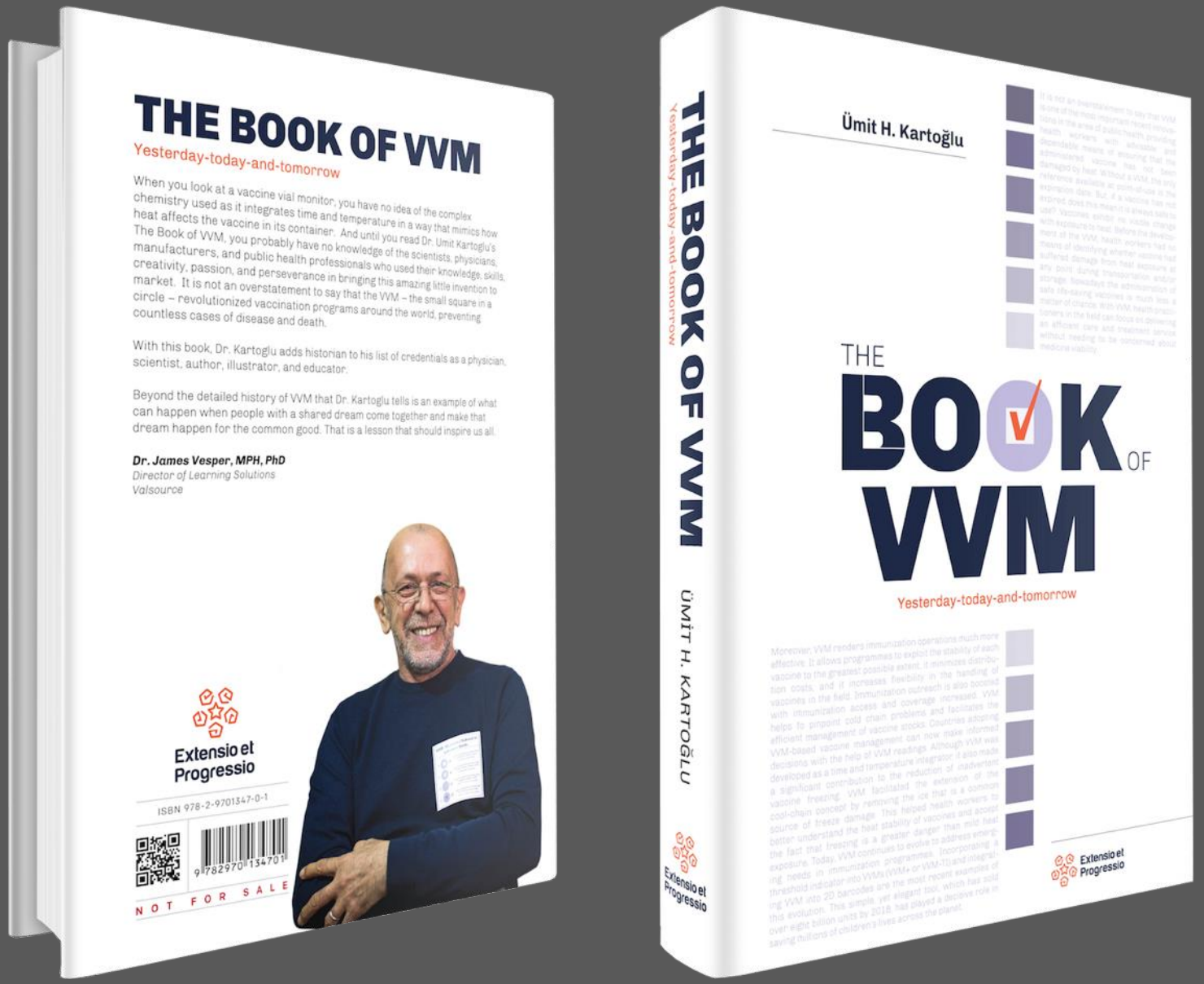
VVM BASED VACCINE MANAGEMENT

Umit Kartoglu
Co-founder and CEO
Extensio et Progressio
Collonge-Bellerive
Switzerland

Debbie Kristensen
Director, Vaccine Technology
Strategy and Policy
PATH
Geneva, Switzerland

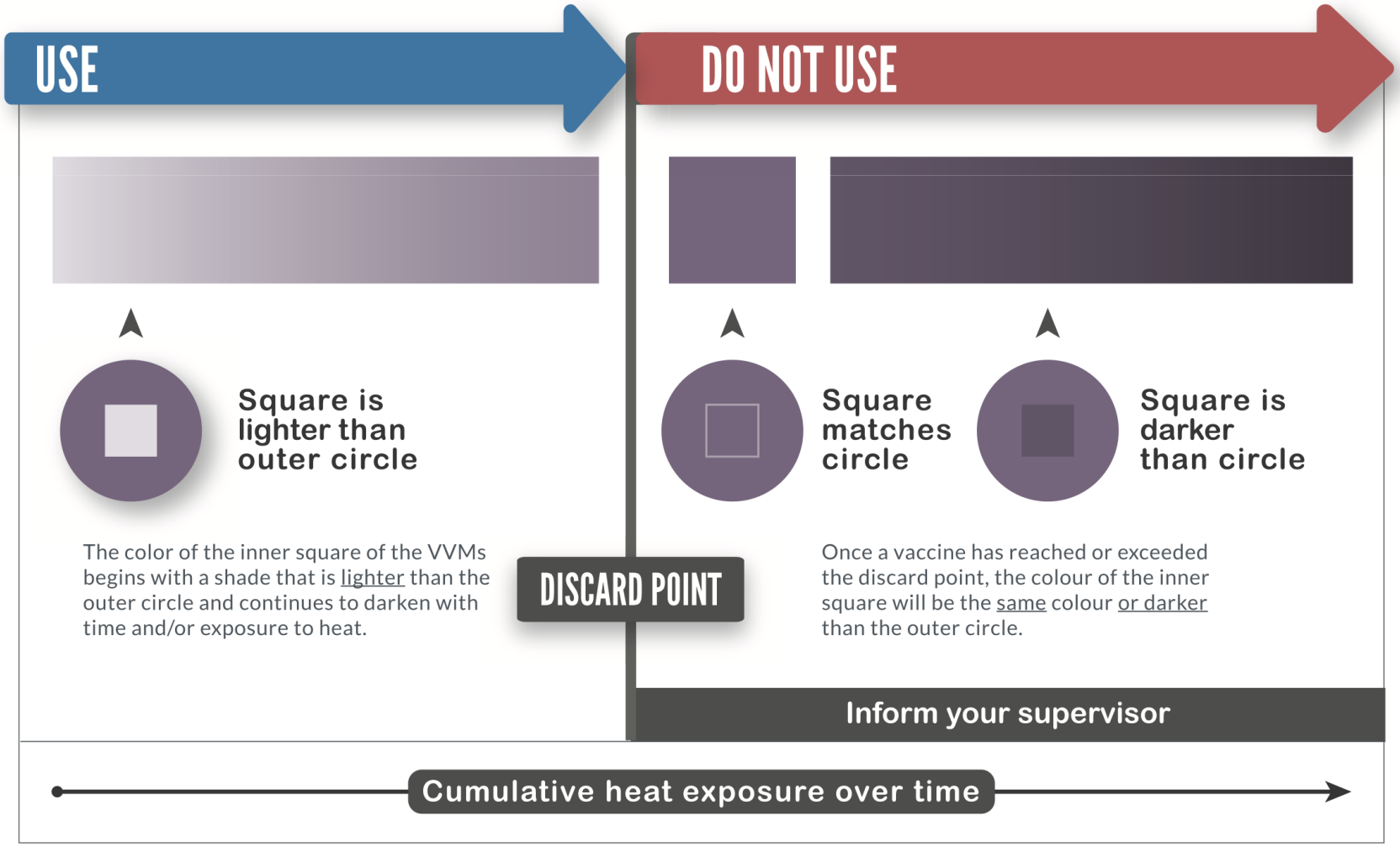
Ted Prusik
Senior Vice President
Temptime Corporation
Morris Plains, NJ
USA



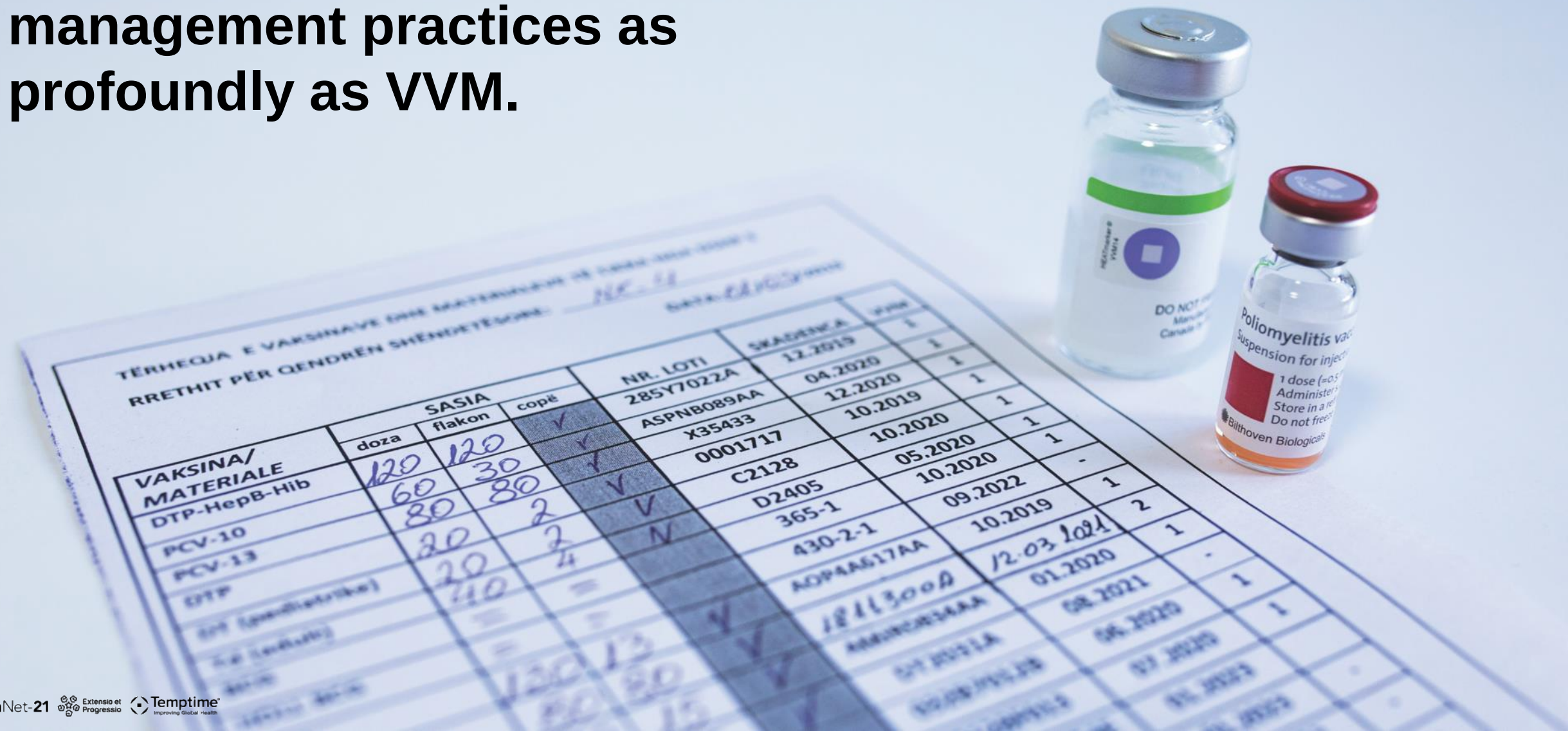
http://kartoglu.ch/vvm

TechNet-21 Extensio et Progressio Temptime Improving Global Health

Vaccine Vial Monitors

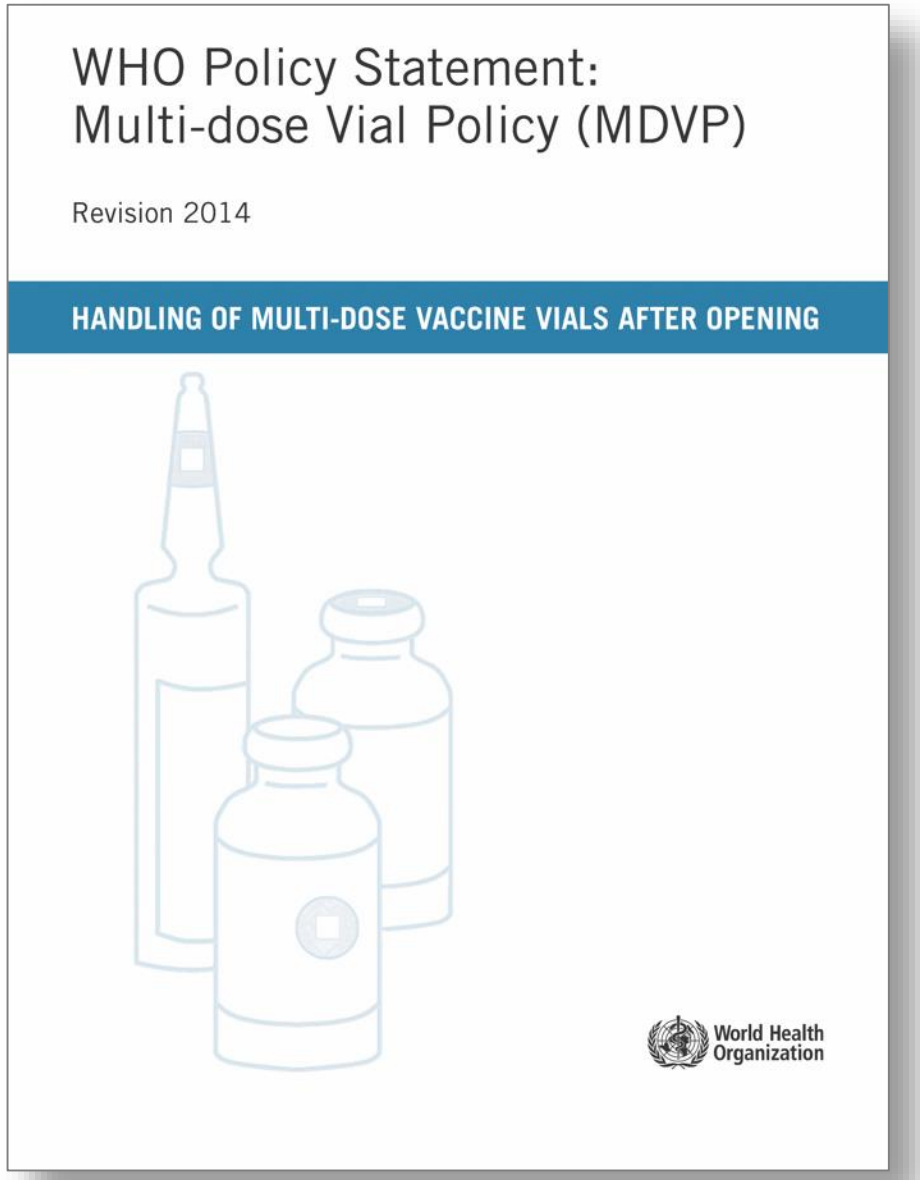


There is no temperature monitoring device that has changed vaccine management practices as profoundly as VVM.



TechNet-21 Extensio et Progressio Temptime Improving Global Health


Some critical approaches we have today in vaccine management have only been made possible with the help of VVM, and others have been made more effective.
PERTUSSIS VACCINE ADSORBED
HEATmarker ® VVM14
DO NOT FREEZE
B.NO.: 2828X0068
EXP.: JUN. 2020
LTD. 20012712/1
(01)08901213051174



- The vaccine is currently prequalified by WHO.
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO.
- The expiry date of the vaccine has not passed.
- The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard-point, and the vaccine has not been damaged by freezing.

THE VISUAL CUE

Proper handling of 2-dose vial Cervarix HPV Vaccine

Vaccine Vial Monitor (VVM) placed on cap

Proper handling of 2-dose vial Cervarix HPV Vaccine

1. After opening, this vaccine vial should be handled in the same manner as a reconstituted BCG or measles vaccine vial.

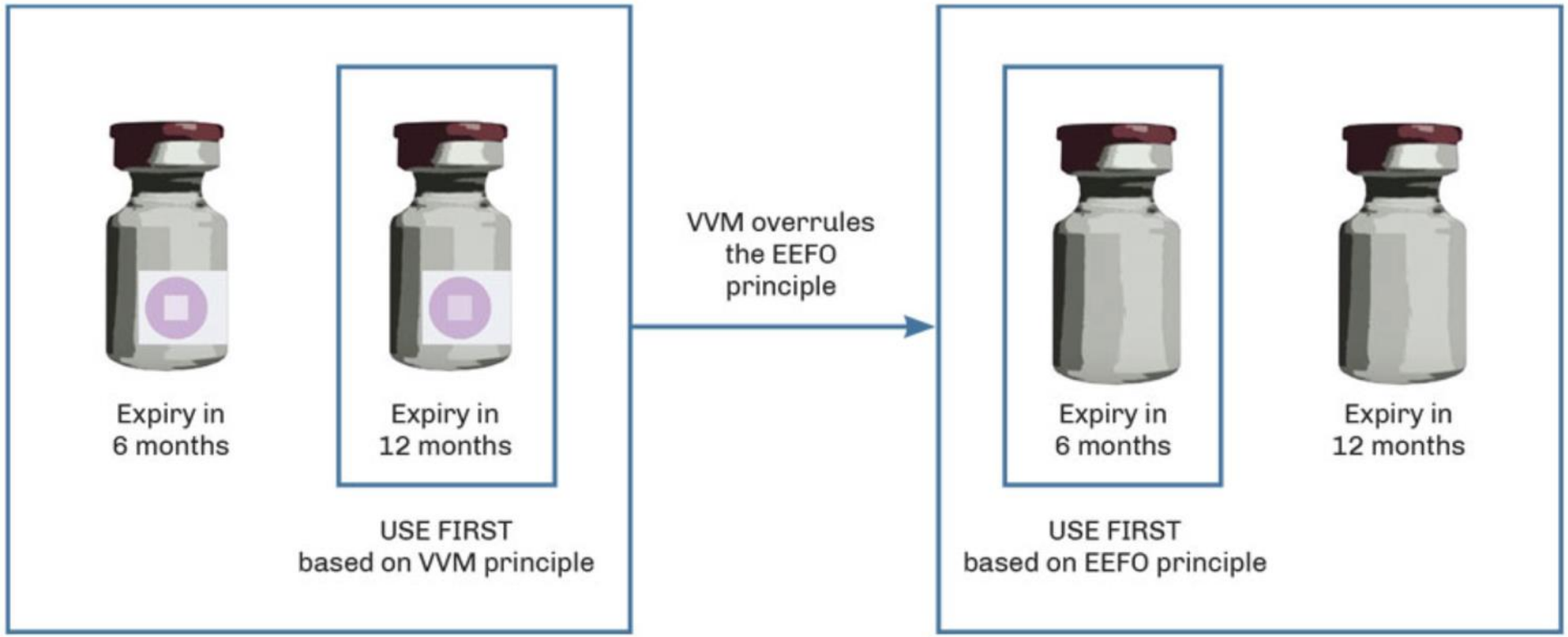
2. Discard any unused dose at the end of the immunization session or six hours, whichever comes first.

3. During the session, put the open vials in the vaccine carrier, do not return them in the refrigerator.

- Shake before use
- Check the expiry date and the VVM before opening the vial
- Store in the cold chain at +2ºC to +8ºC
- Do not freeze, protect from light

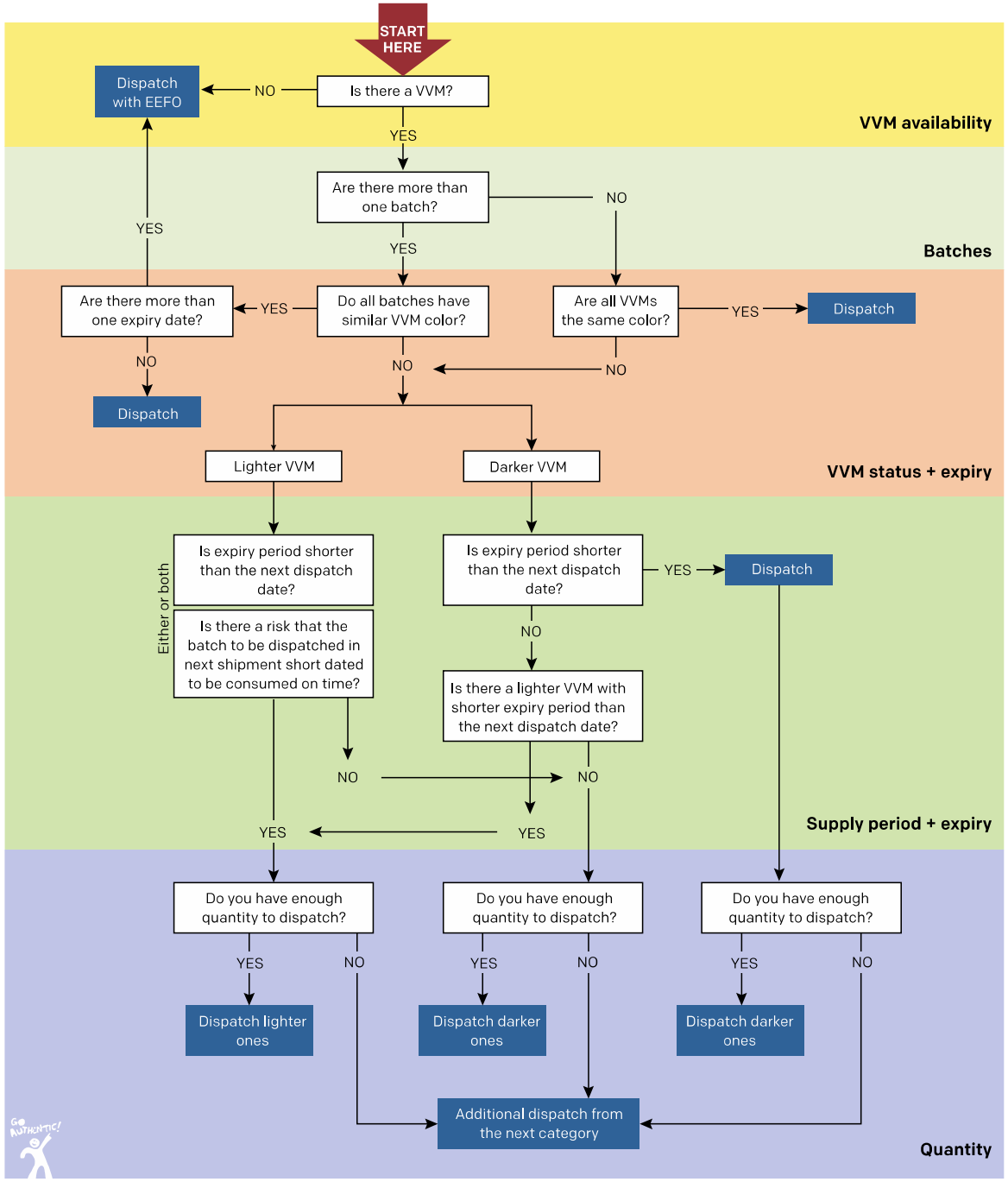
SMART EXPIRY DATE

SMART EXPIRY DATE

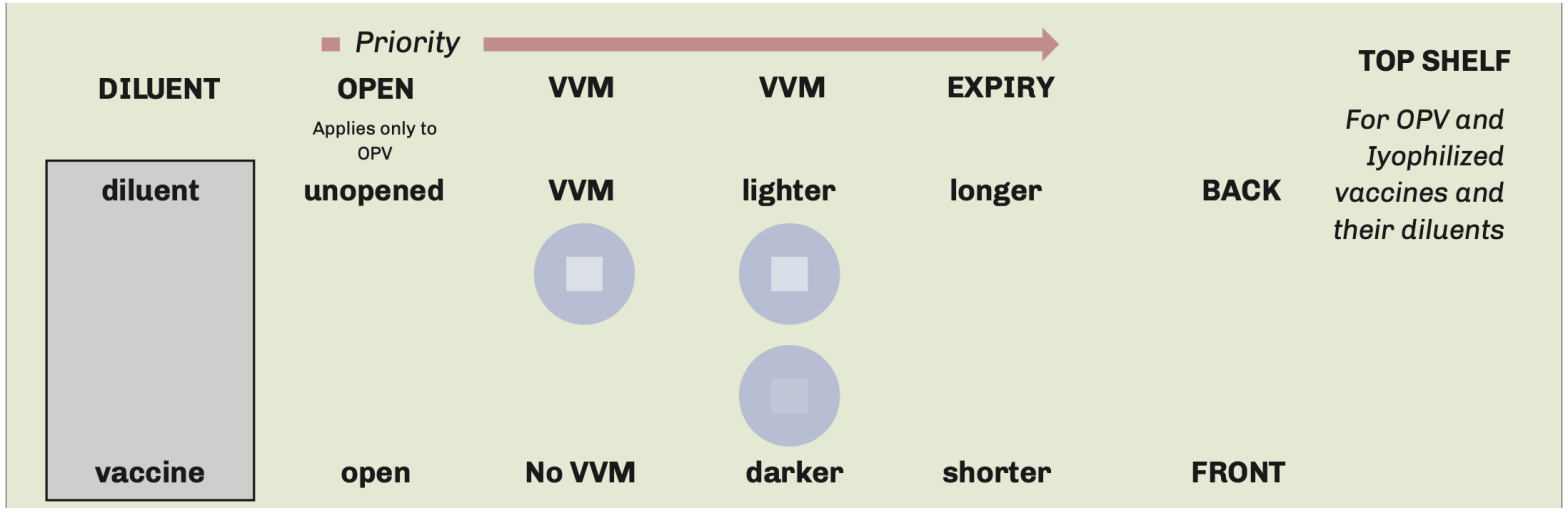


ROTATING STOCKS WITH THE HELP OF VVM

DISPATCHING VACCINES



KEEPING VACCINES IN ORDER



Arranging vaccines in front opening refrigerators

All vaccines must be segregated by type and each type must be kept in a tray to prevent vials from getting mixed up.

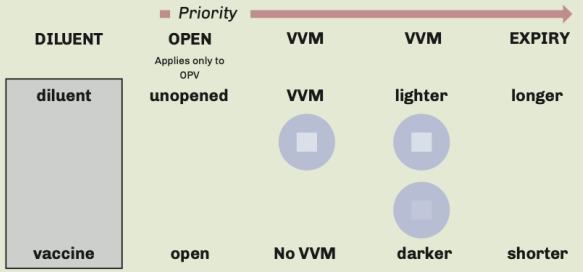
Vaccines that are already expired and with VVMs at or beyond the discard-point must not be kept in the refrigerator. They must be kept outside the cold chain with a clear marking "not for use" to obtain authorization to discard them.

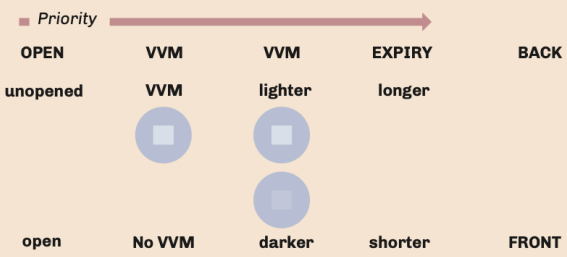
Only matching quantities of Iyophilized vaccines and diluents must be kept in the refrigerator.

Diluents are not interchangeable.

FREEZER

Only for water packs to produce ice





CRISPER

Only for water-bottles

If you have any shelves in the door REMOVE them.

DOOR

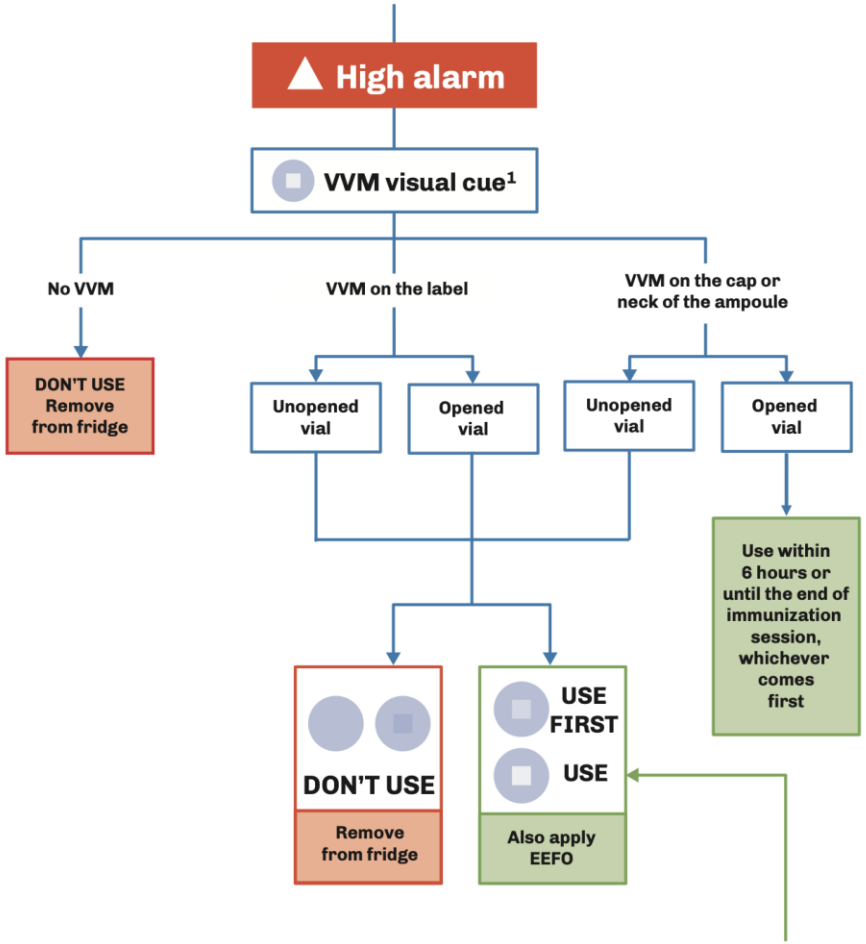
NOTHING

Kartoglu, February 2014

TechNet-21 Extensio et Progressio Temptime Improving Global Health

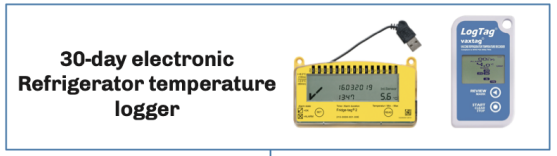
WHICH VIAL TO USE FIRST?

WHEN THERE IS AN ALARM



WHEN THERE IS AN ALARM

Interpretation of temperature monitoring devices



High alarm

VVM visual cue[1]

No VVM → DON'T USE Remove from fridge

VVM on the label → Unopened vial; Opened vial

VVM on the cap or neck of the ampoule → Unopened vial; Opened vial

DON'T USE Remove from fridge

USE FIRST / USE — Also apply EEFO

Use within 6 hours or until the end of immunization session, whichever comes first

Electronic freeze indicator

Low alarm

Al adjuvanted vaccines
DTaP
DTaP-hepatitis B-Hib-IPV
DTwP
DTwP-hepatitis B-Hib
Hepatitis A
Hepatitis B
Hib liquid (Merck)
Human papillomavirus
Meningitis C (polysaccharide-poretin conjugate)
Pneumococcal (polysaccharide-protein conjugate)
TT, DT, dT and
The diluent for MenA PS-PCV

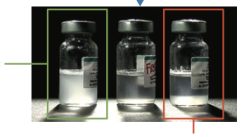
Non adjuvanted vaccines
Cholera (inactivated)
Hib liquid (CIGB)
Influenza (inactivated, split)
Inactivated poliovirus
Typhoid PS

DON'T USE Remove from fridge

Solid frozen OR Non-homogenous

DON'T USE Remove from fridge

Conduct SHAKE TEST[2]



PASS shake test

FAIL shake test

DON'T USE Remove from fridge

[1] All opened WHO-prequalified multi-dose vials of vaccines should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first, UNLESS the vaccine meets all four of the criteria listed below. If the vaccine meets the four criteria, the opened vial can be kept and used up to 28 days after opening. The criteria are as follows.

- The vaccine is currently prequalified by WHO.
- The vaccine is approved for use for up to 28 days after opening the vial, as tedermined by WHO.
- The expiry date of the vaccine has not passed.
- The vaccine vial has been, and will continue to be, stored at WHO- or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

For multi-dose vial policy application and visual cue, refer to WHO Policy Statement: Multi-dose vial policy (MDVP). Handling of multi-dose vials after opening. Revision 2014. WHO/IVB/14.07

Also consult each individual vaccine product sheet at the WHO prequalification website, referencing the description "Handling of opened multi-dose vials"

http://bit.ly/2JECKWq

[2] WHO SHAKE TEST PROTOCOL must be followed. For shake test protocol, refer to **When and how to conduct shake test**, EVM-SOP-E8-01, effective 07 OCT 2011 at

http://bit.ly/32C3CxA and video **Step-by-step how to conduct shake test** at http://bit.ly/2JPAVVC

If only a few vials are available in the refrigerator, shake test may not be conducted, but all freeze suspected vials must then be taken out of the refrigerator for discard.

Do not conduct shake test for opened multi-dose vials, they must be discarded. However, if "same type of unopened vaccine vials" pass the shake test, you may keep the opened one to be used first.

For freeze-sensitive vaccines, check package insert whether it is aluminum adjuvanted.

DO NOT USE IF THERE IS NO LABEL.

REMOVING ICE FROM IN-COUNTRY TRANSPORT

RESEARCH

Use of Cool Water Packs To Prevent Freezing During Vaccine Transportation at the Country Level

UMIT KARTOGLU[1], SERGE GANIVET[2], STEPHANE GUICHARD[3], VENKAT AIYER[4], PETER BOLLEN[5], DENIS MAIRE[6], and BIRHAN ALTAY[7]

[1]Scientist, Family and Community Health/Department of Immunization, Vaccines and Biologicals, Performance, Quality and Safety L267, World Health Organization, 20 Avenue Appia, 27-Geneva 1211 Switzerland; [2]Intercountry Logistician, WHO Regional Office for Africa, Harare, Zimbabwe; [3]Technical Officer, WHO Regional Office for South East Asia, New Delhi, India; [4]World Health Organization (WHO) Consultant, Nepal; [5]WHO Consultant, Myanmar; [6]Technical Officer, WHO Regional Office for Europe, Copenhagen, Denmark; [7]Medical Doctor, Saray Health Centre, Ankara, Turkey

ABSTRACT: **Objectives:** To study the impact of the use of cool water packs (water packs refrigerated at 2 to 8 °C) on the cold life of vaccine transport boxes and the shelf life of the vaccines. **Methods:** Data loggers were used to measure the temperatures of vaccine shipments with cool water packs in laboratory studies and country evaluations. The temperature recordings were mathematically translated into reduction of vaccines shelf life, which are illustrated through degrees of color changes of Vaccine Vial Monitors. **Findings:** Laboratory studies at extreme ambient temperatures (43 °C) showed that, with the use of cool water packs, temperatures inside the cold box rise to around 20 °C within 48 h. When this exposure scenario was repeated four times, the impact of the temperature history on the different heat stability categories of vaccines varied between 2.4 and 36.0% shelf life loss. Oral polio vaccine was found to be the most affected vaccine. All other vaccines were affected with 2.4 to 10.4% life loss. Country assessments (real life situation with temperature variations between day and night) showed between 0.4% to 4.6% life loss when the boxes were exposed to ambient temperatures ranging from 11.7 to 39.8 °C over the 98 h 15 min test period. **Conclusions:** The use of cool water packs is found to be a legitimate and safe practice for vaccines other than oral polio vaccine, so that cool water packs can safely replace frozen icepacks without any serious consequences on the ability of vaccines to confer protection against disease.

KEYWORDS: Cool water packs, Freezing, Transportation, Vaccines, VVM, Nepal, Myanmar, Turkey, Zimbabwe.

Introduction

World Health Organization (WHO) guidelines recommend that liquid formulations of vaccines containing diphtheria, pertussis, tetanus, hepatitis B, *Haemophilus influenzae* type b and their combinations should not be frozen (1). Freezing of these vaccines provokes a loss of potency and, as a consequence, can result in compromised protective immunogenicity in recipients (2–5).

Freezing of vaccines occurs when vials are exposed to temperatures below 0 °C either during storage or transport depending upon a host of factors, including the duration that vaccine is exposed and whether the vaccine is agitated during that time period. Studies have shown exposure of vaccines to both subzero and freezing temperatures at all levels of the cold chain. Practices that put freeze-sensitive vaccines at risk are common not only in the developing world, but also in industrialized countries. Studies have shown freeze damage to vaccines in Australia (6, 7), Bolivia (8), Canada (9), Hungary (10), Indonesia (11), Malaysia (12), Papua New Guinea (13), the United Kingdom (14–17), and the United States (18).

The severity of the problem has been highlighted in a recent publication in which, of 14 shipments that were monitored, 12 experienced temperatures below 0 °C at one or more points in the cold chain in Indonesia (11). Ten of those were exposed to temperatures below 0 °C during district or sub-district transport in cold boxes.

Author to whom correspondence should be addressed. Email: kartogluu@who.int.

TABLE II
Temperature Recordings of RCW25/CF and RCW2/CF During 48 Hours Exposure to 43°C and 32°C Ambient Temperatures at CSIR (in °C)

Box type	Ambient temperature	Initial water packs temperature	Temperature of the cold box/vaccine carrier[a]			VVM readings at the end of the test[b]			
			Average	Min	Max	VVM2	VVM7	VVM14	VVM30
Large RCW25/CF	43.0 ± 0.5	2 ± 0.5	11.5	2.5	20.0				
	43.0 ± 0.5	8 ± 0.5	16.3	8.2	23.6				
	43.0 ± 0.5	No packs	33.5	11.6	41.5				
	32.0 ± 0.5	2 ± 0.5	10.5	5.0	16.1				
	32.0 ± 0.5	8 ± 0.5	14.5	8.2	19.2				
Small RCW2/CF	43.0 ± 0.5	2 ± 0.5	34.1	3.1	42.7				
	43,0 ± 0,5	8 ± 0,5	35,1	9,1	42,2				
	43,0 ± 0,5	No packs	40,9	14,1	43,2				
	32,0 ± 0,5	2 ± 0,5	25,8	4,2	31,3				
	32,0±0,5	8 ± 0,5	27,4	10,8	31,7				

TABLE III
Remaining VVM Life After Storage in Large Cold Box and Small Vaccine Carrier Loaded with 8°C Water Packs, at an Ambient Temperature of 43°C for 48 Hours, CSIR Laboratory

VVM Type	VVM End-Point (Days)	Percentage of VVM Life Used	Remaining VVM Life in Days if Kept at 37°C
RCW25/CF large cold box			
VVM2	1.75	6.3	1.64
VVM7	6.125	1.8	6.02
VVM14	12.25	0.9	12.14
VVM30	26.25	0.4	26.14
RCW2/CF small vaccine carrier			
VVM2	1.75	138.4	Beyond the end-point
VVM7	6.125	39.6	3.70
VVM14	12.25	19.8	9.83
VVM30	26.25	9.2	23.83

TABLE IX
Repeated Temperature Exposure Impact on the VVM Life Simulation (Four Times of Transport at Ambient Temperature of 43°C for 48 Hours)

VVM Type (and End-Point Days)	VVM Life Used (%)	Remaining VVM Life if Kept at 37°C (Days)
1. RCW25/CF (Domestic)		
VVM2 (1.75)	25.2	1.3
VVM7 (6.125)	7.2	5.7
VVM14 (12.25)	3.6	11.8
VVM30 (26.25)	1.6	25.8
2. CB20-50-CF (Blow Kings)		
VVM2 (1.75)	2.8	1.7
VVM7 (6.125)	0.8	6.1
VVM14 (12.25)	0.4	12.2
VVM30 (26.25)	0.4	26.1
3. Insulated Box (PT BioFarma)		
VVM2 (1.75)	36.0	1.1
VVM7 (6.125)	10.4	5.5
VVM14 (12.25)	5.2	11.6
VVM30 (26.25)	2.4	25.6

- Vaccines are transported four times (primary to intermediate 1, intermediate 1 to intermediate 2, intermediate 2 to intermediate 3, and intermediate 3 to health centre)
- Only cold water packs are used
- Ambient temperature is constant 43 °C day and night
- Each and every transport takes 48 h

Repeated temperature exposure is applied to used and remaining VVM life calculation through the Arrhenius equation. Results are shown in Table IX.

In spite of the low impact calculated when the Blow-Kings cold box is used, the VVM2 (OPV) loses 25% of its life with RCW25/CF and 36% of its life with the insulated box. It is therefore obvious that OPV should not be transported with cool water packs. VVMs are classified according to vaccine stability (see Box 1). VVM category to vaccines is assigned by WHO experts based on the stability data of the vaccine examined. It is possible that the same type of vaccines produced by different manufacturers will be assigned a different type of VVM. However, in most cases, freeze sensitive vaccines such as DTP are assigned VVM14 and TT and HepB are assigned a VVM30.

Figure 5 shows the calculated highest impact on VVM readings in a scenario (number 3 in Table IX) in which the transport is repeated four times for 48 h at 43 °C

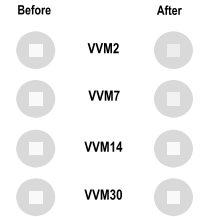


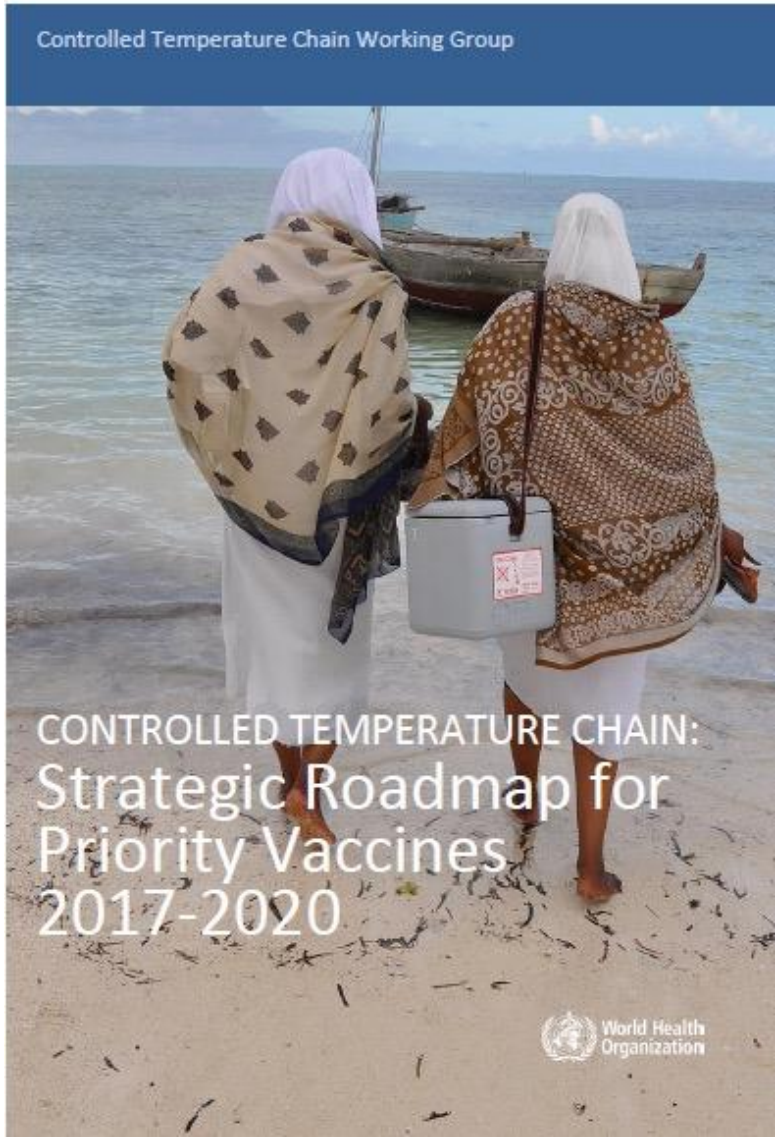
Figure 5
Temperature impact on VVM readings, insulated box.

http://kartoglu.ch/papers/14_Use-of-Cool-Water-Packs-to-Prevent-Freezing-During-Vaccine-Transportation-at-the.pdf


Controlled Temperature Chain Working Group
CONTROLLED TEMPERATURE CHAIN:
Strategic Roadmap for Priority Vaccines 2017-2020
World Health Organization


MenAfriVac
5 ml
Diluent for Meningococcal A Conjugate Vaccine

CONTROLLED TEMPERATURE CHAIN USE OF VACCINES

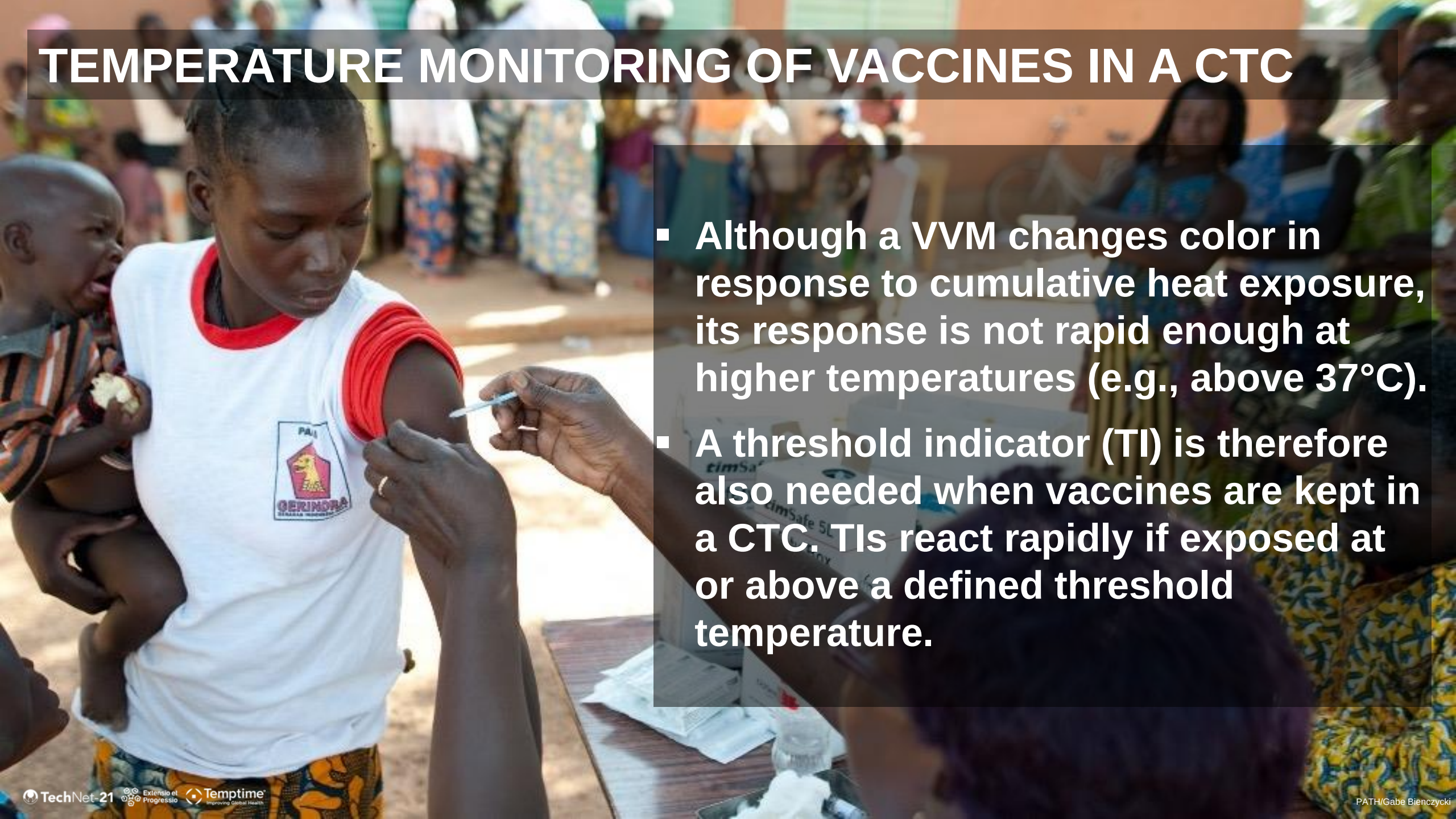


- CTC use of vaccines allows for a single excursion of a vaccine into ambient temperatures not exceeding +40°C for a minimum of 3 days, just prior to administration.
- Heat-stable vaccines differ in the length of time they can be stored in a CTC and the maximum temperature they can endure while remaining stable and potent.
- CTC qualification involves regulatory approval and prequalification by WHO.
- CTC is a priority for vaccines used in campaigns and special strategies.

Status of CTC vaccines

- There are currently three vaccines that are thermostable and qualified for CTC use.
  - Serum Institute of India's MenAfriVac® (conjugate meningitis A vaccine) that can be used for up to **4 days** at temperatures not exceeding **40°C**.
  - Merck's Gardasil® 4 (quadrivalent human papillomavirus vaccine) that can be used for **3 days** at temperatures not exceeding **42°C**.
  - Shantha Biotechnics Shanchol™ (oral cholera vaccine) that can be used for **14 days** at temperatures not exceeding **40°C**.
- A number of vaccine manufacturers are in the process of qualifying their existing and pipeline liquid vaccines for CTC use.
- Some vaccines are inherently heat stable, others may require additional formulation efforts to improve their stability, and some vaccines may never qualify for CTC use.

TEMPERATURE MONITORING OF VACCINES IN A CTC

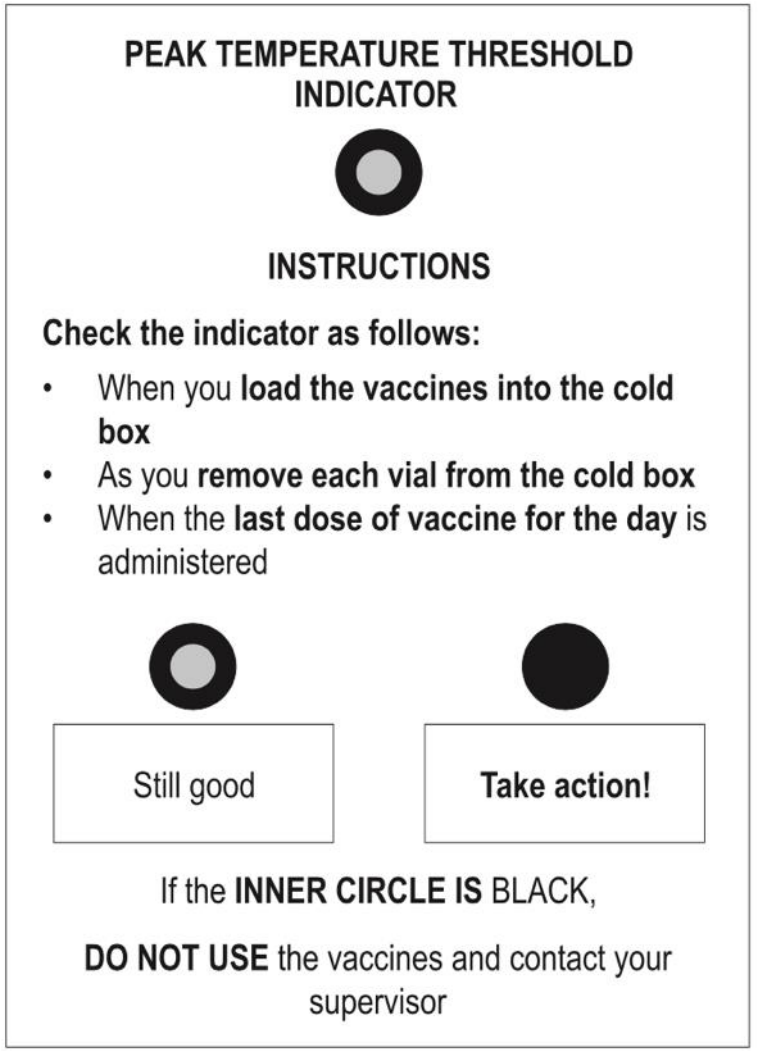


- Although a VVM changes color in response to cumulative heat exposure, its response is not rapid enough at higher temperatures (e.g., above 37°C).
- A threshold indicator (TI) is therefore also needed when vaccines are kept in a CTC. TIs react rapidly if exposed at or above a defined threshold temperature.

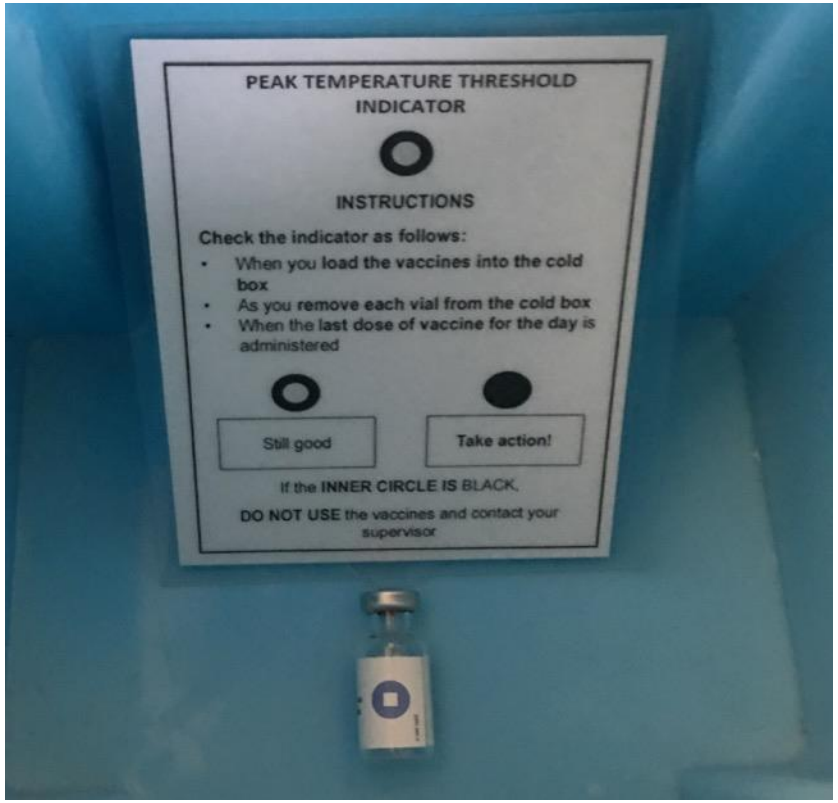
PATH/Gabe Bienczycki

TEMPERATURE MONITORING OF VACCINES IN A CTC

- **At present, a standalone TI is used in vaccine carriers and cold boxes.**
- **The TI is on a card and the indicator changes color from light grey to black as soon as the temperature has exceeded +40°C.**
- **The need to supply, distribute, and provide training on TI cards is a barrier to CTC vaccine introduction.**



VVM with THRESHOLD INDICATOR



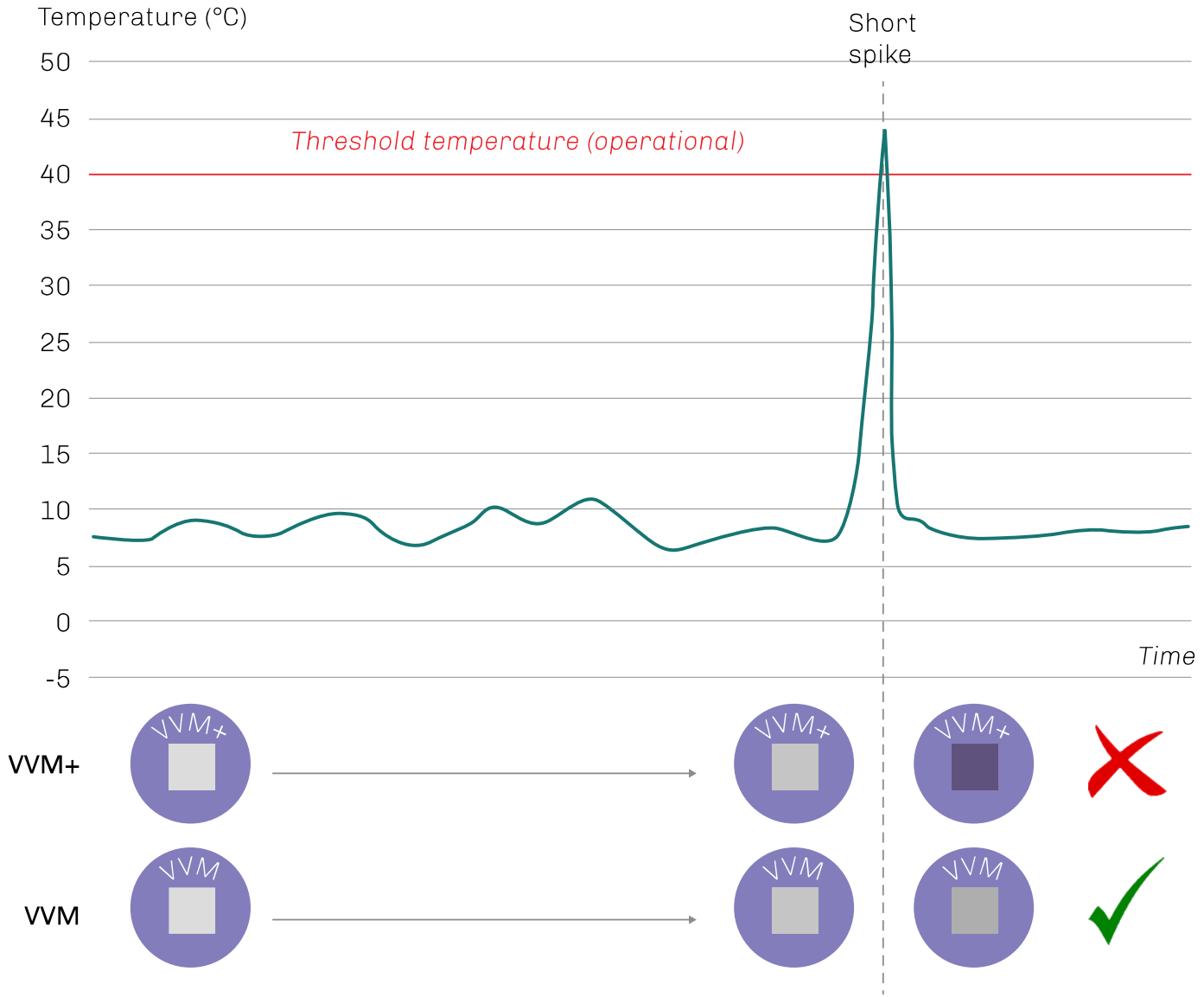
A combined VVM-TI on primary containers undergoes gradual color change up to the specified threshold temperature and rapidly reacts if exposed at or above the threshold temperature.

Integrates the VVM and TI

VVM Plus Threshold Indicator - VVM+®

VVM+ developed for Controlled Temperature Chain(CTC)

- VVM+ reacts like VVM up to 37°C
- At 40°C VVM+ reaches end point rapidly to show exposure to critical peak temperature
- VVM+ supports CTC initiatives



WHO PQS specification for COMBINED VVM and TI

VVM+250, VVM250 and TI Prequalified

PQS performance specification

WHO/PQS/E006/IN06.1
Original: English
Distribution: General

TITLE: Combined Vaccine Vial Monitor and Threshold Indicator

Specification reference:	E006/IN06.1
Product verification:	E006/IN06-VP.01
Issue date:	January 2019
Date of last revision:	New specification

World Health Organization

عربي | 中文 | English | Français | Русский | Español

Search

Home
About WHO
Countries
Health topics
Publications

Product List

PQS Catalogue > Prequalified Devices and Equipment > **Product List**

E006: Temperature monitoring devices

Product	Description	Company	Mfr reference		
E006/058	Vaccine Vial Monitor Type 250	Temptime Corporation	HEATmarker® VVM 250	Download PDF	Copy link
E006/057	Threshold Indicator40	Temptime Corporation	LIMITmarker I-K	Download PDF	Copy link
E006/059	Combined VVM250 and Threshold Indicator40	Temptime Corporation	HEATmarker® VVM+250	Download PDF	Copy link

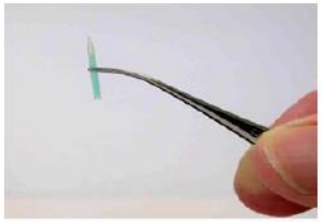
VVM+ shortlisted on VACCINE INNOVATION PRIORITIZATION STRATEGY (VIPS)

Under Phase I, 9 innovations have been short-listed

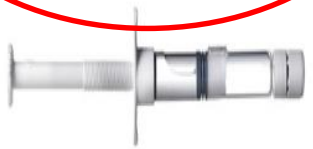
Microarray patches (MAPs)

Combined Vaccine vial Monitor (VVM) and Threshold Indicator (TI)

AD sharps-injury protection (SIP) syringes



Solid-dose implants



Dual-chamber delivery devices

Freeze damage resistant liquid formulations

Heat stable/controlled temperature chain (CTC) qualified liquid formulations

Compact prefilled auto-disable devices (CPADs)

Barcodes / Radio Frequency Identification (RFID)

BARCODES

Gavi announced GS1 barcodes required on secondary packaging

Tenders after

https://www.unicef.org/supply/index_103734.html

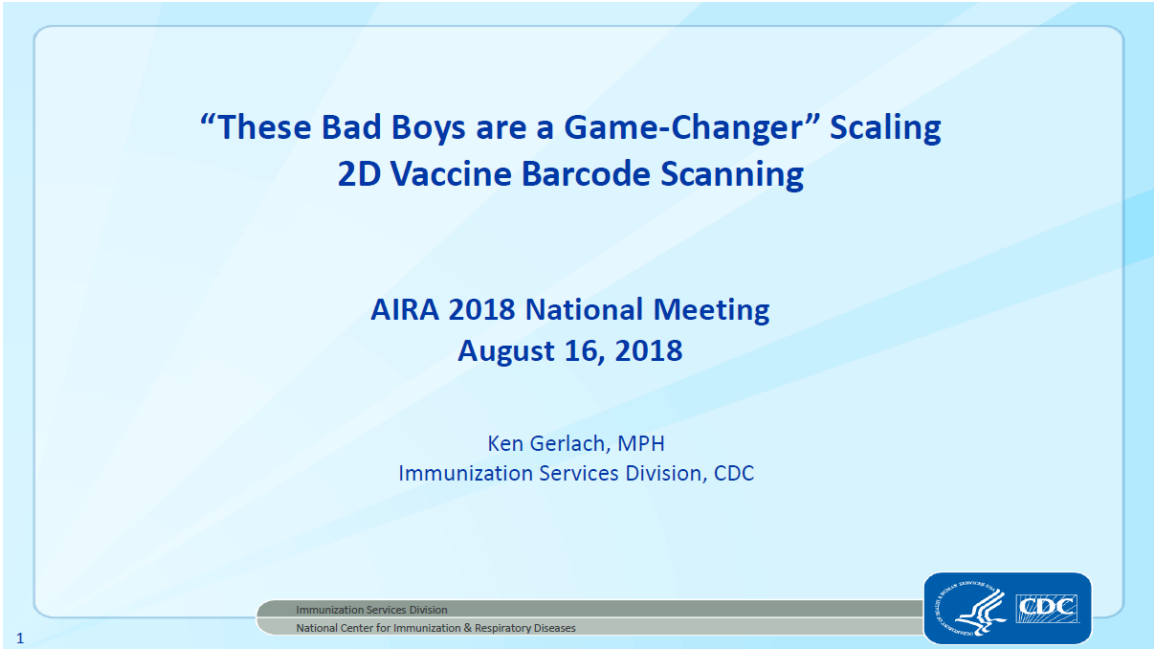
- **First step to transition track and trace system technology on vaccines to a labelling requirement**

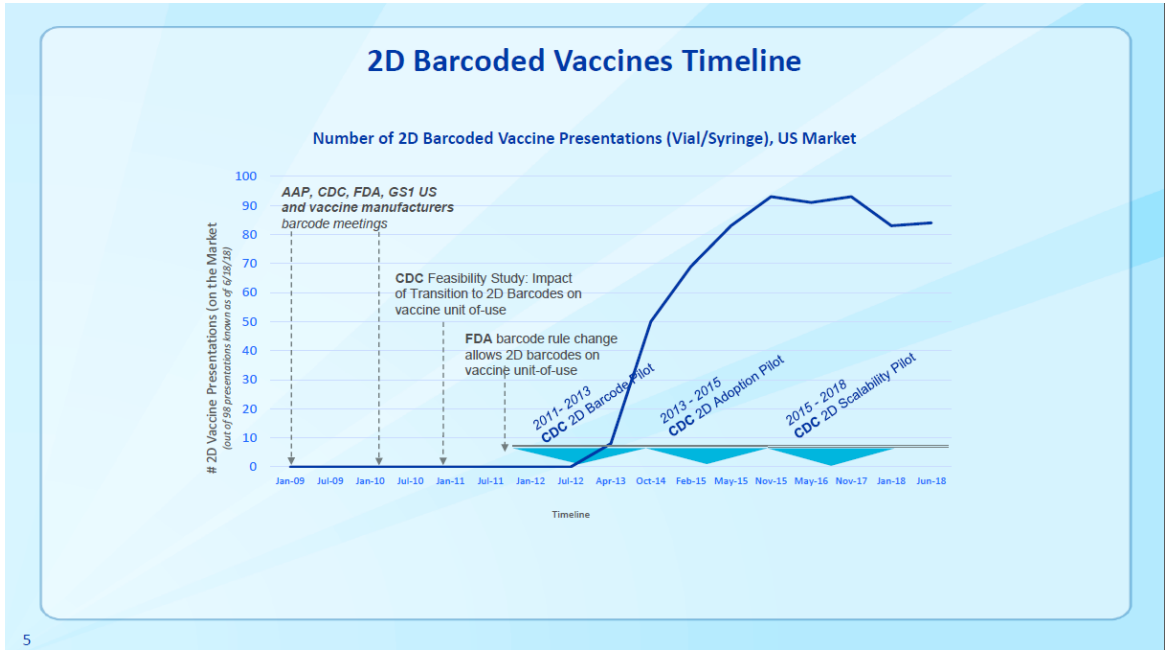
> GAVI announcement: vaccine manufacturer GS1 compliance
>
> **Starting 1st October 2019, for vaccine tenders backed by Gavi financing and issued by UNICEF, GS1 barcoding on the secondary packaging will be a requirement by latest 31st December 2021.**

- **WHO is developing a Track and Trace Policy Brief**

US CDC 2D barcode update

>80% compliance of 2D barcodes on vials and prefilled syringes

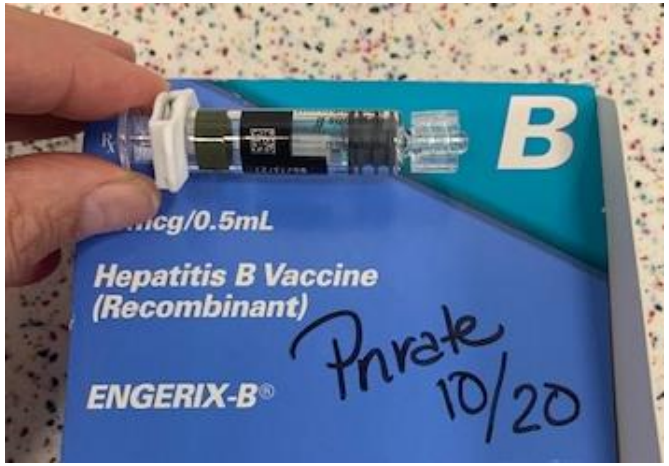




US CDC 2D barcode update

Essentially all US vaccine vials and syringes have 2D barcodes

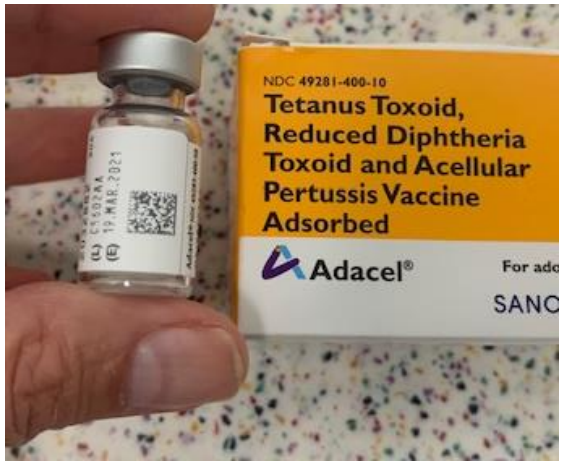
GSK Hep B



Pfizer – Pneumo

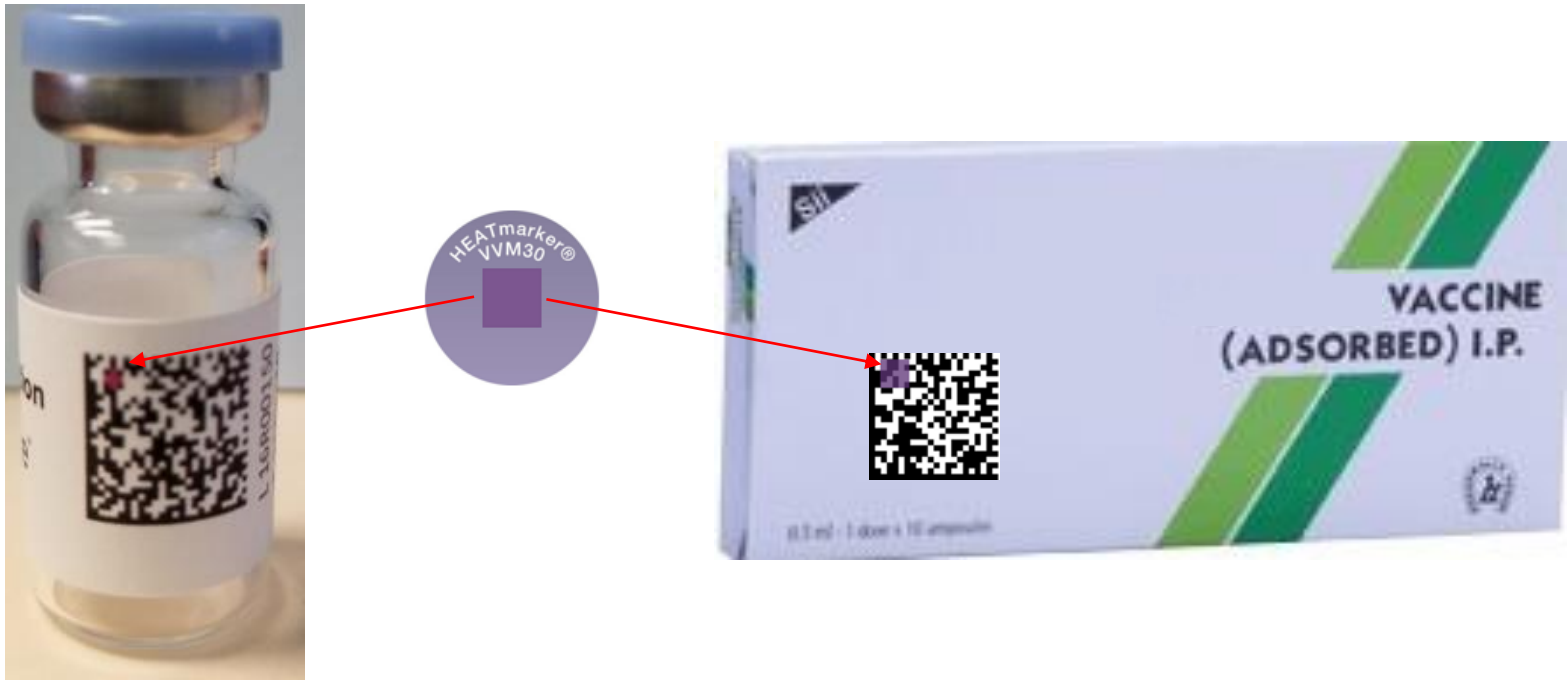
Merck – Gardasil

Sanofi - Tdap



GTIN, lot number, expiry date

2D barcode and digitized VVM (eVVM)

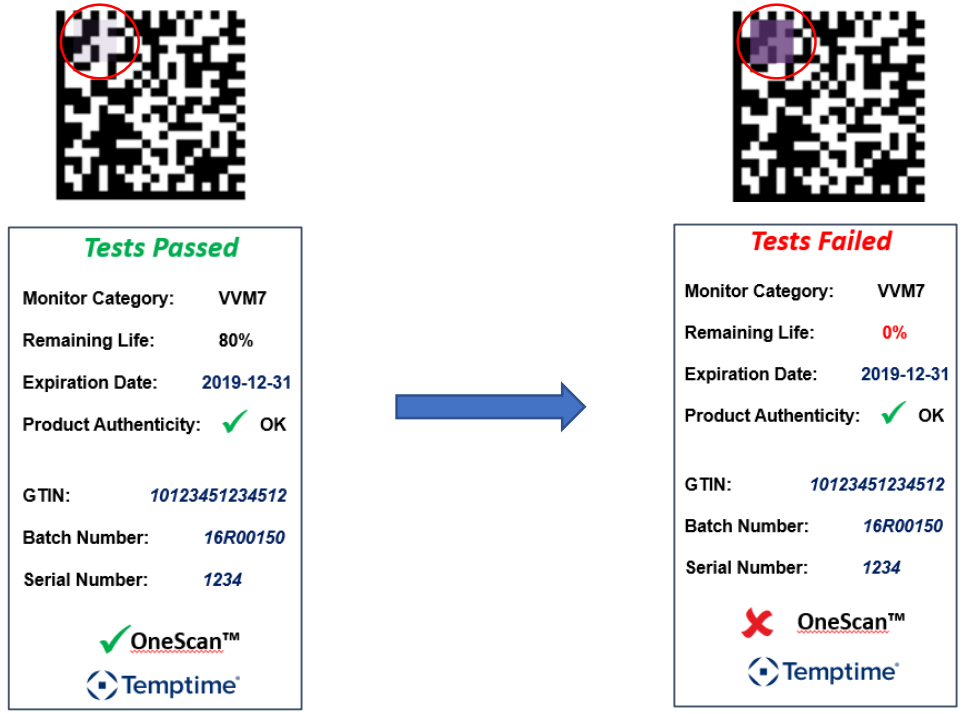


2D barcode with embedded temperature sensor

Digitize chemical indicators with unit of sale level data connection

Enhance the value of 2D barcodes for stock management, patient safety and anti-counterfeiting by incorporating temperature integrity

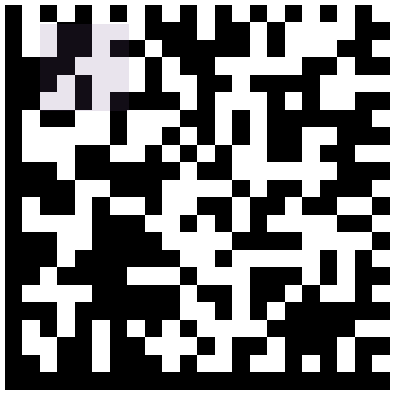
- Specific area has cumulative (VVM) and/or threshold ink printed as part of barcode
- Rapid reading with phone or scanner
- Connect with cloud-based data set of other sensors

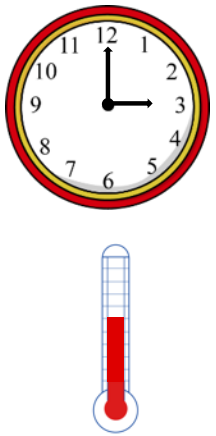


GS1 2D datamatrix with VVM

VVM – gradual, irreversible color change from light to dark develops with cumulative temperature exposure over time

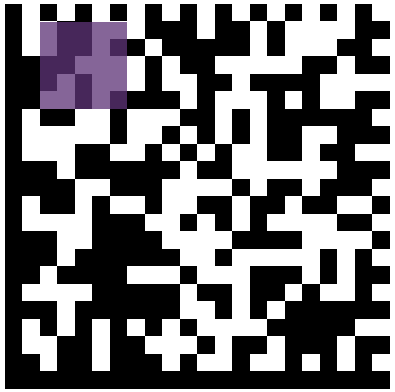
Before heat exposure



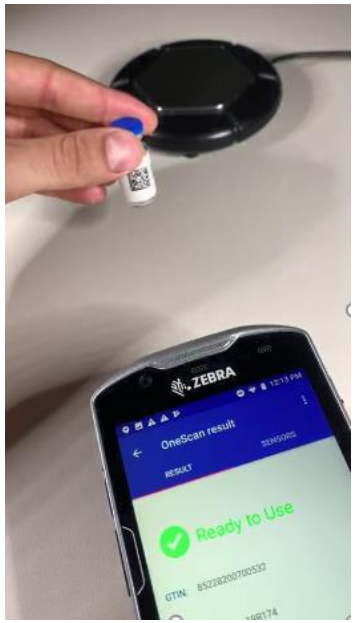


Time and temperature exposure

After excessive heat

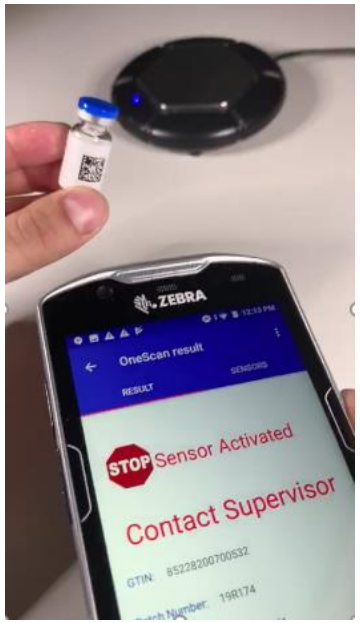


Demo of OneScan™ indicator

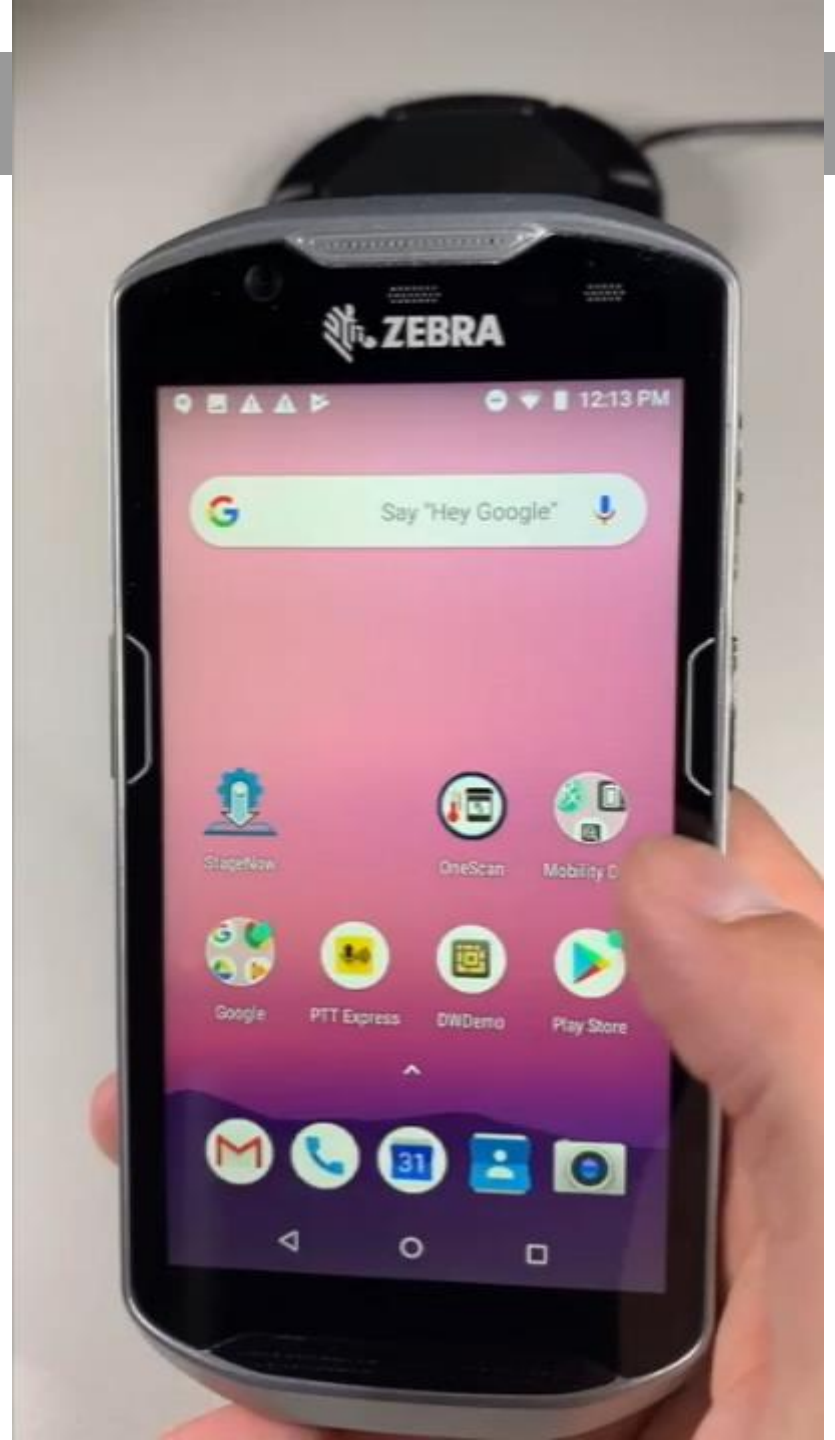


Before Heat

Hot Plate



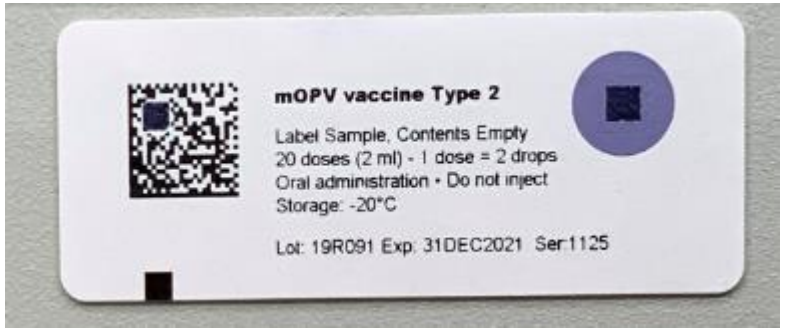
After Heat



2D barcode with embedded VVM active

Color evolution over time

Early adoption would likely maintain classic VVM



Size doesn’t matter for product integrity

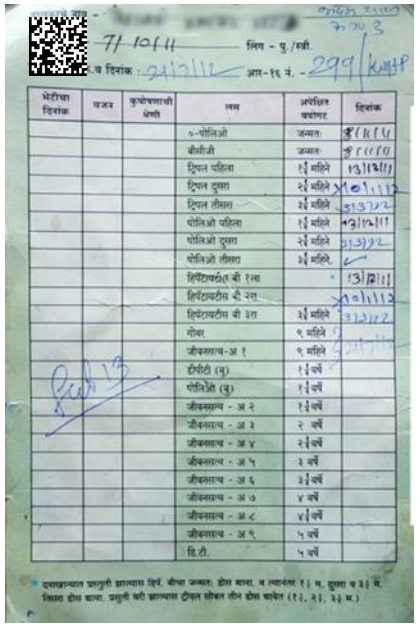
Temperature monitoring and traceability for shipping box, carton box, vial, syringe, ampoule

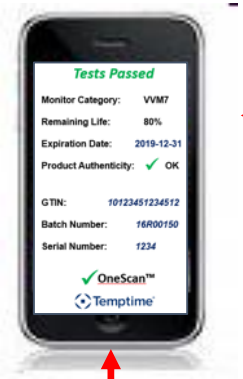
Leverage value of VVM with linkage to HMIS

Link health and logistics management systems

Improve data quality and integrity

Scan Uniquely Identified Immunization Card





Scan Uniquely Identified Vial

Link each infant with the vaccines they receive

Thank you...