Heat-stable vaccine technologies: Opportunities and bottlenecks for development, introduction, and adoption

MSF/Oxfam consultation: Improving access and stimulating vaccine development for use in resource poor settings
Tuesday, 26 January 2010, Geneva, Switzerland
## WHO Recommended vaccines storage temperature

<table>
<thead>
<tr>
<th>Vaccines</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>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>
</tr>
<tr>
<td>BCG</td>
<td></td>
<td>2°C to +8°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, MR, MMR</td>
<td></td>
<td>(-15°C to -25°C also possible)</td>
<td>+2°C to +8°C</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></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></td>
<td></td>
</tr>
<tr>
<td>Hib liquid</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Td</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td></td>
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</tr>
</tbody>
</table>

Never Freeze!
The Cold Chain has served EPI well

The "Cold Chain" has become 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 suitable for developing country cold chains
- Need for more space for storage and transport

New emphases, new strategies & new target groups
- 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 vaccines 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></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>
What is ‘Controlled Temperature Chain’?

Storing & transporting vaccines under controlled temperatures

- Suitable to the vaccine’s stability profile,
- Possibly outside of the traditional +2 to +8°C Cold Chain,

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 could be stored safely at other temperatures in Controlled Temperature Chains (CTC), as appropriate to the vaccine's heat stability profile.
Why move to CTC?

Reach more children
Including those in 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

Enable countries to introduce new vaccines
without requiring large investments in cold chain and transport expansion
What are we aiming for?

Enable vaccines to be kept in CTC settings without requiring ‘off-label’ use.

Collaborative effort:

• True vaccine stability better reflected in prescribing information
• Identify regulatory pathway, necessary testing protocols
• Encourage industry to carry out stability tests at higher temperature ranges & submit data to regulatory bodies
• Develop guidelines for countries that put vaccine quality and safety first.
Precedent exists with heat sensitive injectable pharmaceutical products

Injectable Alkeran (GSK) - US product insert

- *Store at controlled room temperature 15° to 30°C (59 ° to 86°F) and protect from light*

Humalog (Eli Lilly) - US product insert

- *Humalog should be stored in a refrigerator but not in the freezer.*
- *If refrigeration is not possible, (...) can be kept unrefrigerated for up to 28 days, as long as it is kept as cool as possible (below 30°C) & away from direct heat & light (...)*
... as well as for vaccines

**NeisVac-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**
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 two weeks on one occasion only. (…)

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**OPTIMIZE**

PATH World Health Organization
Three Working Streams …

COUNTRY LEVEL EVIDENCE
- Documenting lessons and practices from the field
- i.e. Mali Polio NID study

REGULATORY PATHWAY
- Hep B study in collaboration with manufacturers
- Working to license vaccines to their true stability

PROGRAMMATIC WORKING GROUP
- Develop necessary programmatic guidelines to support implementation of approved policy

Controlled Temperature Chain
Adopted
Country level evidence

- Literature review
- OPV during Campaigns
Literature Review

• Analysis of 8 studies on CTC; 1 study on field performance of VVMs

• Most of the data available was on Hepatitis B; one study on meningococcal C

• **All studies showed no significant serological differences between vaccines used in the cold chain and those used in the CTC**

• VVM study in 4 countries shows the utility of VVMs as a tool for implementing CTC.
Oral polio vaccine
A study during National Immunization Days in Mali, June 2009

Study Objective:
Document an existing practice to determine if transporting OPV without icepacks during a vaccination campaign is feasible and advantageous.
Methodology

- CTC defined as: absence of ice packs in the vaccine carriers

- Temperature monitoring using LogTag recorders: (1) in vaccine carriers and (2) external temperatures

- Vaccines monitored using VVM
  - Vaccines used until VVM reached its discard/end point
  - VVMs status recorded at four points:
    1. Departure from health post (morning)
    2. Vial opened/ first dose administered
    3. Last dose administered
    4. Return to health post (afternoon)
Findings

• **15 000 children vaccinated**
  53% with OPV kept in CTC

• **External temperatures: 25-40°C**
  During an average day of 7h of activities

• **Internal temperatures: peaked at 36°C**
  Temperatures inside the vaccine carrier

• **VVM readings**
  No VVM at discard point at time of vaccine administration

CTC is a useful alternative provided that:
• vaccines have a VVM
• proper training and guidelines are in place.
Defining a regulatory pathway

Hep B study: overview and preliminary results
Objectives of the study

- To assess whether six different WHO prequalified recombinant monovalent hepatitis B vaccines follow Arrhenius kinetics at temperatures up to 45°C

- To determine whether the loss in potency for these vaccines correlates with the color change of the VVM30.
What has been done to date

- **VVMs exposed to 37°C and 45°C:**
  - test color change under these conditions,
  - Results available to compare to the times to VVM end point for test vaccines

- **Vaccines exposed to the temperatures indicated in the study protocol:**
  - 45°C or at 37°C until the VVM changed color.
  - Time period to color change recorded, and vials are then transferred to 2-8°C. These times varied from 5-9 days.

- **Results available for 4 out of 6 vaccines:**
  - Statistical analysis requires entire data set.
Densitometer readings of naïve VVM30s at 45°C
Preliminary results

- Naïve VVMs change color at 9 days at +45°C.
- VVMs on vaccine vials at this temperature changed color at 5-9 days.
  ➜ Provided the vaccines all remain potent after temperature exposure, the VVM can serve as a surrogate marker.
- Preliminary results indicate lots are not losing potency after thermal exposures,
  ➜ VVM can show when vaccine is not longer utilizable, with a measure of security built in.
Nest study steps

- **Stage 2:**
  - Vaccines tested by manufacturers with assay kit validated for them

- **Stage 3:**
  - Tests of immunogenicity in mice (better show vaccine functionality)

**Aim:**

- **To make a recommendation for all prequalified hepatitis B monovalent vaccines:**
  - Supply in the public sector treats the vaccines as generic.
  - In case of failure of one vaccine next steps would need to be reassessed.
Programmatic considerations
Programmatic guidelines and support

- Working group defined to develop guidelines for implementation by countries of Controlled Temperature Chains

- Will work to address the following:
  - Identify practical issues
  - Provide guidance on implementation
  - Assess risks, advantages and implications
  - Develop guidelines for storing and transporting vaccines within CTC
  - Create communications strategies.
What are we aiming for?

Enable vaccines to be kept in CTC settings without requiring ‘off-label’ use.

Collaborative effort:

- True vaccine stability better reflected in prescribing information
- Identify regulatory pathway, necessary testing protocols
- Encourage industry to carry out stability tests at higher temperature ranges & submit data to regulatory bodies
- Develop guidelines for countries that put vaccine quality and safety first.
Merci! Thank you!

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