Vaccine Stabilization—Research, Commercialization, and Impact

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PATH
A catalyst for global health
Vaccine Technologies

- Advancing technologies to improve vaccine performance and delivery.
Vaccine Technologies: Three Areas of Focus

• Cold chain technologies

• Delivery technologies

• Formulation and stabilization technologies
Introduction

• For more than a decade, PATH has been exploring both the technical and commercial feasibility of stabilizing vaccines for use in developing countries.

• To date, we have conducted research on 7 antigen types with 11 vaccine producers and 22 technical collaborators.

• This presentation will summarize lessons learned over the past 10 years.

• Funding: Bill & Melinda Gates Foundation.

Stability Profile of Current Vaccines

Vaccines

Heat sensitivity
- most sensitive
- least sensitive

Days at 37°C
- 2
- 7
- 14
- 30

Freeze sensitivity
- least sensitive
- most sensitive
Lesson 1: Integrate stabilization efforts into early vaccine development.
Integrate Stabilization Efforts Early

- Once a vaccine has an established record of safety and clinical efficacy, there are risks and costs associated with reformulation.

- Improvements in vaccine stability will almost always be less expensive during initial vaccine development than after regulatory approval.
Lesson 2: There are circumstances where it makes sense to stabilize existing vaccines.
Stabilizing Existing Vaccines Can Make Sense When:

- Stability of the product is unacceptable or inferior to other marketed products, e.g., requires frozen storage.
- Reformulation is needed for other reasons, e.g., a change in antigen concentration or production process or inclusion of an additional antigen.
- Proof of principle is needed for a new stabilization method. New technologies are easier to assess and demonstrate with an established vaccine.
Lesson 3: Freeze stabilization is possible for vaccines containing aluminum adjuvants.
Freeze Sensitivity of Vaccines

• Aluminum salt adjuvants are the most prevalent adjuvants in human vaccines.

• Aluminum adjuvants irreversibly agglomerate when frozen then thawed, reducing vaccine potency.

• There are several causes of accidental freezing, e.g.:
  – malfunctioning or inappropriate refrigeration equipment
  – use of cold packs during shipping that are frozen before use
  – low ambient temperatures during shipping
Freeze Sensitivity of Vaccines

- Losses due to freeze damage stress already underfunded vaccine programs in developing countries.

US CDC estimates that the federal Vaccines for Children program alone incurs more than $20 million in vaccine waste annually from accidental freezing.
Meta-analysis of Vaccine Exposure to Freezing Underscores Problem and Need

- 14% to 35% of vaccines were exposed to freezing temperatures.
- More rigorous study designs detected more freeze damage.
# Cold Chain Temperature Studies: PATH / WHO Protocol

<table>
<thead>
<tr>
<th>Country</th>
<th>Transport Freeze Exposure</th>
<th>Refrigerator Freeze Exposure</th>
<th>Overall Freeze Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>50%</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Vietnam</td>
<td>63%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Bolivia</td>
<td>100%</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>Mozambique</td>
<td>75%</td>
<td>80%</td>
<td>100%</td>
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</tbody>
</table>
Protecting Vaccines From Freeze Damage

- Aluminum adjuvant-containing vaccines can be protected from freeze damage by inclusion of GRAS excipients (propylene glycol, polyethylene glycol 300, or glycerin).

- PATH and collaborators have validated protection with hepatitis B, DTP, and pentavalent (DTP-hepatitis B-Hib) vaccines.
Freeze Stabilization of Hepatitis B Vaccine

Immunogenicity of vaccine samples in mice following storage at 4°C or three -20°C/room temperature freeze-thaw cycles, with and without freeze-protecting excipients.

Vaccine Freeze-Protection Technology Is Available to All Companies

- PATH estimates freeze-protecting excipients (e.g., propylene glycol) add only US$0.001 of cost per dose.
- Two vaccine producers are incorporating the freeze-protection technology into childhood vaccines.
- PATH has placed the freeze-protection technology in the public domain for use without charge by all vaccine producers.
- Freeze protection should be considered for all new alum-adjuvanted vaccines.
- PATH staff are available to provide information and assistance.
Lesson 4: Heat stabilization requires a more customized approach, and results will be variable.
Example 1: Heat- and Freeze-Stable Liquid Hepatitis B Vaccine: 12-Month Stability at 37°C

<table>
<thead>
<tr>
<th>Commercial Hep B vaccine</th>
<th>Stable Hep B vaccine formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate, saline</td>
<td>Phosphate, histidine, and propylene glycol</td>
</tr>
<tr>
<td>pH 7.0</td>
<td>pH 5.2</td>
</tr>
</tbody>
</table>

Example 2: Spray-Dried Measles Vaccine

- Most commercial lyophilized measles products lose greater than 1 log_{10} virus titer within one week of storage at 37 C (exception is GSK’s Rimevax).

- PATH and our collaborators have shown that spray drying of measles vaccine has a lower process loss than freeze drying or foam drying.

- Spray drying process parameters, residual moisture, pH, surfactants, excipients, and divalent cations used were systematically examined for effect on process loss and storage stability.
Example 2: Spray Dried Measles Vaccine: 8 weeks stability at 37°C

• **Result**: The optimized spray-dried formulation exhibited a loss of 0.9 log TCID$_{50}$ at 37°C in 8 weeks.

• **Best-performing formulation**: 17% w/v trehalose-sucrose; 50 mM KPO$_4$, 4% w/v L-arginine; 1.25% wt. glycerol; 4% w/v human serum albumin; 1-4 mM CaCl$_2$; 1-4 mM ZnCl$_2$; pH 6.0.

• **Bottom line**: This is a meaningful improvement in stability over some commercial freeze-dried measles products, but only an incremental improvement in stability over Rimevax (time to 1 log$_{10}$ loss = 5 weeks).

Lesson 5: The full benefits of heat-stable vaccines will only be realized after changes are made to storage guidelines.
Controlled Temperature Chain

• All vaccines should be kept in a controlled temperature chain (CTC).
  – Traditionally, this has been the +2°C to +8°C range, known as the cold chain.
  – Work is underway to label some products for higher temperature storage.

• Many vaccines are quite heat stable.
  – Could be stored safely above 2°C to 8°C in CTC.
  – Storage guidelines need to be appropriate to the vaccine's heat stability profile.
  – Vaccine vial monitors can be used to help ensure against excessive heat exposure.
Precedents Exist for Vaccines To Be Stored at Controlled Room Temperature

- **NeisVac-C® Meningococcal C Vaccine** - Baxter, under license to GSK - Canadian product insert:
  - Store at 2°C to 8°C.
  - Within the indicated shelf life the product may be stored at room temperature (up to +25°C) for a single period not exceeding 9 months.

- **Dukoral® Cholera Vaccine** - Sanofi Pasteur - Canadian product insert:
  - Store at 2°C to 8°C.
  - The vaccine can be stored at room temperature (<27°C) for up to 2 weeks on one occasion only.
Experience Using Vaccines Outside of Refrigerated Storage

• Multiple studies have reported that hepatitis B vaccine used for birth dose can be stored outside of refrigerated storage with no effect on seroconversion rates. (Data from China, Indonesia, and Vietnam.)


• Meningococcal group C vaccines have been stored at controlled room temperature for 6 months prior to administration, with no effect on immune response.

Four Steams of Work Needed for Success

COUNTRY-LEVEL EVIDENCE
- Identifying strategies and conditions where ambient temperature storage makes sense.

CHANGES TO STORAGE GUIDELINES
- Working to license vaccines, esp. new vaccines, to their true stability.

TEMPERATURE MONITORING
- Vaccine vial monitors (VVM), threshold heat indicators, electronic temperature monitors.

PROGRAMMATIC GUIDELINES
- Protocols.
- Training.
Preferred Product Profile for Vaccines

• Developed by the Vaccine Presentation and Packaging Advisory Group (VPPAG) - led by WHO with input from public health entities, nonprofits, governments agencies, and industry.

• Among the recommendations in VPPAG’s new Preferred Product Profile:
  - Maximize heat and freeze stability.
  - License products for higher-temperature storage.

* VPPAG membership includes GAVI, PATH, UNICEF Supply Division and Programme Division, WHO Expanded Programme on Immunization, US CDC, among many others.
Lesson 6: Trade-offs may need to be made between the heat stability and the format characteristics of a vaccine.
Heat Stability vs. Vaccine Format

• Some heat stability improvements result in suboptimal product formats, while others enable new, beneficial formats.

• Trade-off between stability and other attributes may be encountered. For example, freeze-dried formulations may have superior stability but can be more complicated for users, with increased potential for error. Packaging and shipping costs may be higher for freeze-dried vaccines, and they can require more storage space.
Heat Stability vs. Vaccine Format

• Heat stabilization technologies may yield superior product formats. For example:
  
  – Spray drying can yield free-flowing powders of controlled particle size, facilitating aerosol delivery, dry powder jet injection, coated microneedles, and erodible implants.
  
  – Freeze drying can be used to create fast-dissolving tablets for convenient oral delivery.
Lesson 7: Products with enhanced stability can benefit both vaccine producers and purchasers.
Stable Vaccines: Benefits to Vaccine Producers

• Enhance product features and competitiveness.

• Potentially reduce costs through bulk production efficiencies.

• Reduce risk of recalls when the cold chain is breached during shipment.

• Decrease shipping and storage costs.
Stable Vaccines: Benefits to Purchasers and End Users

- Widen the reach of immunization.
- Improve vaccine effectiveness.
- Reduce vaccine wastage and cost.


- Relieve the pressure on the cold chain.

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Conclusions

- Many stabilization technologies exist to protect technologies from freeze and heat damage.
- Heat stabilization requires a customized approach, with variable results.
- In general, it is easier and less expensive to address vaccine stability during initial development, but reformulation of existing vaccines is sometimes warranted.
- Many existing vaccines could be stored at controlled temperatures higher than the traditional cold chain, but additional studies and policy changes are needed.
- Thermostable vaccines can benefit producers as well as purchasers and end users.
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