Case Studies on Monitoring the Heat and Freeze Sensitive of Vaccines

DCVMN Workshop "Vaccine quality management systems for manufacturing excellence"

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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/



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 exipry 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



The combined effects of time and temperature cause a gradual, predictable, cumulative and irreversible color change from clear to dark





Polymerization

HEATmarker VVM Categories

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 Vacine - 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

Pharmaceutical Product	Indication	<u>Customer</u>	<u>Temptime</u> <u>Product</u>	<u>Value</u> <u>Delivered</u>
	Children's Immunization Campaigns for a range of contagious diseases: • BCG • Diphtheria • Tetanus • Pertussis • DTP • Hep B • HiB • Meningococcal A and C • Measles • Mumps, Pneumococcal • OPV • Rotavirus • Rubella • Tetanus Toxoid • Yellow Fever Other Campaigns: • HPV • IPV • Rabies • Typhoid	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

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



Example: Improving Access to Immunization in Remote Areas of China

<u>Objective:</u> To evaluate the feasibility and effectiveness of a villagebased, 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.



Lixia Wang et al Published in the Bulletin of the World Health Organization

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.
- <u>Taking vaccine out of the cold chain could potentially</u> <u>decrease the risk of vaccine damage due to inadvertent</u> <u>freezing</u> (this study did not follow up on the children who were given potentially frozen vaccine).



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 years¹, 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



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	All vaccines	Proof of feasibility and intent to apply a VVM to the proposed vaccine,	
monitor		as defined below.	
(VVM)		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 orVVM30)	
		or a future VVM type approved by WHO(WHO/V&B/99.187,	
		WHO/IVB/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 Insititute 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)

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





Source: California Department of Public Health¹⁷

US Vaccines for Children Program Vulnerabilities in Vaccine Management¹

Office of Inspector General June 2012

Department of Health and Human Services OFFICE OF INSPECTOR GENERAL

VACCINES FOR CHILDREN PROGRAM: VULNERABILITIES IN VACCINE MANAGEMENT



Daniel R. Levinson Inspector General June 2012 OFL04.10.00430

- 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.

Ice on box of influenza vaccine





FREEZEmarker[®] Used in US CDC Vaccines for Children Program

• In shipments of vaccine from distributor to each provider's practice



Before Freezing

M<u>K</u> ESSON

Empowering Healthcare

IMPORTANT CHANGES TO SHIPMENTS BEGINNING September 14, 2009

Centers for Disease Control & Prevention Vaccines for Children Program

The cold temperature monitor indicator 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 Freezemarker 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





After Freezing



FREEZEmarker[®] Used in US CDC Vaccines for Children Program

Studied for use during vaccine storage in providers' practices



After Freezing

Visual Freeze Indicators On Each Box of Vaccine Are An Early Warning Tool to Identify Potential for Freeze Damage¹ Monday, October 28, 2013

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Before Freezing

Obrigado Gracias

Thank You

