Report on the Freeze-Preventive Passive Container Meeting

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Contents

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Executive summary

A meeting on freeze-preventive passive equipment was held in April 2015 to review problems and solutions regarding vaccines being exposed to sub-zero temperatures during transportation using passive vaccine containers. Experts compared different approaches to solve the problem and reviewed three novel potential freeze-preventive technological solutions: a freeze-preventive vaccine carrier, phase-change material coolant packs, and a phase-change material sleeve. In addition, participants helped develop a generic evaluation framework for innovative approaches and outlined the steps necessary to get them to market.

1. Introduction

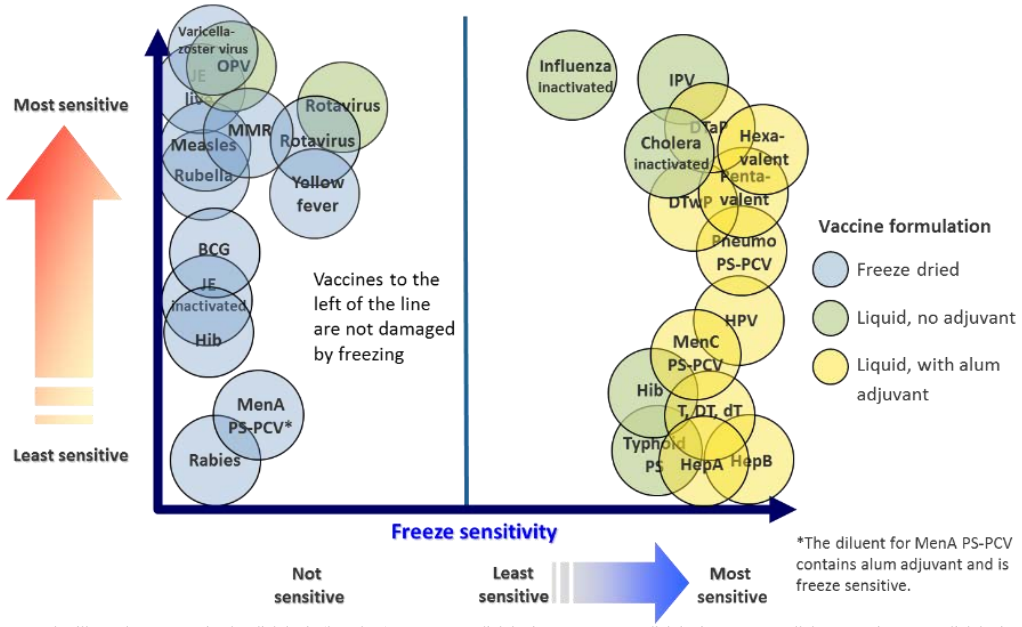
On April 28 and 29, 2015, the United Nations Children's Fund (UNICEF) organized a meeting in New York on freeze-preventive passive vaccine equipment that included cold boxes and vaccine carriers. Experts from the Clinton Health Access Initiative (CHAI); Gavi, the Vaccine Alliance; PATH; and the World Health Organization (WHO) participated in discussions on cold chain technology, outreach, and supplementary immunization activities (SIAs). The meeting objectives included:

- Establishing a common understanding of the existing evidence base on vaccine freezing in passive vaccine containers and the need for user-independent freeze-preventive devices.
- Reviewing potential technological solutions.
- Agreeing on evaluation parameters for new technological solutions.
- Outlining the steps needed to get innovative approaches to market.
- Providing a decision-making framework that is evidence-based so that countries can properly plan for new equipment introduction.

2. Background

Vaccines are biological products that are temperature sensitive. WHO recommends that most vaccines be kept at 2°C to 8°C during storage and distribution. Exposure to freezing temperatures can result in the loss of potency for freeze-sensitive vaccines (Figure 1 shows an overview of the temperature sensitivity of vaccines). In 2007, PATH conducted a systematic literature review of studies from 1990 to 2006 that analyzed freezing temperatures in the vaccine cold chain. The literature review reported that 14% to 35% of refrigerators or transport shipments studied had exposed vaccines to freezing temperatures.[1]

Figure 1. Temperature sensitivity of different vaccines.[2]



Alum: aluminum; BCG: bacillus Calmette–Guérin; dT: diphtheria (low-dose) tetanus; DT: diphtheria tetanus; DTaP: diphtheria, tetanus, acellular pertussis; DTwP: diphtheria, tetanus, and whole-cell pertussis; HepA: hepatitis A; HepB: hepatitis B; Hib: *Haemophilus influenza* type B; HPV: human papillomavirus; IPV: inactivated polio vaccine; JE: Japanese encephalitis; MenA: meningitis A; MMR: measles, mumps, and rubella; OPV: oral polio vaccine; PS: polysaccharide; PS-PCV: PS-protein conjugate vaccine; T: tetanus.

The literature review raised global awareness about freezing (exposure to sub-zero temperatures) during transportation of vaccines using passive vaccine containers and highlights the lack of health worker compliance to WHO's current recommendation for freeze-sensitive vaccines: the conditioning of frozen ice packs.[3] To condition ice packs, health workers must remove frozen ice packs from the freezer and let them warm at room temperature (approximately 25°C). Health workers should shake the packs frequently until the water inside the packs can be heard, and only then can they place the conditioned ice packs in the vaccine carrier or cold box.[4]

3. Meeting proceedings

Joanie Robertson (PATH) discussed the existing guidance and practices around usage of water and coolant packs. WHO handbooks[4,5,6,7] provide clear recommendations as to the circumstances under which frozen, conditioned, cool, or warm water packs should be used. The now-published WHO *Vaccine Management Handbook* contains a module called "How to use passive containers and coolant-packs for vaccine transport and outreach operations"[8] that shows which type of coolant packs can be used based on the presence/absence of vaccine vial monitors (VVMs) and type of storage condition (e.g., liquid, lyophilized) and highlights the complexity of selecting the appropriate approach as shown in Table 1.

Table 1. Coolant-pack options for vaccines with VVMs (left) and without VVMs (right).

Product	Frozen ice-packs	Conditioned ice-packs	Cool water-packs	Warm water-packs
Transport from primary store to health facility				
Liquid vaccines: freeze sensitive		✓	✓ (at sub-zero ambient)	✓ (at sub-zero ambient)
Liquid vaccines: NOT freeze sensitive	✓	✓	✓ (for greater than VVM 7)	
Lyophilized vaccines: separate diluent	✓	✓	✓ (for greater than VVM 7)	
Lyophilized vaccines: packed with diluent		✓	✓ (for greater than VVM 7)	✓ (at sub-zero ambient)
Diluent packaged alone		✓	✓	✓ (at sub-zero ambient)
Transport to outreach sessions				
Liquid vaccines: freeze sensitive		✓	✓	
Liquid vaccines: NOT freeze sensitive	✓ (for campaigns)	✓	✓	
Lyophilized vaccines with diluent		✓	✓	

Note: During outreach sessions, opened vials of unpreserved liquid vaccine and reconstituted vials of lyophilized vaccine must always be kept at a temperature between +2°C and +8°C. If cool water-packs are used for transport, one or more ice-packs must also be taken to the session, unless there is ice-making capacity at the outreach site.

Product	Frozen ice-packs	Conditioned ice-packs	Cool water-packs	Warm water-packs
Transport from primary store to health facility				
Liquid vaccines: freeze sensitive		✓	✓ (at sub-zero ambient only)	
Liquid vaccines: NOT freeze sensitive	✓	✓		
Lyophilized vaccines: separate diluent	✓	✓		
Lyophilized vaccines: packed with diluent		✓	✓ (at sub-zero ambient only)	
Diluent packaged alone		✓	✓	✓ (at sub-zero ambient)
Transport to outreach sessions				
Liquid vaccines: freeze- sensitive		✓	✓ (except for RotaTeq®)	
Liquid vaccines: NOT freeze sensitive	✓	✓	✓	
Lyophilized vaccines with diluent		✓	✓	

Note: During outreach sessions, opened vials of unpreserved liquid vaccine and reconstituted vials of lyophilized vaccine must always be kept at a temperature between +2°C and +8°C. If cool water-packs are used for transport, one or more ice-packs must also be taken to the session, unless there is ice-making capacity at the outreach site.

VVM: vaccine vial monitor.

Adapted from: WHO. How to use passive containers and coolant-packs for vaccine transport and outreach operations. In: *Vaccine Management Handbook*. Geneva: WHO; 2015:7–8.

Pat Lennon (PATH) and Anupa George (UNICEF) provided an update to the 2007 literature review and presented a summary of recently published studies[1,9–16] and grey literature concluding that freezing during transport using passive vaccine containers is a major concern. A 2006 study in Thailand[12] reported 18% (12 out of 67) and a 2013 study from India[11] reported 27% (28 out of 103) of the passive vaccine container shipments were exposed vaccines to freezing temperatures. Unpublished UNICEF studies in two Asian countries in 2010 also showed similar results with 17% (3 out of 18) and 45% (5 out of 11) of shipments exposed. These exposures corresponded to 12% (61 hours of 486) and 27% (27 hours of 99) of the total transport time as detailed in Table 2. This analysis shows that exposure to sub-zero temperatures during transport remains prevalent.

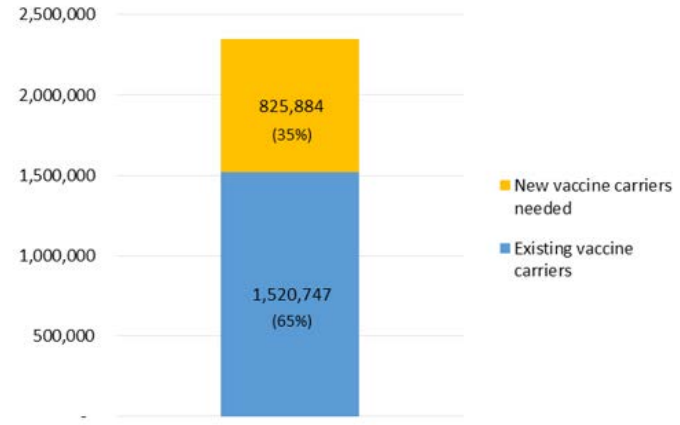
Table 2. Freeze exposure data from two UNICEF studies in Asia (2010).

Country 1				
Level of supply chain	**Time (%)**			
	< 0°C	**0°C to 2°C**	**2°C to 8°C**	**> 8°C**
National	0.0%	0.0%	99.7%	0.3%
Province	0.4%	0.6%	93.7%	5.4%
Health facility	1.2%	5.5%	90.6%	2.7%
Transit (486 total hours)	12.5%	9.5%	61.9%	16.1%
Country 2				
Level of supply chain	**Time (%)**			
	< 0°C	**0°C to 2°C**	**2°C to 8°C**	**> 8°C**
National	0.0%	0.0%	99.8%	0.2%
Province	0.2%	3.6%	89.0%	7.2%
Health facility	3.8%	10.5%	66.0%	19.7%
Transit (99 total hours)	26.7%	18.2%	47.0%	8.1%

Benjamin Schreiber (UNICEF) summarized key findings from the global data analysis of the Effective Vaccine Management Assessment (EVM Assessment)[17] based on data from 58 countries from 2010 to 2013. The analysis showed that passive vaccine containers are the predominant equipment used for transporting vaccines. They account for 96% to 99% of vaccines transported at the subnational, lowest distribution, and service-point levels of the vaccine cold chain. Refrigerated vehicles are rarely used except for isolated cases at the national level. On the other hand, the EVM Assessment data showed that 70% to 85% of health workers at all levels can condition ice packs in accordance with WHO guidelines.[17] It was noted that the EVM Assessment did not evaluate whether health workers actually put this knowledge into practice.

During his presentation on the usage of passive vaccine containers, Gregory Kiluva (UNICEF) reported that the UNICEF Supply Division procured 152,620 vaccine carriers/cold boxes (including coolant packs) as well as 252,448 additional coolant packs in 2014 for various countries. The Supply Division procures only Performance, Quality and Safety (PQS) listed equipment; however, many countries procure cold chain equipment through non-UNICEF channels. Matt Morio (PATH) reported on the market analysis conducted for vaccine carriers for the 73 Gavi-eligible countries. The projected total market for passive vaccine carriers in 2020 is about 2.3 million vaccine carriers (see Figure 2)—US$117.3 million in market value.[i]

Figure 2. Projected market for passive vaccine carriers in 2020.



Note: Projections are based on 73 Gavi-eligible countries.

As is evident, vaccine carrier usage will steadily increase—thus, the issue of vaccines freezing while being transported in them needs more attention.

[i] Market value assumes an estimated selling price of US$50 per vaccine carrier.

4. Problem statement

Current vaccine management handling guidance recommends the conditioning of ice packs to prevent vaccine freezing in passive vaccine containers.[3] However, evidence shows that vaccines are nonetheless exposed to freezing temperatures in these devices, probably due to lack of compliance with conditioning of ice packs. This can affect the potency of freeze-sensitive vaccines. When there is evidence of freezing, vaccine is discarded. This results in a loss of resources and in extreme cases can lead to stockouts. If undetected, the immunogenicity imparted by the vaccines could be compromised. As such, immunization programs need access to technical solutions to avoid freezing during transportation.

5. Technological solutions

Participants compared the different approaches to prevent freezing in passive vaccine containers based on their current status, availability, and other system criteria such as cost, level of disruption,[ii] and cold life. For the system criteria evaluation, participants compared the current recommendation (conditioning ice packs) to other approaches. In addition, participants compared the user independence and acceptability of each approach. Table 3 summarizes the results.

Table 3. Classification of approaches to prevent freezing in passive vaccine containers.

Freeze-preventive approaches	Status	Available	Cost	Level of disruption	Cold life	Is the approach providing a user-independent freeze-preventive solution?	Perceived acceptability to health workers
			Compared to current recommendation of conditioning frozen ice pack				
Condition frozen ice packs	Status quo; recommended practice for all vaccine types in EPI, including all VVM types except in extremely cold ambient temperatures.	Yes	N/A	N/A	N/A	No	Current practice but not always implemented. Proper conditioning of ice packs is a potential burden for health workers.

[ii] The level of disruption is the likelihood a new technology will require system wide changes to a country's vaccine supply chain.

Freeze-preventive approaches	Status	Available	Cost	Level of disruption	Cold life	Is the approach providing a user-independent freeze-preventive solution?	Perceived acceptability to health workers
			Compared to current recommendation of conditioning frozen ice pack				
Cool water packs (that is, stop using ice packs)	Cool water packs are an option in WHO guidelines in certain settings and for certain vaccines, but they have not been widely rolled out, and limited published field research is available.	Yes	Requires separate refrigerator, training, and route profiling to understand if transit times allow for the application of this approach.	Counter to existing guidance/ culture. No major disposal of existing ice packs required.	Shorter and thus maybe adequate for selected routes and vaccines (depends on VVM) only and certain climates.	Yes	Limited at this time—low uptake by countries; counter to historical training; difficult culture change.
Freeze-prevention technologies	Several solutions are under development and in field trials.	2016	TBD, but all solutions will have additional costs compared to conditioning ice packs.	Depends on technology.	Comparable to conditioned ice packs.	Depends on technology.	TBD; depends on solution; will be evaluated in field trials.

EPI: Expanded Programme on Immunization; TBD: to be decided; VVM: vaccine vial monitor; WHO: World Health Organization.

Denis Maire (WHO) presented the approach from the PQS team on exploring freeze-preventive options that can be used during transport where no (or limited) user intervention would be required. PQS is adding user-independent freeze-preventive ratings to equipment specifications, and the PQS team is exploring active transport refrigeration options; however, they are currently expensive. In 2014, WHO published PQS specifications for freeze-preventive vaccine carriers,[18] and the meeting attendees anticipate that—once sufficient products are available on the market—this category will replace the current carriers and cold boxes for freeze-sensitive vaccines. Product developers such as Savsu Technologies (Santa Fe, NM) have explored this territory (NanoQ™ product was tested in Vietnam[19]). However, to date no product developer has come forward with a product for PQS prequalification.

Several options are currently being explored by different partners. Many of these involve the use of engineered phase-change materials (EPCM), which have not been endorsed by WHO PQS based on limited past experiences; however, the team is currently reviewing this stance. Three potential solutions that are exploring safe and leak-free phase-change materials (PCM) were presented at the workshop as detailed below.

Freeze-preventive vaccine carriers

A redesigned carrier that creates a physical barrier between the ice packs and the vaccine compartment.

Pat Lennon reported that PATH has successfully demonstrated bench-level performance for a low-cost freeze-preventive vaccine carrier design using an off-the-shelf passive vaccine carrier with a barrier solution that does not contain any proprietary EPCM.[20] When laboratory tested at 10°C ambient (frozen ice packs at -25°C), the vaccine compartment temperature did not drop below 0°C, and at 43°C ambient (frozen ice packs at both -25°C and 0°C), holdover exceeded 30 hours. Even when used with non-conditioned ice packs, the freeze-preventive carriers will protect vaccines from temperatures below 0°C, preventing vaccine freezing. Advantages of freeze-preventive designs could include longer holdover times than carriers that use cool water packs and a reduced training burden. PATH is also exploring the potential for the redesigned carriers to maintain competitive costs to current carriers. PATH is currently working with three manufacturers to bring this new design to market.

Phase-change material coolant packs

Coolant packs that contain non-water phase-change material (PCM) to replace the current ice packs in current vaccine carriers.

Andrew McCourt reported that the UNICEF Supply Division has tested two paraffin-based PCMs (after eliminating a few other types of PCMs). Without conditioning, they were able to keep the internal temperature of the vaccine carrier within a 2°C to 8°C range for over 24 hours (UNICEF unpublished data). Although the PQS Working Group does not recommend PCMs because of the potential risks to users if there is leakage, the PCMs that were tested are in safe, leak-proof packs. Some of the additional benefits include reduction of bench-time conditioning of frozen packs, optimized payload capacity with minimized weight, and maintenance of design cold-life performance as opposed to subjective conditioned ice packs. Some of the challenges are: PCMs without conditioning can cause cold shocks if placed in carriers after freezing at or below -20°C, PCMs that solidify at positive temperature have a much shorter cold life, inability to use current PQS prequalified water packs as these are non-fluorinated, and potential complexity of disposal at end of life cycle.

Phase-change material freeze-protection sleeve

A retrofit of existing vaccine carriers that wraps a buffer layer around the vaccines to prevent direct contact with the frozen ice packs.

Gopal Nadadur reported that the Clinton Health Access Initiative (CHAI) is currently field testing PCM freeze-protection sleeves, which have been widely used by the pharmaceutical industry. The PCM used in the sleeve is a water-based gel (water and salt). The manufacturer is in Minnesota, USA, and the cost is $30 per unit if bought in large quantities. CHAI is studying the product performance, usability, suitability for underlying system, and total cost of ownership of this technology, and the results will be available soon. One drawback of this technology is that it is not user independent; however, it does eliminate ice pack preconditioning. Regardless, the sleeves may be better suited as an interim solution.

Table 4 compares three potential freeze-prevention solutions in terms of what changes, what additional equipment may be required, and programmatic fit. All three options eliminate the need for conditioning ice packs and reduce vaccine wastage by preventing exposure to sub-zero temperatures. However, it is essential to understand the environment through which vaccines must travel in each country: therefore, transport route profiling is recommended before introducing any new technology.[21] Furthermore, Tables 5a, 5b, and 5c map the advantages and disadvantages that differentiate each solution.

Table 4. Freeze-prevention technology solutions.

Technology and description	What changes	What supporting equipment is needed	Programmatic fit	Other comments	Expected cost (estimated)
Freeze-preventive vaccine carrier	Carrier itself changes, but coolant packs remain the same.	Freezers (unregulated, conditioning independent).	Uses 0.6 L packs; 0.4 L and 0.3 L packs will fit but with an impact on the cool life.	Need to determine impact to holdover for cool water packs.	Estimated cost of US$50 per freeze-safe vaccine carrier.
			Phasing in of new technology and phasing out of old technology.	No conditioning required.	
PCM coolant packs	Coolant packs and the time taken to freeze them change, but the carrier itself remains unchanged.	Freezer (unregulated plus conditioning) or freezer (regulated to specific/higher temperature without conditioning) or refrigerator (set at 2°C).	Phasing in of new technology and phasing out of old technology.	There may be a safety/environmental risk.	$32 to $48 per pack.
				New version of water packs to track may complicate stock management.	
Freeze-preventive PCM sleeve	Requires an additional piece, but the carrier and coolant packs remain unchanged.	Freezers (unregulated, conditioning independent).	Uses 0.6 L packs; 0.4 L and 0.3 packs will fit but with an impact on the cool life.	Need to determine impact to holdover for cool water packs.	$30 per unit.
				Need to determine robustness and stock management impact.	

Technology and description	What changes	What supporting equipment is needed	Programmatic fit	Other comments	Expected cost (estimated)
			Phasing in of new technology.	There may be a safety/environmental risk.	
				Reduces vaccine holding capacity.	

PCM: phase-change material.

Table 5a. Advantages/disadvantages of the freeze-preventive vaccine carrier.

Freeze-preventive vaccine carrier	
Advantages	
All ice packs fit.	Competition (based on similar design).
Works with conditioned packs.	Training simplified.
Cold life (maintained).	Durability (long life).
Assured vaccine potency.	Easily visually identified as freeze preventive.
No leaking PCM/other unknown materials.	May fit in system.
Disadvantages	
Ice pack slot may be too big.	Increased weight and size and/or reduced vaccine capacity.
Price increase.	Cleaning more difficult.
Competition may discourage manufacturers until at least one has been qualified; limited suppliers initially.	Disposal of old carriers.
PQS testing required (laboratory and field).	May confuse system. New model so may require advocacy to each country.
Chilled water pack performance may be negatively affected.	

PCM: phase-change material; PQS: Performance, Quality and Safety.

Table 5b. Advantages/disadvantages of the PCM coolant pack.

PCM coolant pack	
Advantages	
No remolding of current equipment/no extra equipment required.	Minimal training needs.
Simple to use.	Easier implementation/integration into current system.
Freeze safety.	Low investment to bundle with current products/carriers.
Disadvantages	
Will need to retest the current equipment with the PCM.	Long freezing time.
Transition/mixing risk with current ice packs.	Possible customs/regulatory issues because of PCM (though this particular one may be safe).
Cool life reduced if PCM coolant packs inadvertently conditioned.	Cold chain freezing capacity may need to be increased.
Increased cost (shipping).	Risk of leaking.
May have disposal issues.	

PCM: phase-change material.

Table 5c. Advantages/disadvantages of the freeze-protection PCM sleeve.

PCM sleeve	
Advantages	
Do not have to differentiate between freeze-preventive versus normal passive containers according to vaccines.	May have fewer training needs because of health worker familiarity with wrapping vaccines.
Simple to use; easier implementation/ integration into current system.	Minimal difference in weight.
Affordable cost.	Fits in with PQS freeze-free challenge.
Easy to flood market with product.	
Disadvantages	
There may be different sizing for different passive containers.	Sleeve can be removed/lost/stolen; another component in inventory.
Additional work in loading/unloading vaccines.	Reduces available capacity.
Interim solution only.	Risk of leaking; questions about sturdiness/fragility.
There may be disposal issues.	Will need to retest current equipment with the sleeve.
There may be customs/regulatory issues due to PCM (though this PCM has no safety issues and is even drinkable).	

PCM: phase-change material; PQS: Performance, Quality and Safety.

6. Evaluation parameters for new technology

During the meeting, the participants developed a generic framework to evaluate the different solutions. The evaluation parameters that technology developers should consider were clustered into four categories: 1) performance, 2) usability, 3) programmatic fit, and 4) cost as shown in Table 6. Though the parameters are listed for the three solutions described above, they can be applied to any technology.

Table 6. Evaluation parameters for freeze-prevention technological solutions.

	Freeze-preventive vaccine carrier	PCM coolant pack	PCM sleeve
Performance	Were freezing temperatures observed? What is the impact on cold, cool, and warm life?	Did anything freeze? What is the impact on cool life?	
	Reliability: ▪ Performs consistently ▪ Rate of failure (near term)		
Usability	User-independent freeze safety Ease of use/user acceptability/training		
Programmatic fit	Safety and environmental risks Stock management considerations: ▪ Availability, re-supply, logistics ▪ Additional supporting infrastructure Training burden		

	Freeze-preventive vaccine carrier	PCM coolant pack	PCM sleeve
	Policy changes to standard operating procedures (at all levels): ▪ Improve coordination between innovation investments. Disposal		
Cost	Capital expenditure Operational expenditure		

7. Getting innovative approaches to market

The process and engagement opportunities for manufacturers or partners bringing new technologies to market are mapped out below:

1. Define the opportunity to manufacturers:
   1.1. Raise awareness of the potential market need.
   1.2. Provide market size/forecasts.
   1.3. Alert manufacturers to changes or shifts in PQS specifications.
   1.4. Invest and develop product; engage technical partners, (e.g., WHO via PQS, UNICEF, Gavi, the Bill & Melinda Gates Foundation).

2. PQS:
   2.1. Obtain defined specifications/target product profiles for technology category.
   2.2. Participate in drafting or wait for final target product profile documents.
   2.3. Field studies for new technologies.
   2.4. PQS prequalification for new product.
      2.4.1. Barriers/considerations: Information is shared publicly but not broadcast to entire market. Generally, only manufacturers that PQS is aware of are directly informed of the changes.
      2.4.2. Support: PQS website, technical partners, TechNet.
3. UNICEF catalog:
   3.1. Obtain PQS prequalification.
   3.2. Submit bid during long-term agreement (LTA) window.
   3.3. Provide lead times, pricing, production capacity.
   3.4. Manufacturer review by UNICEF.
   3.5. Approval and entry of product(s) into catalog.
      3.5.1. Barriers/considerations: LTA two-year window; different process if outside of the LTA window. Spot procurement is possible. Industry consultations occur before LTA window opens.
      3.5.2. Support: UNICEF websites, industry consultation meetings. UNICEF also supports import and transportation of product to country. Strong communication and advocacy assistance and reach in countries in association with manufacturers and partners.
4. Gavi:
   4.1. Cold Chain Equipment Optimization Platform will potentially create an enabling environment for freeze-preventive equipment by providing funding countries can use preferentially for equipment.

8. Limitations and gaps

There is little published data that exposure of vaccines to freezing temperatures damages their potency. That being said, a literature review conducted by PATH that highlights the effects of freezing on potency can be found here: http://www.path.org/publications/detail.php?i=945. We advocate that more data be collected.

In addition, the prevalence of non-PQS vaccine carriers and cold boxes in many countries is problematic and should be tracked. Some countries tend to reuse international shipping containers for in-country distribution, although these should be discarded. This may impact the market size and also shows that the implementation of vaccine management standards needs improvement.

Furthermore, the experiences of different countries with the usage of cool water packs is not well documented. Documenting how cool water packs are currently used is important to inform the global approach towards cool water packs and other freeze-prevention technologies. .

A thorough literature review of other plausible freeze-prevention technologies that have been studied or are being studied would be beneficial to the global supply chain community.

9. Conclusion

Immunization programs need user-independent freeze-preventive vaccine carriers. The meeting highlighted that several technological solutions are currently being explored. Additional research on technical solutions and field testing of different products is still necessary and funding for this is important. This report does not endorse any specific technology, but serves to raise awareness about problems around vaccine exposure to freezing temperatures while being transported in passive vaccine containers using current guidance and freeze-preventive technologies that may already be available or may become available in the near future. The process to identify advantages and disadvantages for each technology can be adopted by countries and can be redone in a specific context to determine best fit. The testing parameters and processes for getting technologies to market and for introduction in countries will vary depending on the technology and the country; however, the information provided here may serve as a starting point for any freeze-prevention technology.

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