Case Studies on Monitoring the Heat and Freeze Sensitive of Vaccines

DCVMN Workshop
"Vaccine quality management systems for manufacturing excellence"

Michael Rush, MBA
Executive Director - Global Health Policy

October 24-25, 2013
WHO Global Learning Opportunities for Vaccine Quality (GLO/VQ)

- e-Pharmaceutical Cold Chain Management

http://epela.net/epela_web/
WHO E06 Temperature monitoring devices
performance specifications and verification protocols

- Recommended temperature monitoring devices for storage and transportation of vaccines

1. Acoustic and/or visual alarm units (AL01)
2. Cold Chain Monitor (IN02)
3. Irreversible freeze indicator (IN03)
4. **Vaccine Vial Monitor (IN05)**
5. Portable electronic thermometer (TH01)
6. Fixed gas or vapour pressure dial thermometer (TH02)
7. Portable alcohol stem thermometer (TH03)
8. Integrated electronic thermometer, with or without alarm function, for vaccine refrigerators and freezers (TH06)
9. Programmable electronic temperature and event logger systems with integral alarm and auto-dialer options (TR03)
10. Wall-mounted pen recording thermometer (TR04)
11. User programmable temperature data loggers (TR05)
12. 30-day electronic refrigerator temperature logger (TR06)
13. Electronic shipping indicators (TR07)

http://www.who.int/immunization_standards/vaccine_quality/pqs_e6_temp_monitoring/en/

Examples and main use of WHO recommended temperature monitoring devices for storage and transportation of vaccines

<table>
<thead>
<tr>
<th>Device</th>
<th>Int. transport</th>
<th>Primary store</th>
<th>In-country transport</th>
<th>Intermediate store</th>
<th>In-country transport</th>
<th>Service level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic temperature monitor with LCD screen</td>
<td>![Image]</td>
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<tr>
<td>Vaccine cold chain monitor</td>
<td>![Image]</td>
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<tr>
<td>Vaccine vial monitor</td>
<td>![Image]</td>
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<tr>
<td>Freeze indicator</td>
<td>![Image]</td>
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<td>Multi-channel computerized temperature recording sys.</td>
<td>![Image]</td>
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<tr>
<td>Electronic refrigerator temperature logger</td>
<td>![Image]</td>
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<tr>
<td>Downloadable electronic temperature data logger</td>
<td>![Image]</td>
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</tbody>
</table>

Dr. Umit Kartoglu - WHO
Monitor Cumulative Heat with HEATmarker VVM

- The Active Square is the color changing reactive portion
- It is light at the start and progressively and irreversibly darkens
- The color change is faster at higher temperatures
- End point is reached when the color of the Active Square area is equal to the Reference Circle
The HEATmarker Is Easy To Read

The Active Square is lighter than the Reference Circle.
If the expiry date is not passed, USE the vaccine.

The Active Square matches or is darker than the Reference Circle.
DO NOT USE the vaccine.
The Chemistry of the HEATmarker TTI

Polymerization Reaction

(Colorless)

R-C≡C - C≡C-R
R-C≡C - C≡C-R
R-C≡C - C≡C-R

Polymerization

C≡C-C≡C - C≡C-R
C≡C-C≡C - C≡C-R
C≡C-C≡C - C≡C-R

(Black)

- The principle of operation is based on the solid-state polymerization of substituted diacetylenic monomers
- The combined effects of time and temperature cause a gradual, predictable, cumulative and irreversible color change from clear to dark
The VVM (Vaccine Vial Monitor) is the TTI used by WHO/UNICEF in the global immunization program. Temptime has more than 17 different categories of TTIs available from days at refrigerated temperature to years at room temperature.
VVM Response is Correlated with Vaccine Stability

Yellow Fever Vaccine - Freeze Dried

- VVM should reach endpoint before vaccine potency drops below efficacy requirements
- Dossier with these stability data supports VVM7
- For WHO prequalified vaccines, WHO makes decision on VVM category and sends letter to vaccine manufacturer and Temptime
- For other applications, vaccine manufacturer makes VVM category decision
## HEATmarker VVM for Use on Vaccines

<table>
<thead>
<tr>
<th>Pharmaceutical Product</th>
<th>Indication</th>
<th>Customer</th>
<th>Temptime Product</th>
<th>Value Delivered</th>
</tr>
</thead>
</table>
|                        | Children's Immunization Campaigns for a range of contagious diseases:     | GSK, Sanofi Pasteur, Merck, Crucell, Pfizer, Novartis, Serum Institute of India, Biofarma, Japan BCG, BB-NCIPD, Bharat Biotech, Statens Serum Institute, Biological E, Bharat Serums and Vaccines, Haffkine, plus others | VVM2, VVM7, VVM14, VVM30 | • Prevents immunization with heat damaged vaccines  
• Expands reach of immunization programs to remote populations  
• Increases immunization programs efficiency |
|                        | • BCG  
• Diphtheria  
• Tetanus  
• Pertussis  
• DTP  
• Hep B  
• Hib  
• Meningococcal A and C  
• Measles  
• Mumps, Pneumococcal  
• OPV  
• Rotavirus  
• Rubella  
• Tetanus Toxoid  
• Yellow Fever  
Other Campaigns:       |                                                                 | VVM2, VVM7, VVM14, VVM30 |                                                                 |
Value of VVM in Global Immunization Programs

Vaccine Vial Monitors – helping save lives!

Time temperature indicator known as vaccine vial monitor (VVM) absolutely vital to eradication effort, allowing health workers to know vaccine has not been exposed to excessive heat.
Improving vaccine effectiveness.
Example: Pinpoint Cold Chain Problem and Identify Heat Damaged Vaccine – India

- Inspection of VVMs on JE vaccine in outlying district was at the endpoint
- The local health officials conducted an investigation and found that the 450,000 doses of JE vaccine were stored in a walk-in refrigerated storage facility at the Government Medical Store Depot outside of Delhi that had experienced power interruptions for an unknown amount of time, and the back-up generator failed to function properly
- VVMs avoided administration of vaccine exposed to excessive heat due to equipment failures and identified equipment problems
Enabling vaccine outreach.
Expanding vaccine coverage.
Objective: To evaluate the feasibility and effectiveness of a village-based, out-of-cold-chain strategy for improving the on-time administration (within 24 hours) of the HB vaccine birth dose in remote areas of China, especially among children born at home.

Strategy possible because of use of VVM.
Conclusions of Study in China

• Village health workers using an out-of-cold-chain immunization strategy can improve the on-time administration of the hepatitis B birth dose among home-born infants.

• Simple tools such as VVMs, AD syringes, and Uniject can ensure vaccine quality and injection safety when vaccines are administered by village health workers.

• Taking vaccine out of the cold chain could potentially decrease the risk of vaccine damage due to inadvertent freezing (this study did not follow up on the children who were given potentially frozen vaccine).
Facilitating stock management.
WHO Global Learning Opportunities for Vaccine Quality (GLO/VQ)

- e-VVM Based Vaccine Management Course – coming soon

http://epela.net/epela_web/
Preventing vaccine wastage.

Yogyakarta earthquake 2006.
Example: Reduce Wastage of Vaccine
Earthquake in Yogyakarta, Indonesia

- Damaged the infrastructure, including the cold store facilities at the district and health centers
- Electricity was out for several days and generators were either not used or not functioning.
- Vaccine in 5 districts and more than 50 health centers was saved from being discarded prematurely (wasted) due to the presence of the VVM on the vials
Over the last 10 years\(^1\), it is estimated that VVMs have:

- Saved developing country immunization programs $140 million in vaccines that are no longer discarded due to suspected heat exposure.
- Facilitated the delivery of 1.46 billion doses of vaccine through outreach.
- Averted 100,824 deaths from potential heat exposed vaccine and avert 57,725 deaths by extending vaccine delivery.

\(^1\) PATH 2013
Helping to save lives!

D. Kristensen
PATH
UNICEF/WHO Policies on Criticality of VVMs

2007 UNICEF/WHO Joint Policy Statement Urging Member States, Donor Agencies and NGOs to Include VVMs As Minimum Requirement for Purchase of Vaccine

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification

| Vaccine vial monitor (VVM) | All vaccines | Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type approved by WHO(WHO/V&B/99.187, WHO/IWB/07.048). Signed declaration, as part of the cover letter submitted along with the file for prequalification confirming that the manufacturer will apply a VVM to the vaccine, and has the technical capacity to do so if requested by the purchasing specifications.
Sinopharm Group Held Seminar on VVM Implementation
Changchun, PR China 22 June 2010

• Participants from MoH, SFDA, National CDC, Six Institutes of Biologic Products, WHO and PATH
• The need to improve vaccine quality, enhance the vaccine cold chain and strengthen the public’s opinion of vaccine quality and safety was discussed
• It was concluded that implementation of VVMs would help to achieve these goals
• Some Institutes have started implementation of VVMs for domestic vaccines
Feasibility of VVM implementation in China
Lanzhou Institute Study

• In the first semester of 2010, Lanzhou Institute carried out a feasibility study on the VVM implementation in China
• 20,000 VVM were labeled on Hib vaccines which were distributed in 13 municipal CDCs, 16 district CDCS and 14 POV in Guangdong Province
• The feasibility of the VVM implementation from manufacturing by Temptime, through each step of the supply chain from vaccine manufacturer, to vaccine distributor, to vaccine users
Cold Chain Problems are Global

Vaccines – US San Francisco Bay Area 10 County Region (2006)

<table>
<thead>
<tr>
<th>Category</th>
<th># of Incidences</th>
<th>Loss (dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigeration Problems</td>
<td>16</td>
<td>$42,958</td>
</tr>
<tr>
<td>Shipping/ Receiving</td>
<td>4</td>
<td>$34,772</td>
</tr>
<tr>
<td>Improper Storage</td>
<td>6</td>
<td>$187,133</td>
</tr>
<tr>
<td>Expired Vaccines</td>
<td>51</td>
<td>$127,289</td>
</tr>
<tr>
<td>Total Losses</td>
<td>77</td>
<td>$392,717</td>
</tr>
<tr>
<td><strong>Extrapolation to state</strong></td>
<td></td>
<td><strong>$2,352,426</strong></td>
</tr>
</tbody>
</table>

Source: California Department of Public Health
VACCINES FOR CHILDREN PROGRAM:
VULNERABILITIES IN VACCINE MANAGEMENT

Office of Inspector General
June 2012

- Vaccines for Children (VFC) program provides free vaccines to eligible children
- 82 million VFC vaccine doses were administered to an estimated 40 million children at a cost of $3.6 billion in 2010

Study
- Vaccine storage unit temperatures were monitored in 45 providers for a 2-week period

Finding
- 76 percent of the 45 selected providers were exposed to inappropriate temperatures for at least 5 cumulative hours during that period

Impact
- Exposure to inappropriate temperatures can reduce vaccine potency and efficacy, increasing the risk that children are not provided with maximum protection against preventable diseases.

1 https://oig.hhs.gov/oei/reports/oei-04-10-00430.pdf
FREEZEmarker® Used in US CDC Vaccines for Children Program

- In shipments of vaccine from distributor to each provider’s practice

Before Freezing

After Freezing

IMPORTANT CHANGES TO SHIPMENTS BEGINNING September 14, 2009

Centers for Disease Control & Prevention Vaccines for Children Program

The cold temperature monitor included in all vaccine shipments to providers will be changed beginning September 14, 2009. The TransTracker® C FREEZEmarker® temperature indicator will replace the ColdMark™ Freeze Indicator. The Freezemark indicator has been tested by McKesson and proved to be effective in consistently and accurately assessing the exposure to temperature variants during the shipping process. The heat indicator (3M MonitorMark™) will not be changing.

Please review the instructions attached to the new Freezemarker temperature indicator to ensure you are reading the device correctly.

• If you have any questions about this change or the Freezemarker temperature indicator, please feel free to contact McKesson 877-TEMP123 (877-836-7123) or your Project Grantee PPOC.

McKesson
Specialty Care Solutions

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FREEZEmarker® Used in US CDC Vaccines for Children Program

Studied for use during vaccine storage in providers’ practices

Visual Freeze Indicators On Each Box of Vaccine Are An Early Warning Tool to Identify Potential for Freeze Damage

Monday, October 28, 2013

Ronald Angoff, M.D., Yale University School of Medicine, Department of Pediatrics and The Child Study Center, New Haven, CT
Jillian Wood, Connecticut Chapter American Academy of Pediatrics, Hartford, CT, Maria Chernock and Diane Tipping

FREEZEmarker shows exposure to freezing temperatures

Before Freezing

After Freezing

Obrigado
Gracias

Thank You