

# **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

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**Immunization systems and technologies for tomorrow**



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# WHO Recommended vaccines storage temperature

	Primary vaccine store Up to 6 Months	Intermediate vaccine store		Health centre Up to one month	Health post Up to one month
		Region- up to 3 months	District- up to one month		
OPV	-15°C to -25°C		<b>+2°C to +8°C</b>		
BCG	<b>2°C to +8°C</b> (-15°C to -25°C also possible)				
Measles, MR, MMR					
YF					
Hib freeze-dried					
Meningococcal A&C					
HepB	<b>+2°C to +8°C</b> <b>Never Freeze !</b>				
IPV					
DT, DTP, DTP Hep B					
Hib liquid					
Td					
TT					

## 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

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

# 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° to 8°C*
- *The vaccine can be stored at room temperature (<27°C) for up to two weeks on one occasion only. (...)*

# 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**

**OPTIMIZE**



# 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**

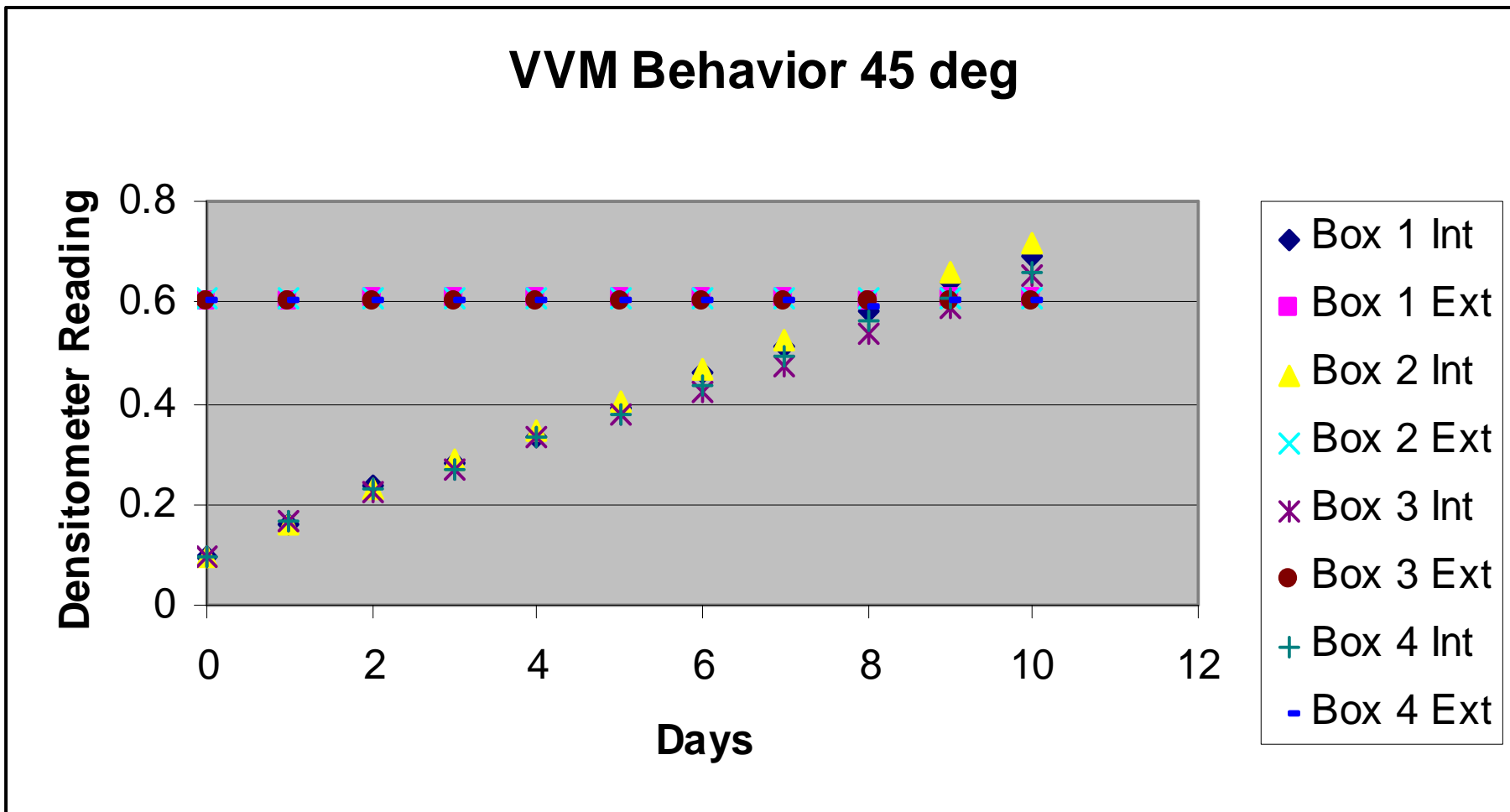
## Objectives of the study

- 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° 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 d 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 no longer usable, 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:

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**Merci! Thank you!**

**For more information:**

**[www.technet21.org](http://www.technet21.org) | [www.path.org](http://www.path.org) | [www.who.int](http://www.who.int)**

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