Making optimal use of the heat stability of vaccines in low and middle income countries

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## WHO Recommended vaccines storage temperature

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Primary vaccine store</th>
<th>Intermediate vaccine store</th>
<th>Health centre</th>
<th>Health post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Up to 6 Months</td>
<td>Region- up to 3 months</td>
<td>District- up to one month</td>
<td>Up to one month</td>
</tr>
<tr>
<td>OPV</td>
<td></td>
<td>-15°C to -25°C</td>
<td></td>
<td></td>
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<tr>
<td>BCG</td>
<td></td>
<td>2°C to +8°C (-15°C to -25°C also possible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, MR, MMR</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>YF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib freeze-dried</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal A&amp;C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepB</td>
<td></td>
<td></td>
<td>+2°C to +8°C</td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT, DTP, DTP Hep B</td>
<td></td>
<td></td>
<td>+2°C to +8°C</td>
<td></td>
</tr>
<tr>
<td>Hib liquid</td>
<td></td>
<td></td>
<td>Never Freeze !</td>
<td></td>
</tr>
<tr>
<td>Td</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
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</tbody>
</table>
The Cold Chain has served EPI well

The "Cold Chain" has been the backbone of immunization programmes

- Simple rules and practices
- Easy to convey, understand and implement
- Equipment designed to meet precise specifications
However there are some challenges...

- Very high focus on avoiding exposure to heat
- Requires relatively expensive specialized equipment
- Risks of freezing long neglected
- Few antigens with poor heat stability characteristics
- No evolution to meet the changing realities of vaccines and immunization programmes
A changing environment

More vaccines require more space

- New vaccines are more expensive and better suited to single dose presentations
- Vaccines packaging developed for industrialised countries not always optimized for developing country cold chains

⇒ Need for more space for storage and transport

New emphases, new strategies & new targets

- Infants at birth with Hep B vaccine
- Women of child bearing age with TT
- Adolescent girls with HPV vaccine
- Unreached populations without access to reliable energy
- Pandemic flu vaccine deployment
Vaccines stored at 2-8°C … Despite stability

<table>
<thead>
<tr>
<th>Storage at up to 40°C</th>
<th>Vaccine</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 months</td>
<td>JE (inactivated)</td>
<td>Current, liquid</td>
</tr>
<tr>
<td></td>
<td>Rotavirus</td>
<td>Spray-dried</td>
</tr>
<tr>
<td></td>
<td>BCG</td>
<td>Spray-dried</td>
</tr>
<tr>
<td></td>
<td>Cholera (WC/rCTB)</td>
<td>Liquid</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>Current, liquid</td>
</tr>
<tr>
<td></td>
<td>YF</td>
<td>Lyophilized</td>
</tr>
<tr>
<td>2–6 months</td>
<td>Influenza</td>
<td>Spray-dried</td>
</tr>
<tr>
<td></td>
<td>Diphtheria</td>
<td>Current, liquid</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>Current, liquid</td>
</tr>
<tr>
<td></td>
<td>Men A conjugate</td>
<td>Spray-dried *</td>
</tr>
<tr>
<td></td>
<td>Rabies</td>
<td>Lyophilized</td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>Current, liquid</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>Hepatitis A</td>
<td>Current, liquid</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>Spray-dried</td>
</tr>
<tr>
<td></td>
<td>Typhoid (live)</td>
<td>Vacuum-dried</td>
</tr>
</tbody>
</table>

OPTIMIZE
What is ‘Controlled Temperature Chain’?

Storing & transporting vaccines under controlled temperatures

• Possibly outside of the traditional +2 to +8°C Cold Chain,
• According to guidelines suitable to the vaccine stability and the environment

KEY PRINCIPLES

• All vaccines should be kept in a controlled temperature chain. Traditionally this has been the +2 to +8°C range, known as the "Cold Chain".

• Many vaccines are quite heat stable
  They can be safely stored at other temperatures in a "Controlled Temperature Chain" (CTC), as appropriate to the vaccine's heat stability profile.
Why move to a Controlled Temperature Chain (CTC)?

Reach more people
Hard-to-reach areas & marginalized populations

Deliver vaccines to the right groups at the right time
Hep B birth dose, TT to women, HPV to adolescent girls

Reduce/eliminate the risk of freezing
Heat stable vaccines are often damaged by freezing

Facilitate synergies across different supply chains
Integrated distribution of heat stable vaccines and drugs

Reduce reliance on costly, specialized equipment
Less stringent equipment performance specifications
Advancing the CTC Agenda
Three inter-linked streams of work

Vaccines
Define a Regulatory Pathway to allow vaccines to be licensed to reflect their true stability

Technologies
Identify and Develop Technologies to enable the implementation of a CTC

Countries
Develop Guidelines for national programmes on how to operationalize CTC at country level
What are we aiming for?

Enable CTC strategy without requiring ‘off-label’ vaccines use

Collaborative effort:

- True vaccine stability better reflected in vaccine prescribing information
- Identify regulatory pathway, necessary testing protocols
- Encourage industry to carry out stability tests at higher temperature ranges & submit data to regulatory bodies

Vaccines

Vaccines licensed to reflect their true heat stability
What would it take for the Hep B product insert to read....

"(...)Store between 2-8°C. (...) Hepatitis B vaccine can be stored for up to 28 days, as long as it is kept below 37°C, and away from direct heat and light. At the end of the 28 day period, the vaccine should be discarded. Do not use the vaccine if it has been frozen, as freezing destroys potency. At no point should a vaccine be used beyond the expiration date on the label (...)"
Precedents exist with vaccines

**NeisVac-C® Vaccine** (Baxter) - Canada 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** (Sanofi Pasteur) – Canada product insert:

- **Store at 2°C to 8°C**
- **The vaccine can be stored at room temperature (<27°C) for up to two weeks on one occasion only. (…)**
Hepatitis B vaccine - WHO collaborative study

Purpose: To determine

- Is there a drop in potency when recombinant hepatitis B vaccines are held at 45° until the VVM expires?
- Do vaccine still meet release specification at this time?
- Do changes in potency correlate with changes in VVMs?

Methodology

- Six manufacturers of recombinant hepatitis B vaccines prequalified by WHO
- Three batches of each, at different points towards the end of their shelf life
- Vaccines held at 2-8°C, 37°C and 45°C
- Testing at NIBSC: in vitro potency tests using Murex HBsAg kit and a GSK-type in vitro potency assay. VVMs read by densitometry
Two study rounds

Round 1- NIBSC testing

• Lots from manufacturers held at the recommended 2-8°C, 37°C and 45°C until the VVM on the vials held at 45°C expired

• 2 independent series of dilutions of each lot and of homologous reference vaccine.

Round 2 - Manufacturer and NCL testing

• 3 assays on a vial of each of 3 batches of vaccine held at 2-8°C, +37° and +45° until expiry of VVMs at +45°

• Using assay cited in marketing authorisation, plus product specific reference

• VVMs read on day of test
Round 1 results

- NIBSC testing using 2 types of assays in comparison with densitometer readings on VVMs.

Mean Potency Vs VVM score- NIBSC data using GSK type inhibition assay
Results round 2

Potency relative to reference vaccine - 95% Upper Confidence Limit
Results round 2 (cont.)

Mean potency of the 3 batches relative to mean of sample held at 2-8°C
Conclusions (1)

• All batches of vaccine by manufacturers A, D, and F, met release specification following storage at 45º until expiry of the VVM.

⇒ Meeting stability specification for 30 days at 37 degrees is predictive of meeting stability specification for 7 days at 45 degrees

⇒ Samples tested show correlation between VVM reading and potency, except for manufacturers B and E.
Conclusions (2)

- Vaccines from manufacturer B and E did not meet release specification after storage at 37° and 45° before the VVM expired.
  - These vaccines could not be stored out of the 2-8°C range with reliance on the VVM indicator.
- Data consistent with Arrhenius relationship of in vitro potency with temperatures up to 45° C.
  - VVM can be used as predictor of potency up to 45°C (in vitro testing), if the vaccine meets stability specification (37°C for 30 days).
- Characteristics tested do not appear to be a function of shelf life
CTC agenda - Technologies

2. Technologies

Proven technologies are available to enable CTC implementation

Storage and transport technologies

Indicators

• Expand the use of VVMs
• Threshold indicators to alert of heat peaks/limits

Pre-filled compact devices

• e.g. Uniject
CTC agenda - Operational Guidelines

3. Countries
Guidance available for national programmes on how to operationalize CTC at the country level

• Document field experiences
  – Literature review
  – Studies in Mali and Chad
  – Temperatures studies in Vietnam and Uganda

• Establish working group
  – Sub-Group of WHO IPAC
  – Development and field testing of guidelines

• Endorsement of guidelines
  – WHO Immunization Practices Advisory Committee
Chad CTC field Study

Objectives

• Demonstrate that the potency of mOPV3 used in a controlled temperature chain*, following flexible cold chain management guidelines, is still within the acceptable range (over $10^{5.8}$ CCID50/dose using standard potency assay)

• To add field-generated evidence demonstrating the effectiveness of Vaccine Vial Monitors (VVMs) to warn when a vaccine has been exposed to such levels of heat that potency could be negatively affected.

* For purposes of this study, controlled temperature chain, CTC, was defined as ambient temperature
Rationale

- Polio National Immunization Days (NIDs) in Africa face logistics challenges
  - Limited availability of cold chain equipment and limited capacity for ice and cold pack production
  - Maintaining OPV at 2-8°C during outreach activities is a challenge.

- Countries advised to use WHO guidelines on flexible vaccine management for polio*, to ensure safety and quality when compliance with 2-8°C is not possible
  - Potency testing on vaccines kept under these guidelines had not been conducted

Study Location and Antigen

- The study took place in N’djamena, Chad, during the April National Immunization Days
  - Test vials were in circulation in two districts (N’djamena North and Centre)
  - Catchment areas included: urban, peri-urban and semi-rural locations
- The antigen used was monovalent OPV, type 3
  - Antigen used by the MoH for this campaign
  - Test vials selected at random from the same lot and batch number as vials used in the campaign itself
Methodology

- **20 test vials along with vaccinators during regularly scheduled activities**
  - Vials numbered and divided into two groups:
    - **1 Day vials**: accompanied vaccinators for one day of activities
    - **2-Day vials**: accompanied vaccinators for two days of activities
  - Each test vial accompanied by digital temperature recorder, recording temperature every 2 minutes
  - Test vials were kept at ambient temperature during vaccination activities
  - Visual readings of VVMs were conducted at specified intervals
  - Test vials remained closed and unused throughout the study

- **At the end of the campaign vials were transported to the Belgian National Control Laboratory**
  - Standard quality control potency testing to assess potency level
  - Densitometer readings to validate visual VVM readings in the field
Findings

- **Test vials exposed to ambient temperatures of up to 47.1°C**
  - Maximum length of time over 8°C: **86.9 hours**
  - Maximum length of time over 37°C: **9.7 hours**

- **VVMs behaved as expected**
  - 5 out of 20 vials had VVMs that had reached their endpoint
    - Indicating the vaccine had been exposed to such levels of heat where the potency could be negatively affected

- **All 20 vials tested were above the potency threshold (CI: +/- 0.3)**
<table>
<thead>
<tr>
<th>Location/type of vial</th>
<th>Maximum Temp (°C)</th>
<th>Hours &gt;80°C</th>
<th>Hours &gt; 37°C</th>
<th>Potency</th>
<th>Final VVM reading***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyclinic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1-day</td>
<td>36.6</td>
<td>6.9</td>
<td>0</td>
<td>5.9</td>
<td>50%</td>
</tr>
<tr>
<td>2-day</td>
<td>39.6</td>
<td>25.8</td>
<td>1.3</td>
<td>6.4</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Goudji</strong></td>
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</tr>
<tr>
<td>1-day</td>
<td>38 (37.2-40.2)</td>
<td>21 (20.5-21.2)</td>
<td>0.7 (0.0-0.1)</td>
<td>6.0 (5.9-6.2)</td>
<td>60% (40-80)</td>
</tr>
<tr>
<td>2-day</td>
<td>39 (36.7-40.7)</td>
<td>75 (44.0-86.9)</td>
<td>1.3 (0.0-2.9)</td>
<td>6.0 (5.9-6.1)</td>
<td>90% (70-100)</td>
</tr>
<tr>
<td><strong>Ardeptimane</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>1-day</td>
<td>40 (37.7-43.3)</td>
<td>21 (15-24.6)</td>
<td>1 (0.8-1.3)</td>
<td>6.2 (6.2-6.3)</td>
<td>60% (40-80)</td>
</tr>
<tr>
<td>2-day</td>
<td>41 (39.3-43.0)</td>
<td>29 (21.5-32.5)</td>
<td>5 (4.4-5.5)</td>
<td>6.1 (6.1-6.2)</td>
<td>80% (70-110)</td>
</tr>
<tr>
<td><strong>Hele Houdjaj</strong></td>
<td></td>
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</tr>
<tr>
<td>1-day</td>
<td>42 (40.0-43.8)</td>
<td>13 (10.7-17.9)</td>
<td>4 (3.3-4.4)</td>
<td>5.8 (5.6-5.9)</td>
<td>60% (40-70)</td>
</tr>
<tr>
<td>2-day</td>
<td>44 (42.4-47.1)</td>
<td>21 (17.8-25.5)</td>
<td>9 (7.1-9.7)</td>
<td>6.0 (5.8-6.2)</td>
<td>100% (90-110)</td>
</tr>
</tbody>
</table>
Limitations

- **Study design and small sample size mean the findings are not generalizable**
  - Apply to this specific batch of this specific antigen in these conditions only
  - Can not be generalized to all mOPV3 vaccines, or all OPV vaccines
- **Lack of specificity (high confidence interval) in the laboratory testing usually used for OPV release**
  - Direct correlation between potency and VVMs can not be shown without a much larger sample size, or alternate test
Conclusion

- **This study provides field-level evidence that some types of mOPV3**
  - can be safely kept, for limited periods of time, outside of a 2-8oC cold chain,
  - in alignment with the WHO Flexible Cold Chain management guidelines,
  - without potency levels decreasing to below the release threshold,
  - Provided a VVM is used as a safeguard.
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Questions to DCVMN

What can be done to encourage industry to:

• Generate more stability data on vaccines
• Submit data at time of licensure so it is reflected in prescribing information
• Continue to generate stability data in order to ask for variation after licensure
THANK YOU

For more information:
www.technet21.org | www.path.org | www.who.int