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

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OPTIMIZE Immunization systems and technologies for tomorrow

PATH World Health Organization

WHO Recommended vaccines storage temperature

<table>
<tr><th rowspan="2"></th><th rowspan="2">Primary vaccine store
Up to 6 Months</th><th colspan="2">Intermediate vaccine store</th><th rowspan="2">Health centre
Up to one month</th><th rowspan="2">Health post
Up to one month</th></tr>
<tr><th>Region- up to 3 months</th><th>District- up to one month</th></tr>
<tr><td>OPV</td><td colspan="2">-15°C to -25°C</td><td rowspan="12" colspan="3">+2°C to +8°C</td></tr>
<tr><td>BCG</td><td rowspan="5" colspan="2">2°C to +8°C
(-15°C to -25°C also possible)</td></tr>
<tr><td>Measles, MR, MMR</td></tr>
<tr><td>YF</td></tr>
<tr><td>Hib freeze-dried</td></tr>
<tr><td>Meningococcal A&C</td></tr>
<tr><td>HepB</td><td rowspan="7" colspan="2">+2°C to +8°C
Never Freeze !</td></tr>
<tr><td>IPV</td></tr>
<tr><td>DT, DTP, DTP Hep B</td></tr>
<tr><td>Hib liquid</td></tr>
<tr><td>Td</td></tr>
<tr><td>TT</td></tr>
</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 <u>exposure to heat</u>**
- 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 2-8ºC … 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

- *Possibly outside of the traditional +2 to +8ºC 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 +8ºC 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?

Vaccines

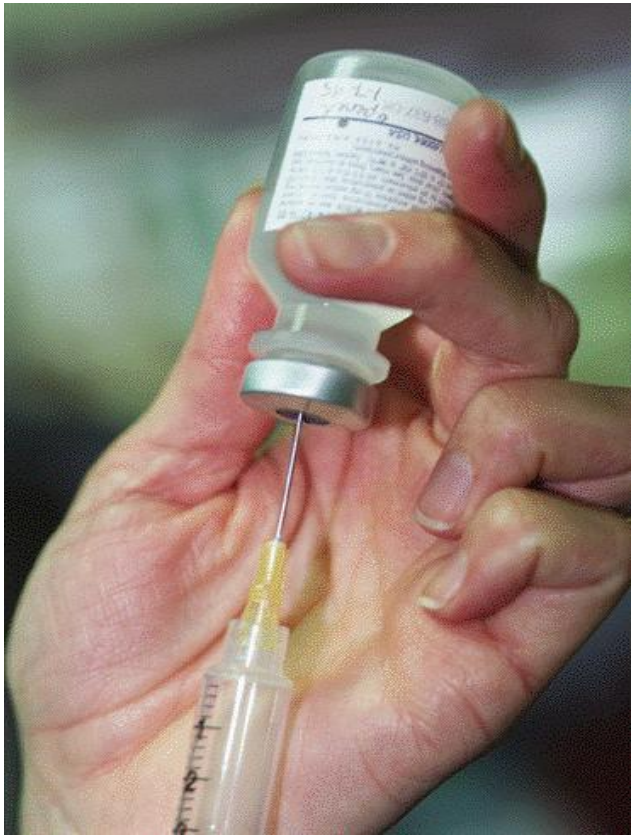
Vaccines licensed to reflect their true heat stability

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

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° 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

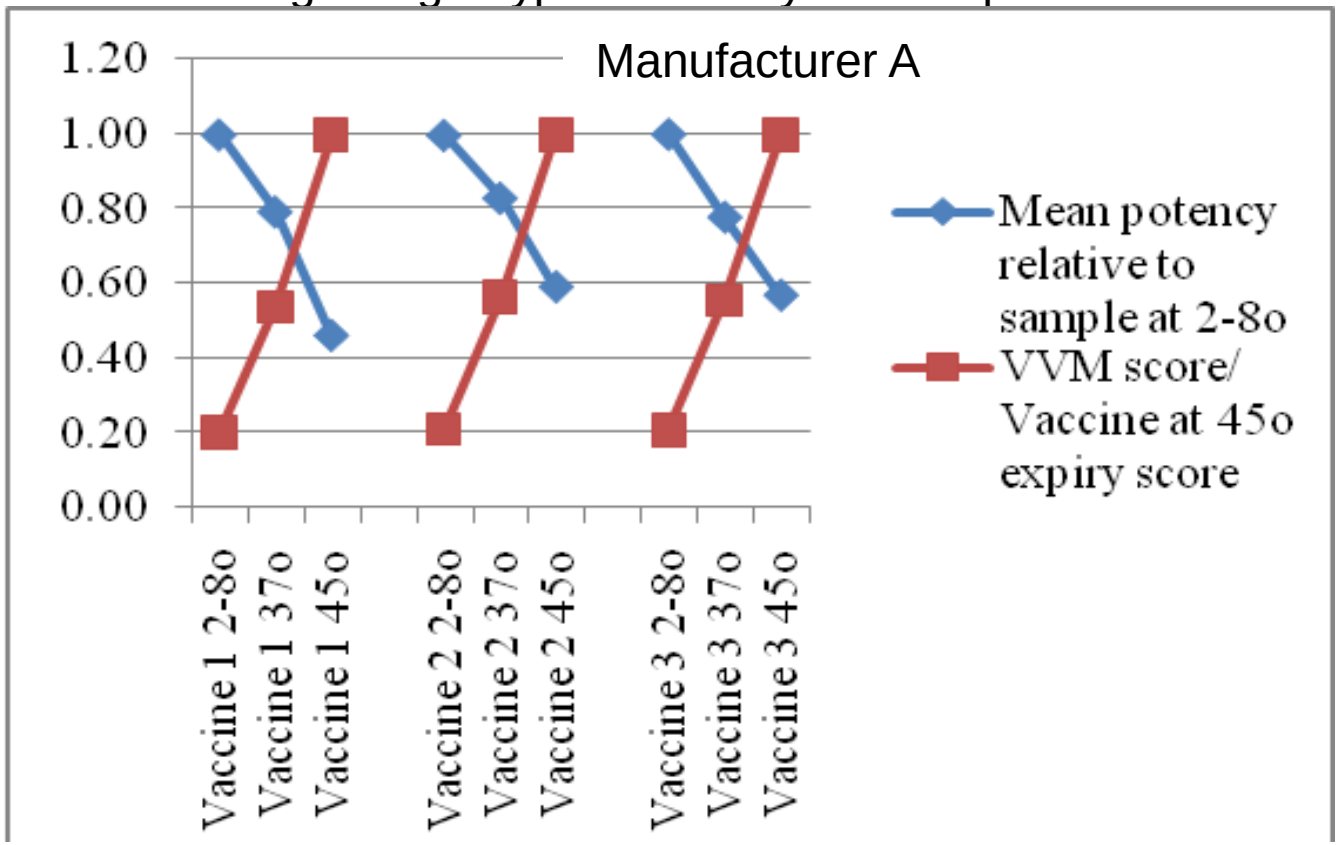
- Lots from manufacturers held at the recommended 2-8ºC, 37ºC and 45°C until the VVM on the vials held at 45º expired
- 2 independent series of dilutions of each lot and of homologous reference vaccine.

Round 2 - Manufacturer and NCL testing

- 3 assays on a vial of each of 3 batches of vaccine held at 2-8ºC, +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

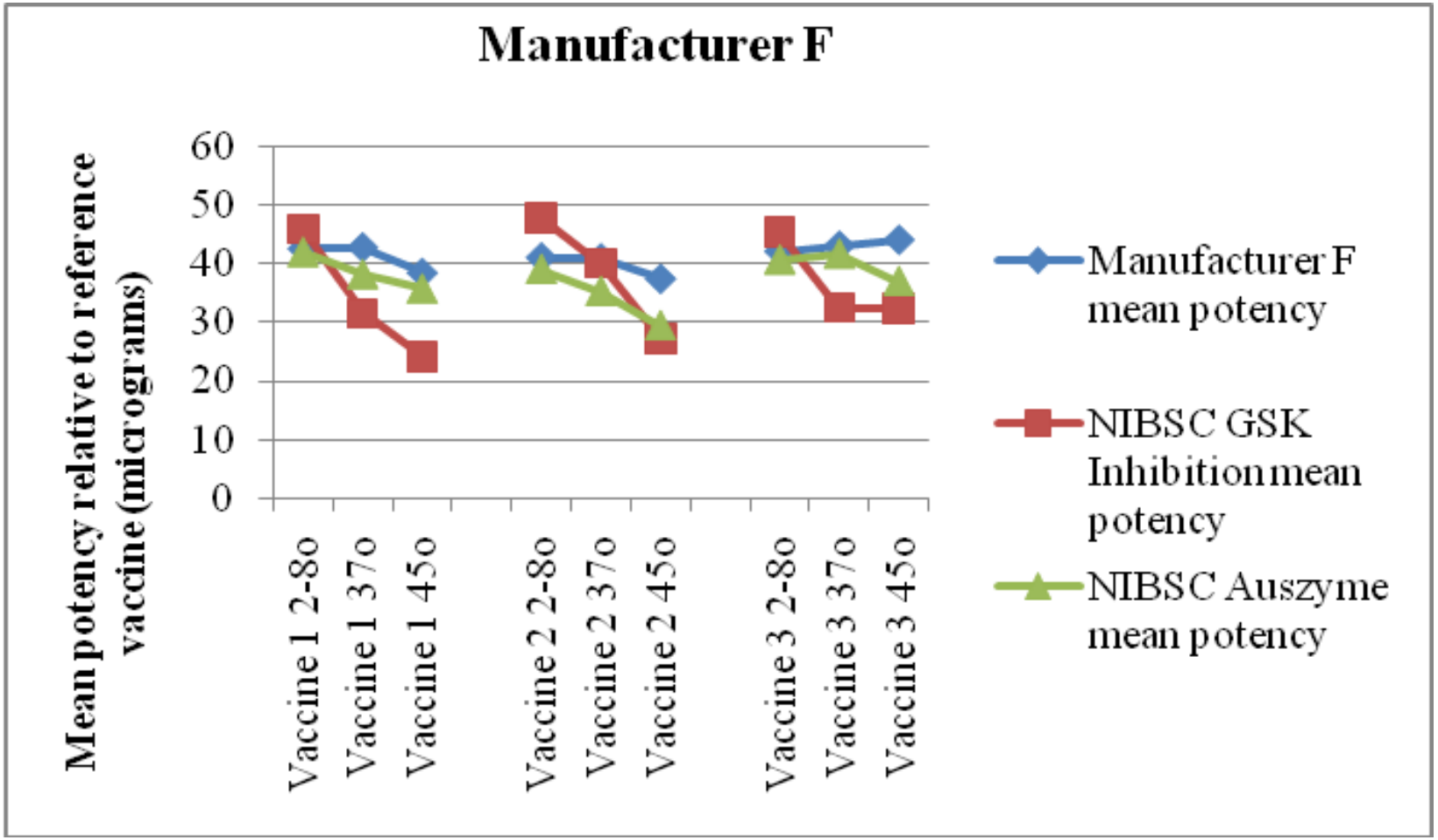
Round 1 results

- NIBSC testing using 2 types of assays in comparison with densitometer



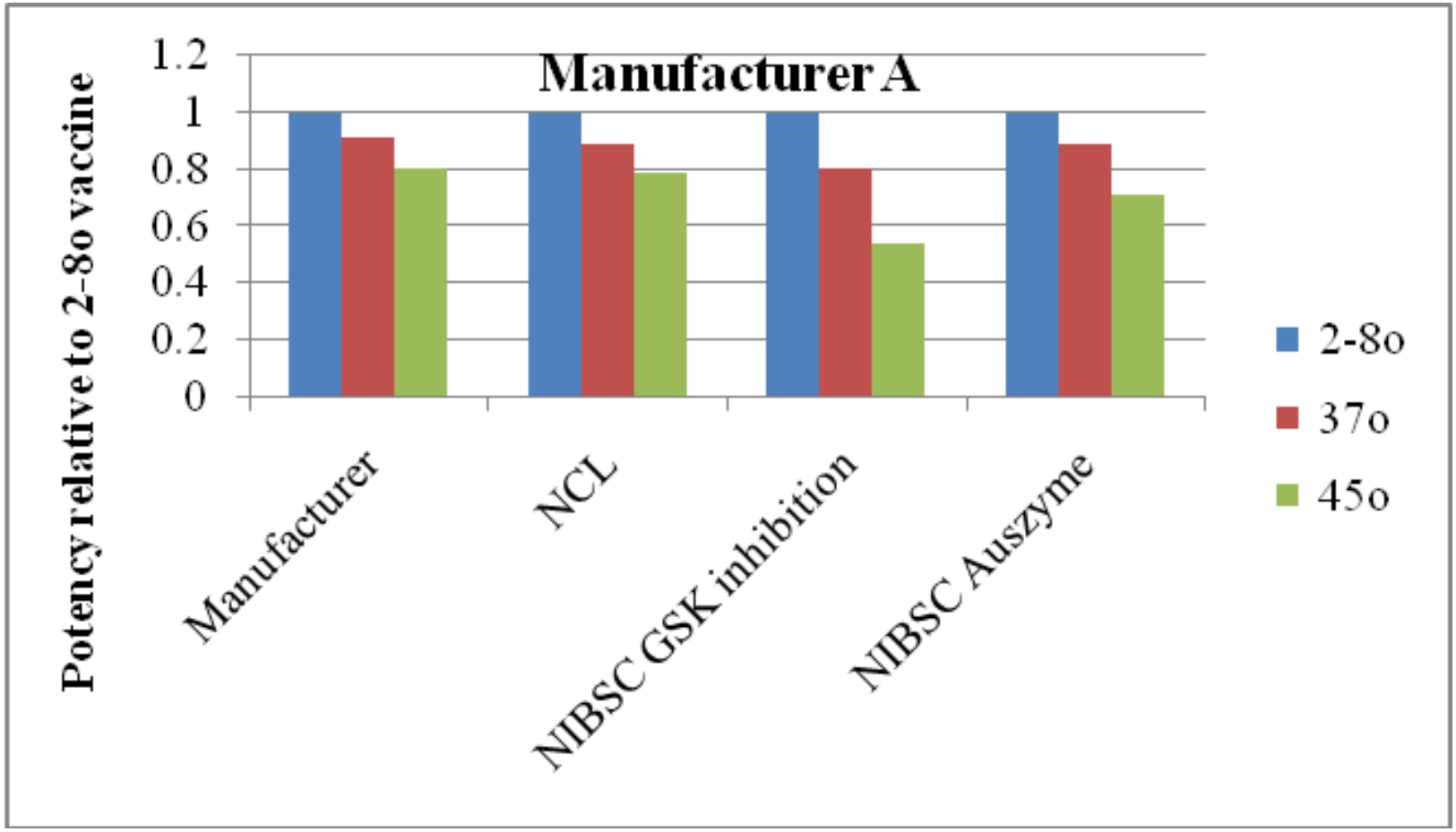
Mean Potency Vs VVM score- NIBSC data using GSK type inhibition assay

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 2-8º

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 37º and 45º 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 an limited capacity for ice and cold pack production
  - ⇨ Maintaining OPV at 2-8ºC 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 2-8ºC is not possible**
  - Potency testing on vaccines kept under these guidelines had not been conducted

* WHO/V&B/00.14. 2000

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 47.1oC**
  - Maximum length of time over 8ºC: **86.9 hours**
  - Maximum length of time over 37ºC: **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)**

Location/ type of vial	Maximum Temp (°C)	Hours >8oC	Hours > 37°C	Potency	Final VVM reading***
Polyclinic					
1-day	36.6	6.9	0	5.9	50%
2-day	39.6	25.8	1.3	6.4	30%
Goudji					
1-day	38 (37.2-40.2)	21 (20.5-21.2)	0.7 (0.0-0.1)	6.0 (5.9-6.2)	60% (40-80)
2-day	39 (36.7-40.7)	75 (44.0-86.9)	1.3 (0.0-2.9)	6.0 (5.9-6.1)	90% (70-100)
Ardeptimane					
1-day	40 (37.7-43.3)	21 (15-24.6)	1 (0.8-1.3)	6.2 (6.2-6.3)	60% (40-80)
2-day	41(39.3-43.0)	29 (21.5-32.5)	5 (4.4-5.5)	6.1 (6.1-6.2)	80% (70-110)
Hele Houdjaj					
1-day	42 (40.0-43.8)	13(10.7-17.9)	4 (3.3-4.4	5.8 (5.6-5.9)	60% (40-70)
2-day	44 (42.4-47.1)	21 (17.8-25.5)	9 (7.1-9.7)	6.0 (5.8-6.2)	100% (90-110)

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