must be for BCG vaccine, which has a small dose volume (0.05 mL) and is administered intradermally. The dose was also delivered subcutaneously (as observed by injection technique and user feedback). Some users thought the container was for a reconstituted vaccine and assumed they were delivering measles vaccine. Even though this observation constitutes a hazard-related use error, in the absence of a label with the vaccine name and an indication for use, this use error was an artifact of the evaluation and so is categorized as a "close call."	 (Video)
USE DIFFICULTIES		
Fumbling, difficulty assembling needle hub with blister. **Observed during naïve use and second use after instructions.**	On naïve use, users spent a lot of time inspecting the device before they attempted to assemble it, including handling the different pieces to try to understand how they fit together. Most naïve users hesitated, and it was evident that assembly was not intuitive. One user dropped the container when fumbling with the device. Almost all naïve users gave up and were not able to complete the injection without coaching and instructions. Their use difficulties also persisted during second use after instructions.	Use difficulties during naïve use: (Video) Use difficulties after instructions: (Video)

Abbreviations: BCG, bacillus Calmette-Guérin; CPAD, compact, prefilled, autodisable; mL, milliliter; MMD, multi-monodose; N, newton; OPV, oral polio vaccine; RUP, reuse prevention.

Vial usability

Overall, the vial design seemed highly intuitive for users, and few errors occurred even before instructions were provided. All naïve users completed the injection without coaching, and most achieved correct use on the first try. Because the design is similar to glass vials, the vial was easy to use since users could rely on prior experience. Common observations with the vial are summarized in Table 7.

Potential use errors that did not occur during the mock-use activity were needlestick injuries and puncturing the side of the container with the needle. In a busy clinic setting, some of the use difficulties and close calls that were observed could have resulted in a use error (such as vaccine spillage/loss or needlestick injury).

TABLE 7. Common vial usability observations.

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
HAZARD-RELATED USE ERRORS		
Attempting to unwrap the plastic overmold from the septum before use. **Observed during naïve use only.** **POTENTIAL HARM:** Contaminated vial.	During naïve use some participants tried, unsuccessfully, to remove the plastic overmold before piercing the vial, including using a pen cap to try to scrape off the plastic to expose the septum. Although glass vials have an aluminum crimp seal similar in shape to the plastic overmold, in a glass vial the seal is flush with the septum rubber and offers a larger open area through which to puncture the needle. This may have contributed to the perception that the overmold served as a cap that needed removal.	 (Video)
Piercing through the top plastic and septum together without removing the vial from the strip. **Observed during naïve use only.** **POTENTIAL HARM:** Injection of plastic particles into patient.	One naïve user drew from the vial when it was still connected to the strip. It is assumed this behavior occurred because removing the container from the strip was not in line with the user's expectations, and the user did not realize the container needed to be removed from the strip.	 (Video)
CLOSE CALL		
Holding an uncapped syringe while manipulating device. **Observed during naïve use and second use after instructions.**	Occasionally, a user would hold an uncapped syringe in one hand when they removed the vial from the strip with both hands. Although no errors occurred, holding the syringe during removal of the container could have resulted in the user dropping the container/syringe and potentially pricking themselves, or at least made it more challenging to remove the vial.	 (Video)

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
USE DIFFICULTY		
Propping up the vial. **Observed during naïve use and second use after instructions.**	While preparing the syringe, users often propped the vial upright after detaching it from the strip. Because the BFS vials do not have a flat bottom like glass vials, users had to carefully prop up the vial since the users were working on uneven work surfaces with limited equipment for propping up the vial.	
Difficulty piercing stopper. **Observed during naïve use and second use after instructions.**	Some users had challenges in piercing the stopper. It took several attempts before the needle went into the vial after they tried different amounts of force and angles.	(Video)
Difficulty drawing liquid from vial. **Observed during naïve use and second use after instructions.**	Some users required multiple attempts to draw the entire contents from the vial into the syringe; they tried different angles and moving the syringe around within the vial.	(Video)

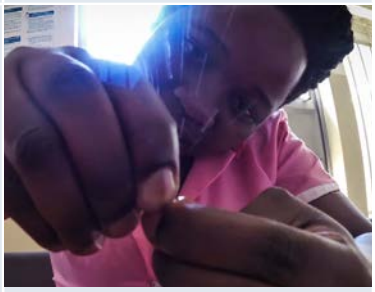
Abbreviation: BFS, blow-fill-seal

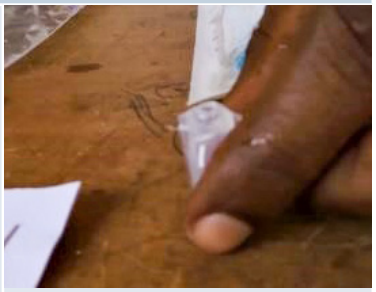
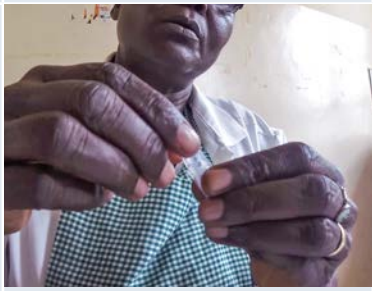
Ampoule usability

Users found the ampoule easy to use, and all users completed the injection on the first try without instructions. One common behavior was the attempt by most participants to stand the ampoule on its base or lean it against something so that it remains upright. While the BFS ampoule can be inverted without the contents spilling due to surface tension, users were concerned that the liquid could spill. As with a glass ampoule, most participants held the ampoule at a slight angle when drawing the vaccine, angling the tip of the needle diagonally into the corner of the tilted ampoule. All but one user correctly separated a single ampoule from the strip, removed the cap, and drew liquid using the standard injection method on the naïve use, although only two individuals thought to tap out liquid from the top of the container before twisting off the cap. Common observations with the ampoule are summarized in Table 8.

One anticipated possible use error that did not occur during the mock-use activity was needlestick injuries. Needlestick injuries were of particular concern because of the small size of the ampoule and its orifice. Moreover, due to the ampoule's size there was also a concern that if the user were rushing during typical clinic flow, he or she might drop the container, which could result in vaccine loss and an incomplete dose being delivered. Although it was not observed, there was a possibility that the open ampoule could have fallen over, and the contents of the container would have spilled out. Most users propped up the ampoules on their work stations, and the ampoules usually were not able to stand up without support due to uneven work surfaces.

TABLE 8. **Common ampoule usability observations.**

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
HAZARD-RELATED USE ERRORS		
Liquid trapped in the cap spilled after not tapping the cap to knock down the liquid. **Observed during naïve use and second use after instructions.** **POTENTIAL HARM:** Risk of incomplete dose being delivered.	It was not intuitive to naïve users to tap down liquid trapped in the cap before opening the ampoule since it is not part of their normal routine when opening an ampoule. After instructions, most users simply forgot to tap the cap before opening, which caused liquid in the cap to spill out the side as the seal was broken.	 (Video)
Liquid splattering while opening container. **Observed during second use after instructions.** **POTENTIAL HARM:** Risk of incomplete dose being delivered.	In one instance, when too much force was used to remove the cap (twisting and pulling using a back-and-forth motion), the liquid splattered into the user's face when they removed the ampoule from the strip.	 (Video)
Piercing side of device instead of removing the cap and drawing through the orifice. **Observed during naïve use only.** **POTENTIAL HARM:** Injection of plastic particles into patient.	Participants chose to pierce the needle through the side of the container to draw out the vaccine in some cases of naïve use. Although they were unable to articulate the reason they concluded this was the appropriate method for drawing out the vaccine, it should be noted that there are use cases where a HCW may pierce a plastic container during the course of her job duties—for example, drawing water for injection from a sterile plastic bottle (however, it is unknown if this is a recommended practice or a "shortcut" by HCWs).	 (Video)
Using ampoule as an oral dropper. **Observed during naïve use only.** **POTENTIAL HARM:** Reduced vaccine efficacy, increased local adverse reactions.	Administering the dose orally rather than intramuscularly (in the video, the condom represented a patient's mouth). The misconception was related to the shape of the ampoule, which looks more like an oral vaccine dropper, such as oral polio vaccine and oral rotavirus vaccine, than an ampoule.	(Video)

OBSERVATION	BEHAVIOR/MISCONCEPTION THAT LED TO ACTION	PHOTO/VIDEO
USE DIFFICULTIES		
Standing ampoule upright. **Observed during naïve use and second use after instructions.**	Users had to set the ampoule down very carefully to get it to stand, and some users had difficulty keeping the ampoule standing upright due to its small size and weight. There was some fumbling observed when attempting to stand it upright after it had been opened.	 (Video)
Difficulty drawing liquid from ampoule. **Observed during naïve use and second use after instructions.**	Users slowly inserted the needle into the orifice, and fumbling was observed during drawing of liquid due to the small overall size and orifice of the ampoule. It took some users multiple attempts to draw the entire contents from the ampoule into the syringe, and they had to try different angles and move around the syringe within the container.	(Video)
Removing cap. **Observed during naïve use and second use after instructions.**	Some users struggled to remove the cap from the ampoule, and fumbling was observed. In some instances, it took several attempts to successfully remove the cap.	 (Video)

Abbreviation: HCW, health care worker.

ACCEPTABILITY

The acceptability of BFS containers varied among users and stakeholders in this evaluation. In general, BFS containers were considered useful because (1) single-dose formats (in general) can reduce wastage; (2) they are easier to dispose of with pit burning; (3) they are perceived to be lighter than glass vials; and (4) they are perceived to not break as easily as glass vials. However, users and stakeholders in both countries also expressed concerns about the utility and acceptability of the different BFS container designs and had concerns over the perceived safety of the BFS container material. Moreover, BFS containers are not suitable for lyophilized vaccines requiring reconstitution; therefore, they could only be used for liquid vaccines. This was not evident to most participants without prompting.

In general, the BFS container material was regarded differently in Vietnam and Uganda, which was influenced

User trying for the second time to assemble compact, prefilled, autodisable device.

by the perceived value of the plastic product. In Uganda, users and stakeholders found the design appealing and considered the BFS containers to be superior to glass vials because they were novel. In contrast, stakeholders in Vietnam preferred the look of glass vials to that of plastic containers. They considered glass to be of higher quality than BFS containers since it appears more expensive, sturdier, and visually appealing. Although the value was perceived differently between countries, interviewees from both Vietnam and Uganda agreed that the BFS container material would reduce vaccinators' concerns about glass vials breaking during transport. This was especially relevant to outreach settings where vaccinators travel long distances with vaccines across uneven terrains. Likewise, stakeholders in both countries had concerns about the ability of the BFS plastic material to protect vaccines from freezing temperatures—they wondered whether the plastic would subject vaccines to freezing faster than glass.

Single-dose containers were considered advantageous because they could reduce wastage compared to multidose containers. However, increasing the cold chain footprint compared to current multidose vial presentations was a potential issue cited by some users and stakeholders.

Device-specific considerations

CPAD acceptability

In gauging the overall acceptability of the CPAD, stakeholders weighed the speed and usability of the device once it was assembled with the potential usability difficulties that contributed to the device leaking and delivering insufficient dose. Users in Uganda found the novel design appealing and expressed delight when they discovered how to assemble it, but assembly was usually incomplete or incorrect, which led to frustration as the user attempted to manipulate the device. Once they learned how to assemble it correctly, Ugandan users perceived the CPAD as a convenient tool because they believed it would take less time to administer a vaccine compared to the standard needle-and-syringe technique since fewer steps are required. This advantage was also noted by stakeholders in Vietnam, who were primarily concerned with the challenging usability of the device but noted that, because of its size and speed of delivery once assembled, the CPAD would be good for outreach settings. The CPAD was also perceived as having a lower risk of needlestick injuries than the standard needle and syringe.

After initial use difficulties, a user has an "aha" moment once she figures out how to correctly assemble the needle hub and blister.

Stakeholders in both countries noticed that it was difficult to squeeze the blister to expel the contents and expressed concern over the ability to deliver the sufficient dose with one squeeze and the potential for hand fatigue. They were also worried about the potential for the user's fingers to contaminate the hub or nozzle during assembly, a hazard-related error.

Perceived advantages and disadvantages are summarized in Table 9.

TABLE 9. Acceptability of compact, prefilled, autodisable device.

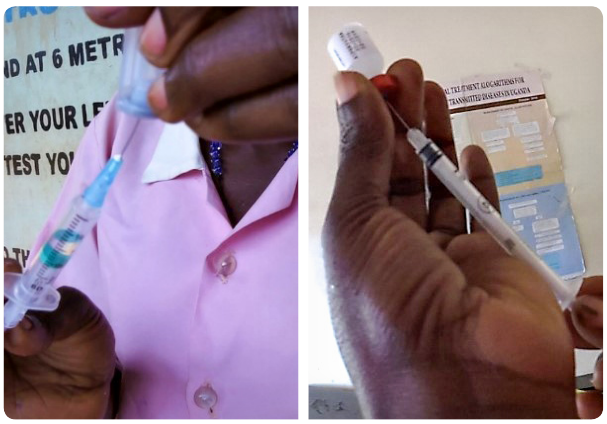
PERCEIVED ADVANTAGES	PERCEIVED DISADVANTAGES
• Ease of use (after assembly is complete). • Speed of delivery (faster than needle and syringe—no drawing required, which makes work easier). • Novel design (appealing). • Ease of transport (few components, so carries well).	• Insufficient dose volume with one squeeze—multiple squeezes needed, need to apply force. • Multiple squeezes potentially harmful or injurious to babies. • Stiff material—hand will get tired. • Difficulty of use—assembling needle hub and blister correctly was challenging. • Need for training—hard to teach, takes time, steep learning curve. • Challenging design—no top, container is open; bottom is round; might lose vaccine.

Vial acceptability

Users in Uganda and stakeholders in both countries liked and appreciated the vial presentation due to its familiarity. They found the process of drawing liquid out of the vial intuitive since it mimics their current technique. In addition, among stakeholders in both countries, the vial was perceived as being safe from contamination because of the septum; this was particularly emphasized among stakeholders in Vietnam. However, the risk of water/contamination seeping in between the plastic overmold and the septum was also raised as a potential concern. Furthermore, stakeholders raised concerns that the opacity of the vial walls could make it difficult for users to correctly perform the shake test. There also was concern among some stakeholders that it would be difficult to draw the complete dose from the vial. PATH bench testing found, however, that the shake test was similarly accurate for glass vials and BFS containers.

In general, stakeholders' statements related to the acceptability of the vial were limited by the familiarity of the design. Perceived advantages and disadvantages are summarized in Table 10.

A user examining the vial strip before naïve use.



The same user drawing from a blow-fill-seal vial (left) and glass vial (right).

TABLE 10. Acceptability of vial device.

PERCEIVED ADVANTAGES	PERCEIVED DISADVANTAGES
• Familiar and easy-to-use. • Easy to hold and manipulate. • Easy to store in vaccine carrier. • Safe since septum prevents contamination and spilled vaccine. • Easy to remove from strip, and no uncapping required once removed from strip. • Unbreakable due to thick walls.	• Vial is opaque and stopper limits visibility—cannot see if vial is empty or contents are damaged. • Vial does not have a base, so it cannot stand. • The size of the container is large compared to the dose volume. • Appearance is less desirable than standard vial (Vietnam only). • It is difficult to draw through the septum, which could dull the needle (Vietnam only).

Ampoule acceptability

Among stakeholders in both countries, the folding "accordion" single-dose format of the strip of five ampoules was appealing due to its small cold chain footprint. However, a final design of the BFS ampoule would require inclusion of labeling space, including vaccine-specific information such as the vaccine name, VVM, expiry date, and lot number. Depending on the impact of this additional labeling on product size, the potential space-saving benefits of the accordion-style design of the ampoule compared to single-dose glass vials (or other single-dose presentations) could be reduced.

Size comparison of ampoule to the two-dose pneumococcal conjugate vaccine vial.

Moreover, users in Uganda liked that the ampoule stands upright when (carefully) set down. In Vietnam, stakeholders noted that the absence of a septum ensures the needle will not be blunted by penetration through the rubber prior to injection. However, stakeholders were concerned about contamination due to the proximity between the vaccinator's fingers and the ampoule orifice during removal of the cap, a hazard-related use error. Similarly, the possibility of vaccine spillage during opening was a concern to stakeholders in both countries. Furthermore, the risk of a needlestick injury—while attempting to insert the needle into the small orifice or in cases where the user pierces through the plastic wall—influenced stakeholders' perceptions of the overall acceptability of the ampoule. Perceived advantages and disadvantages are summarized in Table 11.

TABLE 11. Acceptability of ampoule device.

PERCEIVED ADVANTAGES	PERCEIVED DISADVANTAGES
• Small cold chain footprint. • Ease in opening. • Perception of ability to stand it up due to base. Ease in packing and transporting (for outreach activities).	• Small size—difficult to insert needle, might result in needlestick injury. • Possibility of puncturing the side of the container—risk of needlestick injury and vaccine loss. • Contamination risk—between fingers and orifice. • Possibility of vaccine spillage when opening—patient may not get full dose.

Discussion

Stakeholders were concerned about potential contamination when vaccinators' fingers touch the orifice of the ampoule during uncapping.

In both Uganda and Vietnam, participants chose the vial design over the CPAD or ampoule as their preferred container design. In Uganda, participants ranked the CPAD second and the ampoule third. In Vietnam, a subset of participants ranked the ampoule as their preferred container design and one participant ranked the CPAD as their preferred container design.

Although users and stakeholders highlighted advantages and disadvantages of all the three BFS containers, when considering trade-offs in choosing a product, perceived sterility, familiarity, and cold chain flexibility (ability to take individual containers out of the cold chain) were prioritized over speed of delivery and cold chain volume. For these reasons, the vial was most acceptable among stakeholders in both countries. While stakeholders recognized the advantages of the CPAD—namely that a separate needle and syringe would not be required and, once assembled, the speed of delivery is superior—users and stakeholders alike perceived it as not intuitive to assemble. Moreover, design challenges, like the stiff blister and the insufficient dose volume delivered per squeeze, outweighed the perceived advantages of the device. Similarly, while stakeholders admired the compact design of the ampoule, the small size raised concerns of orifice contamination and risk of needlestick injury. Although the vial did not have the novel appearance of the CPAD nor the compact cold chain volume of the ampoule, it addressed stakeholders' high-priority concerns and needs and was therefore preferred overall.

OPERATIONAL FIT

Clinic flow

The BFS containers fit well within the standard task flow of immunization sessions in the clinic setting. They can be stored the same as glass vials in the refrigerator or vaccine carrier during use. BFS containers would also be used at the same time during an immunization session, without adding additional steps to current practice or introducing other users, compared to the existing task flow.

"ASSEMBLY-LINE" FLOW OBSERVED IN A ROUTINE IMMUNIZATION SESSION IN UGANDA:

- Arrive and wait.
- Weigh child.

Lesser-trained health care worker records weight in child health booklet.

- Wait.
- See vaccinator.

Health care worker evaluates which vaccines are indicated and records in the vaccine register and child tally.

- Wait until most mothers have arrived.
- Health talk in group setting.

Child receives vaccines and other interventions from skilled health care worker as indicated.

- Depart.

Right-sizing doses to immunization-session size

Vaccine containers staged in foam of vaccine carrier during immunization session.

HCWs in both countries use vaccine carriers to store the allotment of vaccines intended for each immunization session. Generally, the carrier is loaded with vaccines at the start of the day and either is kept at the table or other location where immunizations are given or is sent with the outreach team for the day. Stakeholders in both countries noted that the ability of vials and ampoules to be individually labeled and, therefore, to be removed from the larger strip of five and stored singly in a vaccine carrier is a preferred attribute, as it enables the HCW to right-size the load of vaccines in his or her carrier to the expected size of the immunization session. The particularly small design of the ampoule was viewed both positively and negatively as it applies to these contexts: negatively because the small size could be lost at the bottom of the carrier and positively because the small size is optimal for nesting into the foam at the top of the vaccine carrier, which was appealing, although this is not a recommended practice. In contrast, the entire CPAD MMD strip would have to be stored in the carrier and any unused doses returned to the cold chain at the end of the day, limiting the HCW's ability to align carrier load with the expected size of the session. This poses the risk of intentional misuse, whereby the HCW removes a subset of doses from the strip in the morning and stores them away from the primary label and VVM throughout the duration of the immunization session.

Training requirements

Users in Uganda and stakeholders in both countries noted that training requirements for the vial and ampoule would be minimal and would be easily completed in a peer-to-peer format. However, the ampoule would likely require slightly more training than the vial in order to ensure users are safely handling the small container to prevent needlestick injuries and prevent contamination.

However, stakeholders noted that more intensive training would be required for the CPAD device, and peer-to-peer training would most likely not be sufficient to adequately train vaccinators. In particular, training would need to emphasize attaching the needle hub to the blister and avoiding contamination of the nozzle, needle, and hub during assembly. During the usability testing in Uganda, users spent time fumbling with the device as they attempted to attach the needle hub to the blister and attempted to deliver the full dose by squeezing the blister multiple times. Training on the correct assembly, squeezing technique, and need to avoid squeezing multiple times to deliver the dose would be critical to CPAD use. With adequate training, a proficient CPAD user could reduce administration time compared to current practices with a standard glass vial since filling a syringe is not required. Adequate training to properly use the CPAD with ease would likely require a half-day training session with hands-on practice with the device, in addition to vaccine-specific training (required injection depth, vaccination schedule, adverse event following immunization monitoring, etc.). Refresher training and post-introduction monitoring would also be critical for introduction of a new, unfamiliar product.

Disposal requirements

Disposal of sharps waste is a logistical burden for immunization programs and the facilities in which they operate. All polymer containers, such as BFS, offer advantages over glass containers in settings where the

primary disposal method is burning in a pit. Glass, including vials and prefilled syringes, presents a unique challenge for pit burning as it does not burn easily and can explode and shatter. Stakeholders noted that pit burning of plastic containers would be easier and could result in a more complete burn. However, some stakeholders also noted concerns about the pollution created by burning plastic. WHO states that incineration (which uses a higher temperature that results in a cleaner burn than pit burning) can pose both environmental threats and health risks.[24,25] The environmental impact of pit burning of plastic should be factored into any introduction plan. Moreover, the CPAD's small size compared to a standard needle and syringe could positively impact disposal practices by decreasing the sharps waste volume.

Safety boxes, syringe packaging, and other medical waste are burned in a pit, then buried.

Single-dose presentation

Single-dose BFS containers, including the vial and ampoule, could integrate into existing supply-chain formats in lieu of singe-dose glass vials with minimal disruption to systems. However, single-dose vials are currently only used for a few vaccines in both Vietnam and Uganda, and multidose vials are considered the standard vial size, with many vaccines packaged in 10- and 20-dose vials.

There was mixed feedback from users and stakeholders on their preference for single-dose versus multidose containers. Users and stakeholders highlighted the following advantages of the single-dose containers: (1) single-dose containers would enable vaccinators to right-size the number of doses taken to an immunization session by only removing the appropriate number of containers that are needed from the strip (however, this would require that each individual container have its own label and VVM); (2) in outreach settings, right-sizing the number of doses would reduce the amount of supplies that must be transported to the community during outreach; (3) the single-dose presentation would also reduce vaccine wastage compared to multidose vials, which was a key concern among users and stakeholders in both Vietnam and Uganda.

Vaccine carrier packed with mainly multidose vials for a static immunization session in Uganda.

Cold box filled with multidose vials in Vietnam.

There were several concerns about single-dose presentations—in particular, price per dose and the potential impact on the cold chain, transport frequency and cost, as well as impact on physical and human resources. Stakeholders noted that the price per dose is higher for single-dose than for multidose presentations; however, they also commented that there is a possibility of cost savings through

reducing wastage with single-dose presentations. The impact of BFS presentations on overall costs to the immunization system is vaccine- and context-specific and would need to be further evaluated. In Vietnam, stakeholders were also concerned that the CPAD device would require significant overfill since it is difficult to expel the entire contents of the container and would therefore be costly.

Participants were also concerned about the impact of single-dose BFS containers on the cold chain, since single-dose containers would require a larger cold chain volume compared to multidose vials. In Uganda, cold chain volume was a major concern at the national- and regional-level cold stores. In most of the health centers visited, the refrigerators were not filled to maximum capacity, and the HCWs said they could adjust their supply schedule to be able to store single-dose containers since most of the health centers utilized a pull mechanism and only received new vaccine stocks by request. In Vietnam, the cold chain has already reached capacity, and they are facing challenges with accommodating the new vaccines planned for introduction in 2018. As such, Vietnam's current cold chain volume could not accommodate additional single-dose presentations.

Other concerns were related to transport and distribution of single-dose containers. For example, the single-dose presentation raised concerns for outreach settings. Users and stakeholders cautioned that vaccinators might have to carry multiple vaccine carriers to the community, which could be cumbersome and difficult if they must walk long distances. There was also a concern that single-dose presentations would increase the transport volume and potentially require increased vaccine-distribution frequency, which could disrupt current in-country supply chains. Increased cold chain volume could also impact the number of refrigerated vehicles a country is required to purchase and maintain, as well as the human-resources time to deliver the vaccines. Although the BFS containers could be lighter than multidose glass vials, increased weight was also a concern raised by some stakeholders since shipping is a significant cost when importing vaccines into a country.

While users and stakeholders recognized potential advantages of single-dose containers, in general, most respondents preferred the multidose to single-dose presentations. They requested that the BFS containers be made into multidose presentations, even if that meant using a vial or ampoule design instead of a CPAD.

MMD presentation

Vaccine carriers waiting to be loaded at a Health Centre III in Uganda.

Both the BFS CPAD and ampoule could, in theory, be produced either as single-dose containers (either as separate units or as a strip of individually labeled containers) or in an MMD configuration (containers attached to a strip that are opened upon removal from the strip, thus enabling use of a single label and VVM for all containers on the strip). As a BFS vial remains closed upon removal from a strip, it would require individual labeling regardless of whether the containers were distributed as individual units or on a strip. In general, stakeholders and users did not prefer the MMD configuration over single-dose containers or a strip of individually labeled containers due to the inability to right-size the number of containers loaded into a vaccine carrier to the size of the immunization session. The MMD design was of interest because it would reduce the label size and VVM cost per dose compared to single-dose, individually labeled containers, which were considered potential advantages by supply-chain stakeholders, but not to the detriment of safety (risk of dose disassociated from VVM) or usability (risk of inappropriate injection or insufficient

dose). Some users speculated that vaccinators would likely cut the individual blisters off the strip in order to right-size the number of doses that are transported to the site of the immunization session. As a result, unlabeled vaccines without a VVM would be loaded into the vaccine carrier (which would be a hazard-related use error). Respondents commented that the MMD design could result in less vaccine wastage than a multidose presentation due to a reduction in open-vial wastage, a feature that is also true of any single-dose presentation.

Table 12 summarizes key attributes of the BFS container designs compared to currently available parenteral vaccine containers to allow comparison of the advantages and disadvantages of multidose, single-dose, and MMD presentations.

TABLE 12. Considerations of multi-monodose/strip designs for parenteral vaccine containers.

ATTRIBUTE	MULTIDOSE GLASS VIAL	SINGLE-DOSE GLASS VIAL	UNIJECT™	BFS CPAD (V1. CPAD DESIGN)	BFS SINGLE-DOSE VIAL	BFS AMPOULE
Potential strip format options	NA	NA	Individual containers, strip potentially feasible	MMD strip, non-MMD strip, individual containers	Non-MMD strip, individual containers	MMD strip, non-MMD strip, individual containers
Strip format of prototypes assessed	NA	NA	Individual containers	MMD strip (containers automatically open upon separation)	Non-MMD strip (container closed upon separation from strip)	Non-MMD strip (container closed upon separation from strip)
Labeling and VVM requirements of current format	Multiple doses use single label and VVM	Each dose needs label and VVM	Each dose needs label and VVM	One label and VVM for multiple doses	Each dose needs label and VVM	Each dose needs label and VVM
Vaccine wastage	10%-20% (vaccines with preservatives)[a]	5%[b]	No data[b]	No data[c]	No data[b]	No data[b]
Delivery device logistics	Compatible with standard AD N&S	Compatible with standard AD N&S	Single unit	Uses proprietary AD needle hub.	Compatible with standard AD N&S	Compatible with standard AD N&S
Cold chain volume	~2-3 cm^3 (10-dose vial) ~4 cm^3 (5-dose vial)	~15.0 cm^3	10.5 cm^3	5.5 cm^3	9.0 cm^3	2.6 $cm^{3,d}$
Delivery device volume	43.0 cm^3	43.0 cm^3	None required	16.0 cm^3	43.0 cm^3	43.0 cm^3
Estimated fill/finish costs[20]	~$0.22	~$0.59	~$0.60	~$0.38	No data[e]	~$0.33

Favorable; Less favorable; Unfavorable

Note: Uniject is a trademark of BD.

Abbreviations: AD, autodisable; BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable; MMD, multi-monodose; NA, not applicable, N&S, needle and syringe; VVM, vaccine vial monitor.

[a] Detailed product profiles page. Gavi, the Vaccine Alliance website. Availablle at https://www.gavi.org/about/market-shaping/detailed-product-profiles/. Accessed March 28, 2018.

[b] Likely similar to glass, single-dose presentation, or lower due to reduced breakage.

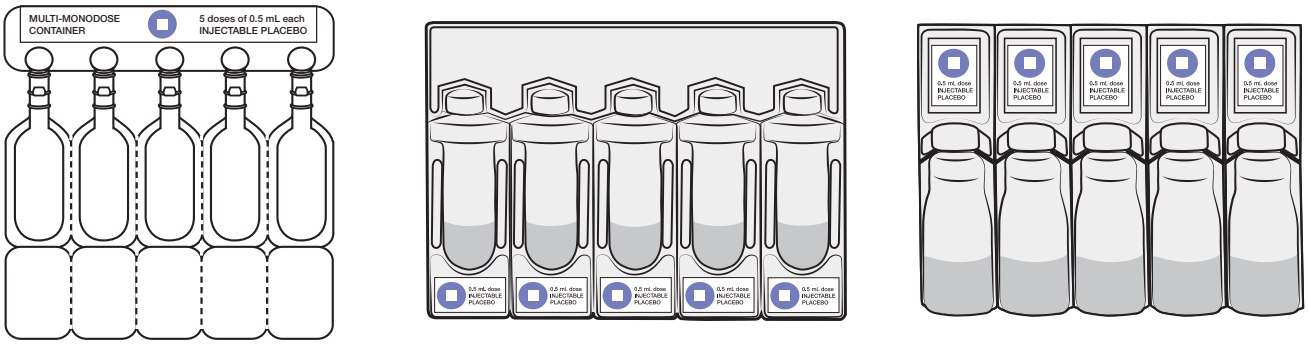
[c] Potentially similar to glass single-dose presentation. Unknown how requirement to store as a strip may impact wastage.

[d] Prototype container has insufficient label space; actual container would require a larger tab, increasing cold chain volume.

[e] Will be higher than other BFS containers due to inset septum.

Discussion

The programmatic suitability of BFS containers in low-resource settings and how well they can integrate into widely varying clinic flows will depend on the particular design of the BFS device, the capacity of HCWs at the clinics, and the strength of peer-to-peer training networks to ensure correct use. BFS containers would not be suitable for lyophilized vaccines requiring reconstitution, which was perceived as a disadvantage among participants, though they can be used for diluents. The integration will also largely rely on the willingness of the clinic managers and national-level EPI managers to select single-dose presentations and the ability of cold chain managers to increase capacity at the necessary levels of the cold chain. These issues should be addressed parallel to product development of BFS containers and development of vaccines in BFS presentations. For countries like Vietnam that manufacture vaccines locally, filling equipment would need to be purchased and facilities set up in-country. Weighing the benefits of reducing wastage with the increased price per dose, cold chain volume, and disposal volume for a single-dose presentation will be critical to country decision-making and the overall value proposition of BFS containers. Moreover, although participants commented on the potential for cost savings, in a recent PATH economic analysis of BFS containers for vaccines, the potential reduction in vaccine wastage of shifting to a single-dose BFS presentation for a parenteral vaccine did not fully offset the estimated increase in fill/finish, transportation, and storage costs compared to a multidose vial. The analysis did find however that BFS presentations have the potential to reduce the overall cost of delivery compared to single-dose glass vials.[26]



Comparison of labeling and VVM requirements of CPAD, vial, and ampoule container designs.

Vaccine manufacturers' perspective

Vaccine manufacturers in Vietnam noted some potential advantages of BFS containers, including the fact that they are convenient for the user and cold chain storage. However, manufacturers cautioned that there is not enough labeling information and space on the containers to meet regulations in Vietnam. There were also concerns about vaccine stability in plastic containers, particularly for adsorbed vaccines. Additional information on user requirements, stability data to confirm that the BFS fill/finish process meets vaccine quality standards, and the price of the product would help incentivize manufacturers to consider adopting BFS containers for their products.

Vaccine vials produced locally in Vietnam.

Vietnamese manufacturers indicated that a change in DPC involves a consultation between different stakeholders and consideration of the trade-offs between program need, cost, and cold chain constraints. The key stakeholders involved in the DPC decision-making process include (1) NEPI, to provide the consultation on DPC as an end user; (2) the Administration of Preventive Medicine and leaders of the MOH, to determine the price of the product; and (3) the manufacturers, to provide rationale on the DPC and determine the cost accordingly. Vaccine manufacturers consider NEPI to be the most important stakeholder in deciding which vaccine presentations to manufacture and use in Vietnam. The director of the Institute of Vaccine and Medical Biologicals described the process as follows: The decision to change the DPC is decided based on the discussion between the manufacturer and NEPI, in which they consider the different immunization settings used in the EPI as well as the production costs. Then the manufacturer submits a DPC proposal to the MOH for approval, since the MOH decides the cost and price of the vaccines.

Vietnam has recently changed the DPC of some of their vaccine products, which suggests they could be open to switching from glass vials to single-dose BFS containers. For example, in Vietnam, the DPC for the BCG presentation was reduced, at the request of NEPI, from 20-dose to 10-dose vials to reduce wastage. The HepB presentation was also switched from 2- to 1-dose vials since the pentavalent vaccine was introduced; the monovalent HepB vaccine is now exclusively used for birth dose.

Recommendations for future BFS development

Based on key feedback from users and stakeholders, as well as bench-testing results, the following recommendations are proposed to improve the current prototype designs—in particular their usability, acceptability, and operational fit. Continued refinement of the prototypes to address key human factor considerations will strengthen the prototype designs and ensure that the final product design is acceptable to users and reflects the programmatic preference within current immunization practices, as well as within EPIs in low-resource settings.

CPAD RECOMMENDATIONS FOR FUTURE DEVELOPMENT

The following improvements to the CPAD design are recommended to improve usability, acceptability, and operational fit of the current CPAD prototype:

- **AD feature.** For the CPAD device, an AD feature in compliance with international standards (ISO 7886) that prevents intentional reuse of both the container and needle hub is a critical feature of any future design; this will be required for WHO prequalification.

- **Squeeze force.** The squeeze force required to expel the complete dose must be within acceptable limits for a repeat task (strain) and also a task requiring precision (safety), per accepted human factors principles. The squeeze force should not exceed a maximum of 15 N pinch force, which is 30 percent of the maximum voluntary contraction.[27] However, the modification of squeeze force must not exacerbate leakage events during opening of the container, which is a potential concern in reducing the squeeze force.
- **Dose delivery.** The need for multiple squeezes is not acceptable to users and represents a significant safety hazard. It is also likely not feasible when administering a vaccine to an infant. As seen in the bench testing, the first squeeze only delivered 54 percent of the dose on average, and a second squeeze resulted in 90 percent of the dose being delivered. In the usability testing, up to eight squeezes were required to expel all the liquid in the container, which suggests the blister should be redesigned to ensure the complete dose is easily and consistently delivered using a minimal amount of squeeze strength.
- **Secure attachment of needle hub to blister.** To prevent the needle hub detaching from the blister due to misalignment with lugs, a revised mechanism of attachment should be considered that allows for nondirectional alignment or more obvious visual cues. Either pushing or twisting mechanisms should ensure that the CPAD is properly assembled.
- **Prevent contamination risk.** Design elements that prevent contamination of the orifice and hub during assembly should be added, since this was a major concern among users and stakeholders.
- **Visual cues.** Users follow visual cues to determine the correct use for a container. Therefore, it should be immediately obvious with the CPAD container that a needle must be attached, or the container should come with the needle already attached to avoid confusion with oral vaccine droppers.

VIAL RECOMMENDATIONS FOR FUTURE DEVELOPMENT

The following improvements to the vial design are recommended to improve usability, acceptability, and operational fit of the current vial prototype:

- **Upright placement.** For the vial, revising the design to enable upright placement once the container is removed from the strip would improve usability.
- **Reduce cold chain volume.** Further size reductions of the single-dose vial may be possible without compromising usability, achieving greater cold-chain volume savings compared to single-dose glass vials.
- **Multidose BFS vial.** Designing a multidose version of the BFS vial would also be favorable because it would leverage the benefits of a plastic BFS container without increasing the cold chain volume.
- **Container transparency.** The design of the container should be improved so that the user can easily confirm that all the liquid has been removed from the container.
- **Individual labeling tabs.** Individual labeling tabs for each vial should be added, as the strip is not an appropriate place for the label of a single-dose container.

AMPOULE RECOMMENDATIONS FOR FUTURE DEVELOPMENT

The following improvements to the ampoule design are recommended to improve usability, acceptability, and operational fit of the current ampoule prototype:

- **Dose delivery/closure design.** Users' concerns about the vaccine getting trapped in the cap and spilling when opening the ampoule could be mitigated with an adjustment to the closure design. Although tapping the cap is effective at knocking down any vaccine trapped in the cap, it is not intuitive to users since it is not part of their current protocol. Therefore, another design feature should be employed to ensure no liquid is trapped in the cap.

- **Prevent contamination risk.** To avoid contamination, future designs should enable the user to remove the closure without handling the area around the orifice of the ampoule. Design files should document this mechanism of preventing contamination.
- **Upright placement.** It was perceived as an advantage that the ampoule had a base; therefore, the bottom of the ampoule should be redesigned for better stability to help the container stand up without risk of falling over or the need for support to prop it up.
- **Visual clues.** Some users confused the ampoule with an oral vaccine dropper; therefore, visual cues to determine the correct use for a container are recommended. The ampoule design should clearly indicate that the container is intended for parenteral vaccines, perhaps by more closely mimicking current glass ampoule form factors.
- **Labeling space.** A larger tab or other feature should be added to the container to ensure that appropriate labeling space is available for important information, including the vaccine name, VVM, expiry date, and lot number.
- **Dose withdrawal.** Future designs should optimize dose withdrawal from the orifice with an AD needle and syringe. For example, increasing the overall size of the ampoule container would improve usability. Users fumbled with the small container and very slowly inserted the needle into the orifice, both of which could be mitigated by increasing the size of the container.

Next steps

The upcoming introduction of GlaxoSmithKline's BFS MMD presentation of ROTARIX® vaccine (ROTARIX is a registered trademark of GlaxoSmithKline Biologicals S.A.), anticipated to receive regulatory approval in 2018 and introduced in 2019, will be a key opportunity to gather programmatic data on the suitability of MMD in different use environments. Such a study would provide key insights into the real-world impact of MMD on supply-chain volumes and managers' trade-offs to inform decision-making. This type of evaluation would be particularly useful since users and stakeholders in PATH's evaluation had concerns about the MMD design. Evaluating an MMD product during programmatic use will also help potential users better understand the labeling and VVM implications of single-dose versus MMD presentations, allowing the provision of better-informed feedback on preferences, as well as an assessment of the impact on vaccine wastage and logistics.

A bench evaluation of the CPAD disposal volume could also be conducted to compare it to a standard AD needle and syringe, evaluating the degree to which the overall disposal volume could be reduced. Participants' concerns about the risk of water/contamination seeping in between the plastic overmold and the septum also could be further qualified through bench testing. More rigorous testing to confirm the results of the shake test should be conducted as well, since stakeholders were concerned about the reliability of the test in BFS containers.

Another future step for BFS containers is to conduct an iterative human factors evaluation with next-generation prototypes that addresses the design challenges identified through this analysis and includes labeling, primary packaging, and VVM placement. Evaluating labeling considerations from a manufacturing and regulatory perspective is critical to designing a product that meets these requirements, as well as user and programmatic needs, since labeling will impact the overall size of the container. Participants in this evaluation requested that the containers include labeling and a VVM to help them better visualize what the final product would look like. This is particularly relevant for the current version of the ampoule prototype, which was designed to be as small as possible, whereas the final product would be larger to

accommodate labeling requirements. A more robust human factors evaluation with refined prototypes will further improve the product designs and ensure that user feedback is gathered throughout the product development process.

Furthermore, it would be useful to explore the value proposition of a multidose BFS vial since most participants preferred multidose presentations. A costing analysis should be conducted to better understand differences in the health impact, increased reach, safety, commodity costs, and delivery costs of multidose BFS vials compared to single-dose BFS vials and multidose glass vials.

Future considerations

BFS containers have the potential to make the benefits of single-dose presentations more accessible to low-resource settings. Moreover, single-dose containers could eliminate vaccinators' reluctance to open multidose vials in fear that they will not be able to use all the doses before the vial must be discarded. As a result, with single-dose BFS containers, more children may be vaccinated on their first contact with health services—instead of being told to return to the clinic at a time when more children could be gathered and vaccinated together—thus increasing vaccine coverage rates.

Single-dose BFS containers might be more suitable for liquid vaccines that cannot be packaged in larger, multidose presentations due to the lack of a preservative, such as HPV or new vaccine candidates in development, which are typically packaged in single-dose presentations. Single-dose or MMD BFS containers could also be advantageous for vaccines that currently come in multidose containers but have high wastage rates since not all the doses are administered before the vaccine must be discarded, such as TT for women of reproductive age and pregnant women; however, the very low price of these vaccines would make the value proposition of a more expensive single-dose container more challenging.

Another scenario where BFS containers could be beneficial is for newborn immunizations like HepB vaccine, which are provided on an as-needed basis and, in some settings, are administered by midwives or other outreach programs. Therefore, the required number of doses is not as predictable as in a static immunization setting, and the doses in a multidose container cannot always be used before the vaccine must be discarded. Furthermore, BFS containers could be more appropriate for low-throughput clinics and remote areas that immunize fewer children and are hesitant to open multidose vials in fear that they will have to be discarded, unlike high-throughput clinics. However, LMICs typically do not have mechanisms to supply different presentations to different geographic areas within a country, like supplying greater DPC presentations to high-throughput clinics and smaller-dose containers to low-throughput clinics and remote areas. Therefore, it might be more challenging for an LMIC to adopt a BFS container if they must switch to a single-dose presentation for the entire country. However, procuring multiple DPC presentations for each vaccine could, in the future, enable right-sizing the amount of vaccines to each immunization session. At the same time, multiple DPC presentations could still offer cold chain savings over exclusively using single-dose presentations.

Conclusion

All three BFS containers offer potential cold chain savings compared to single-dose glass vials. This advantage was more appealing to stakeholders, including program managers and cold chain managers than to HCWS. HCWs who pack vaccine carriers for individual immunization sessions preferred the flexibility of right-sizing the amount of vaccines to each immunization session. HCWs also preferred the single-dose configuration over MMD because of this added flexibility. However, in general, most respondents preferred multidose presentations to single-dose presentations because of the small cold chain footprint, especially cold chain managers. In settings with particularly strained cold chains, the maximum space efficiency of a standard multidose vial strongly outweighed the potential benefits of BFS containers.

The results of this programmatic and human factors evaluation confirm that the BFS process offers a promising alternative to glass containers for vaccine products. As with glass containers, there is no one-size-fits-all container design—different products will be suitable for different delivery settings:

- Some participants perceived that CPADs might offer advantages of more rapid delivery, once assembled, compared to ampoules and vials that require syringe loading prior to injection. The CPAD design is potentially beneficial in campaign and outreach settings, where time and space for supplies are limited.
- Vials offer the balance of a familiar container requiring little to no training and the potential packing efficiency of a five-dose strip compared to single-dose glass vials. However, when compared with a multidose vial, the latter is preferred due to the smaller cold chain volume.
- Ampoules offer cold chain advantages that may particularly appeal to countries with stressed cold chains that still want the advantages of single-dose formats in order to right-size daily vaccine supplies.

The proposed design recommendations based upon feedback from stakeholders and HCWs (summarized in Table 13) are considered the key takeaways from this evaluation. These recommendations are intended to guide user-centered product development to improve usability, acceptability, and operational fit of the current prototype designs.

TABLE 13. Summary of recommendations for future development.

CPAD	VIAL	AMPOULE
• AD feature • Squeeze force • Dose delivery • Secure attachment of needle hub to blister • Prevent contamination risk • Visual cues	• Upright placement • Reduced cold chain volume • Multidose BFS vial • Container transparency • Individual labeling tabs	• Dose delivery/closure design • Prevent contamination risk • Upright placement • Visual cues • Labeling space • Dose withdrawal

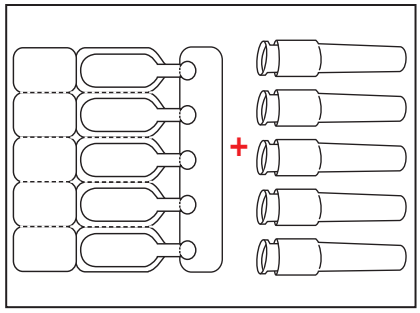
Abbreviations: AD, autodisable; BFS, blow-fill-seal; CPAD, compact, prefilled, autodisable.

Appendix. Product information sheets

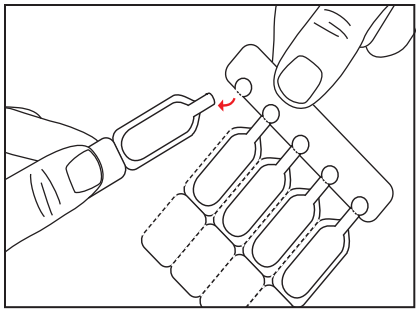
The following product information sheets were used during the usability testing in Uganda and represent the standardized language used by the researchers to describe each device to participants. The language was validated by PATH staff to ensure the instructions were clear and concise for the target audience.

PRODUCT INFORMATION SHEET: CPAD

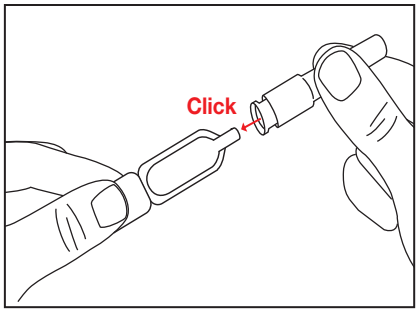
- ☐ Single-dose, plastic container that connects with a specific autodisable needle hub.
- ☐ No need for a needle and syringe.
- ☐ **Five** containers are joined together by a **single** plastic tab.
- ☐ Tab contains a single label and vaccine vial monitor for **all five** containers.
- ☐ Explain multi-monodose: When you remove a container from the tab, it is opened and must be used immediately. We call this "multi-monodose" because once you remove a container from the strip it is "open" the same as drawing into a syringe one dose from a multidose vial.
- ☐ **Step 1:** Remove the container from the strip by grasping the individual tab and twisting until it comes off.
- ☐ **Step 2:** Align the needle hub with the container nozzle so that the lugs (bumps) on the nozzle and round side of the belly align with the corresponding gaps and wings on the needle hub.
- ☐ **Step 3:** Firmly press to attach it to the autodisable needle hub. You may hear or feel a "click" as the lugs snap into place.
- ☐ **Step 4:** The vaccine is delivered by squeezing the container.
- ☐ **Step 5:** Once the vaccine is given, both the container and needle hub should be thrown in sharps waste, just like a needle and syringe.



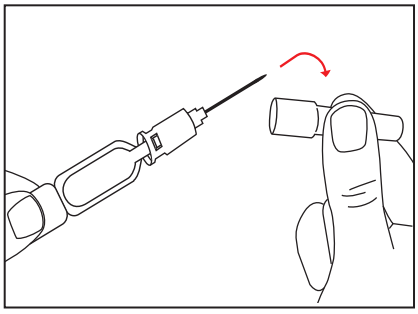
1. Contents



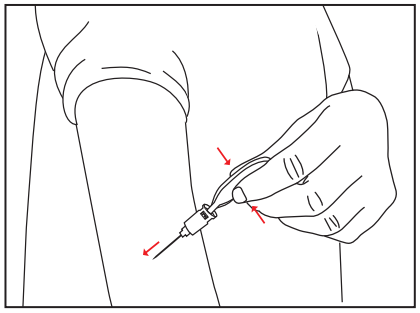
2. Break off one vial



3. Add K6 needle until click



4. Take off cap

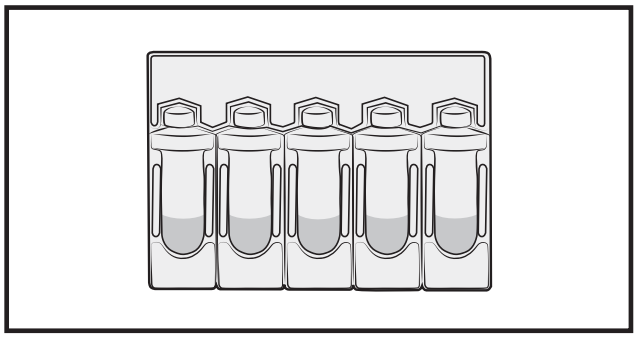


5. Inject

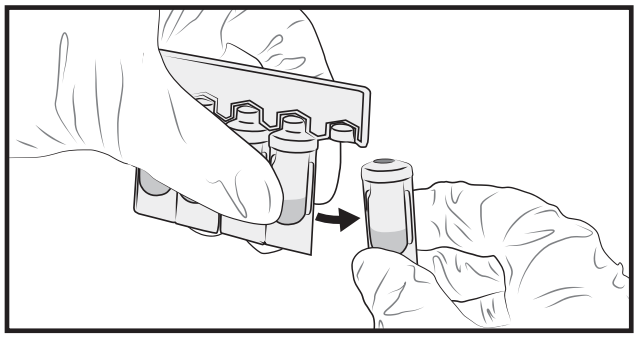
6. Dispose of safely

PRODUCT INFORMATION SHEET: VIAL

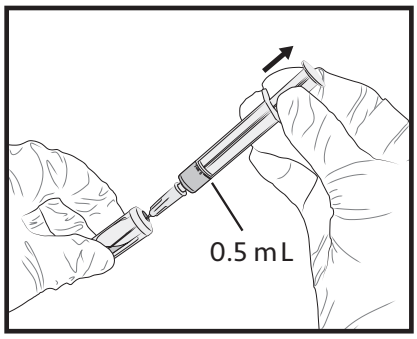
- ☐ This is a strip of five single-dose vials.
- ☐ Mimics a glass vial and has a rubber stopper, just like a regular vial.
- ☐ Each vial on the strip would have its **own** label and vaccine vial monitor, so the actual size may be a bit larger to accommodate the label requirements.
- ☐ **Step 1:** Remove from the strip by twisting and pulling.
- ☐ **Step 2:** Vaccine is drawn with normal needle and syringe.
- ☐ **Step 3:** Deliver vaccine using the standard injection method.
- ☐ **Step 4:** Dispose of the vial in the same way as any other vaccine container and dispose of needle and syringe in sharps waste.



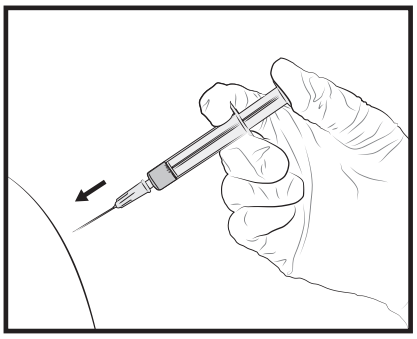
1. CONTENTS



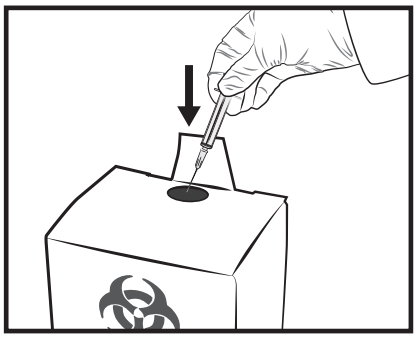
2. BREAK OFF ONE VIAL



3. FILL SYRINGE TO 0.5 mL



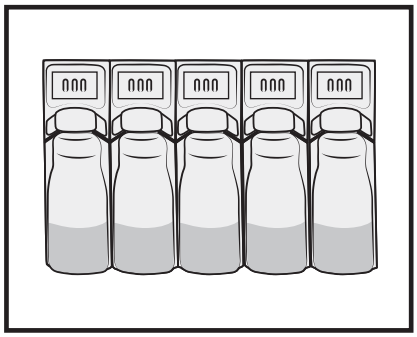
4. INJECT



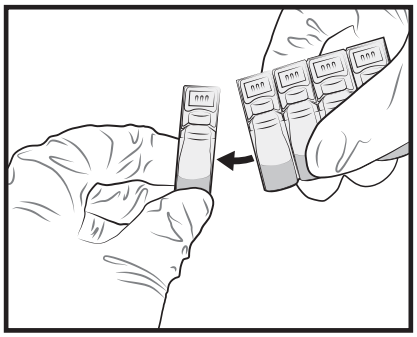
5. DISPOSE OF SAFELY

PRODUCT INFORMATION SHEET: AMPOULE

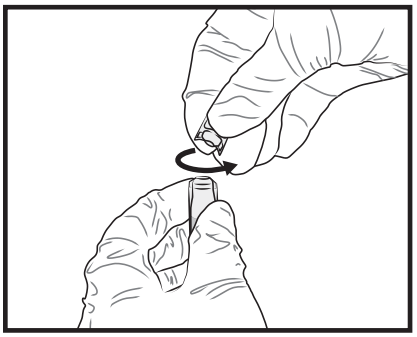
- ☐ This is a strip of five single-dose ampoules.
- ☐ This concept was designed to test the feasibility of folding multiple ampoules into a compact unit to reduce cold chain storage space versus an equivalent number of glass vials.
- ☐ Each ampoule on the strip would have its own label and vaccine vial monitor, so the actual size may be a bit larger to accommodate the label requirements.
- ☐ The ampoules used in this study are separated from each other while remaining sealed, but the ampoules can also be manufactured to tear off from a shared tab (that folds up with the remaining ampoules). We call this shared tab design "multi-monodose" because when you remove a container from the tab, it is opened and must be used immediately. Once you remove a container from the strip, it is "open" the same as drawing one dose into a syringe from a multidose vial.
- ☐ **Step 1:** Remove an ampoule by tearing from the strip.
- ☐ **Step 2:** Tap the ampoule to knock down any vaccine trapped in the cap.
- ☐ **Step 3:** Twist off the cap.
- ☐ **Step 4:** Draw vaccine from the ampoule using a needle and syringe and deliver using the standard injection method.
- ☐ **Step 5:** Throw away in the same way as any other vaccine container and dispose of the needle and syringe in sharps waste.



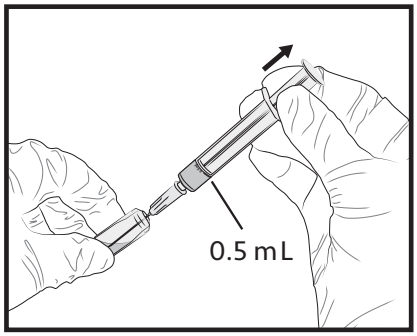
1. CONTENTS



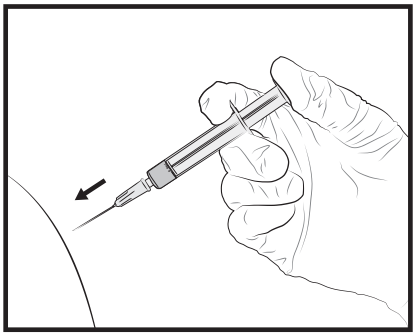
2. BREAK OFF ONE AMPOULE



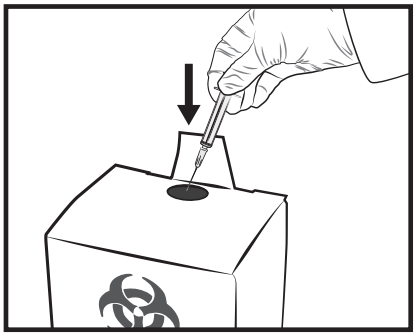
3. TWIST OFF TOP TO OPEN



4. FILL SYRINGE TO 0.5 mL



5. INJECT



6. DISPOSE OF SAFELY

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