What is a VVM?
Background on Attendees & Presenter

<table>
<thead>
<tr>
<th>Years</th>
<th>Role</th>
<th>Entity</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Consultant</td>
<td>ZEBRA</td>
<td>Geneva</td>
</tr>
<tr>
<td>10</td>
<td>Director</td>
<td>Gavi</td>
<td>Bern</td>
</tr>
<tr>
<td>7</td>
<td>Lifecycle Management</td>
<td>Berna Biotech</td>
<td>Bern</td>
</tr>
<tr>
<td>10</td>
<td>Commercial</td>
<td>GlaxoSmithKline</td>
<td>East Africa &amp; London</td>
</tr>
</tbody>
</table>
Two vaccines are ready to be administered

- Lyophilized vaccine (it comes in 2 vials; one is a diluent)
- Both products within expiry date
- Both products look OK
- No issues identified/reported during transport and handling

Would you administer these vaccines?
What about now?
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**
Chemistry of the TTI: Solid-State Polymerization

The color-changing chemistry is based on the solid-state polymerization of colorless diyne diurea monomers to highly colored polymers.

(Colorless)

\[ \text{R} - \text{C} \equiv \text{C} - \text{C} \equiv \text{C} - \text{R} \]
\[ \text{R} - \text{C} \equiv \text{C} - \text{C} \equiv \text{C} - \text{R} \]
\[ \text{R} - \text{C} \equiv \text{C} - \text{C} \equiv \text{C} - \text{R} \]

(Highly colored)

\[ \text{C} - \text{C} \equiv \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{R} \]
\[ \text{R} - \text{C} \equiv \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{R} \]

- The solid monomer particles are formulated into an ink and printed.
- The chemistry can be printed in any shape or format.
- The color developed through polymerization is from light blue/purple to dark blue/purple.
- Covering the printed indicator with an orange film does not alter the polymerization process.
Vaccine Vial Monitor (VVM) – Faster color change at higher temperatures

Slower color development at lower temperature

Before heat exposure

Faster color development at higher temperature

After heat exposure
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 Arrhenius Equation

HEATmarker TTs contain a heat-sensitive material that integrates cumulative heat exposure over time that:

- Is based on a chemical reaction (polymerization) following the Arrhenius equation

\[ k = A_0 e^{-\left( \frac{E_a}{RT} \right)} \]

- Darkens, irreversibly, with time and temperature (cumulative) and faster when the temperature increases
- HEATmarker is a Mean Kinetic Temperature (MKT) indicator

\( k \) rate coefficient
\( A_0 \) frequency factor (pre exponential factor)
\( E_a \) activation energy (J mol\(^{-1}\))
\( R \) universal gas constant (8.314 x 10\(^{-3}\) kJ mol\(^{-1}\)K\(^{-1}\))
\( T \) Kelvin temperature (K)
VVMs have a well defined Arrhenius temperature relationship over time.
Four WHO VVM categories

VVM category chosen is correlated to vaccine stability
Two New VVM Categories Added in 2018

VVM11 – more closely monitors the shelf life of new vaccines
VVM250 – extends the capability to monitor room temperature stable vaccines
VVM Response is Correlated with Vaccine Stability

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 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>Vaccine suppliers</th>
<th>Temptime Product</th>
<th>Value Delivered</th>
</tr>
</thead>
</table>
|                         | Children’s Immunization Campaigns for a range of contagious diseases:  
|                         | • OPV  
|                         | • DTP  
|                         | • Hep B  
|                         | • HiB  
|                         | • Measles  
|                         | • Yellow Fever  
|                         | • MenA  
|                         | • Pneumo conj  
|                         | • Rotavirus  
|                         | • Measles Rubella  
|                         | • JE  
|                         | • TT, Td, BCG  
|                         | Newer Vaccines:  
|                         | • HPV  
|                         | • IPV  
|                         | • Typhoid  
|                         | • Cholera  
|                         | • Rabies  
| | GSK, Sanofi Pasteur, Merck, Pfizer, Serum Institute of India, Biofarma, Japan BCG, BB-NCIPD, Bharat Biotech, Statens Serum Institute, Biological E, Bharat Serums and Vaccines, Haffkine, Biomanguinhos, | | | • Prevents immunization with heat damaged vaccines  
| | | | | • Facilitates last mile immunization (to remote populations)  
| | | | | • Reduces wastage  
| | | | | (See Value of VVM section)
VVM follows the vaccine from time of manufacture to time of use
VVM follows the vaccine from time of manufacture to time of use
VVM follows the vaccine from time of manufacture to time of use

No matter how the vaccine got there!!
Value of VVM in Immunization
Value of VVM in Global Immunization Programs

Vaccine Vial Monitors – helping save lives!

VVM vital to eradication effort, allowing health workers to know vaccine has not been exposed to excessive heat.
Improving vaccine effectiveness.

D. Kristensen
Example: Improving Access to Immunization in Remote Areas of China; strategy possible, made use of VVM.

**Objective:** 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, among children born at home.

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**Hepatitis B vaccination of newborns: evaluation of a village-based strategy, Lixia Wang, Jinhua Li, Haiying Armstrong, Carib Nelson, Wenyi Wang.**

Introduction

Globally, chronic childhood and liver cancer are among the leading causes of death and disability in children (1). Acute viral hepatitis (HVs) is a major concern, with 90% of infections being due to hepatitis B virus (HBV) and hepatitis C virus (HCV). Vaccination against HBV is approximately 90% effective if given within 24 hours of birth (1,2). This strategy is even more critical in regions with high HBV prevalence and a high HBV incidence rate (3).

Growing concerns about HBV infections in infants within 24 hours of birth (1,4) and the substantial risk for Chinese neonates have led to the first dose of HepB vaccine being given at 6 months of age (5). A study by the Chinese Ministry of Health found that a birth dose of HBV vaccine was given to all infants born in 2004, with a coverage rate of 82.2% in the birth cohort (6). This rate decreased to 77% in the birth cohort, or 3.3 among those who had received a birth dose but were not tested for HBV seroprevalence (7). The HBV prevalence rate was 9% among 1500 rural areas in China (8).

As a strategy to improve coverage of the HBV vaccine among neonates (9), birth-dose hepatitis B vaccination was included in the Expanded Program on Immunization (10). In order to enhance vaccine uptake and delivery, a village-based strategy for delivery of hepatitis B vaccine to the home of village members to make the strategy feasible in health facilities, it is important to understand the logistics of home-based immunization here.

Our study explored the feasibility and effectiveness of a village-based delivery strategy for hepatitis B vaccine to the home of village members to make the strategy feasible in health facilities, and further explored the role of a portable vaccine delivery device to overcome the cold chain.

Example: Pinpoint Cold Chain Problem and Identify Heat Damaged Vaccines – India

- Inspection of VVMs on JE vaccine in outlying districts conducted at point of service
- VVMs avoided administration of vaccine exposed to excessive heat
- An investigation to identify where there were equipment problems
- It was found a walk-in cold room, outside of Delhi had experienced power interruptions for an unknown amount of time (back-up generator failed to function)
- 450,000 doses of JE vaccine were found to be heat damaged
Example: Reduce Wastage of Vaccines following Earthquake in Indonesia

Damaged infrastructure, including cold store facilities
Electricity was out for several days and generators were either not used or not functioning

Vaccines in Yogyakarta, 5 districts and more than 50 health centers were saved from being discarded prematurely (wasted) thanks to VVMs
Enabling vaccine outreach.
Expanding vaccine coverage.
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.
Preventing vaccine wastage.
Yogyakarta earthquake 2006.

D. Kristensen
PATH
Impact of VVM

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

Save The Children UK